ISCN 2024

Genetics

An International System for Human Cytogenomic Nomenclature (2024)

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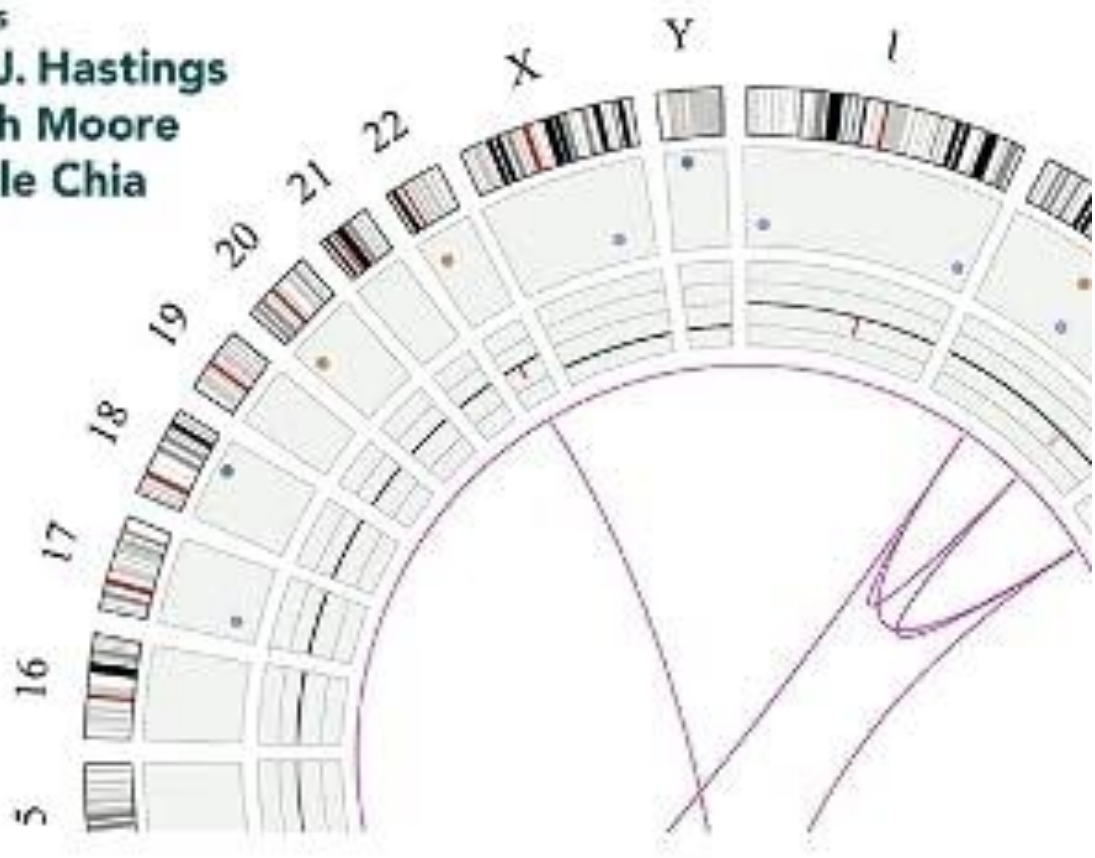

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Contents

1 Historical Introduction

1956:	Tjio and Levan (1956) reported the human chromosome number to be 46 on cultured human embryonic cells and not 48, as previously thought.
1956:	Ford and Hamerton (1956) confirmed the chromosome number on testicular material.
1960:	The Denver Conference (First International Congress of Human Genetics) agreed on a karyotype nomenclature system and published "A Proposed Standard System of Nomenclature of Human Mitotic Chromosomes."
1963:	The London Conference (Second International Congress of Human Genetics) gave the official sanction to the classification of the seven groups of chromosomes by the letters A to G, as originally proposed by Patau (1960).
1966:	The Chicago Conference (Third International Congress of Human Genetics) proposed a standard system of nomenclature for the provision of shorthand descriptions of the human chromosome complement.
1968:	Torbjörn Caspersson and his colleagues published the first pictures of banded plant chromosomes stained with quinacrine dihydrochloride or quinacrine mustard (Caspersson et al., 1968).
1970:	First human karyotype based on quinacrine fluorescence–banded chromosomes (for a review of this work, see Caspersson et al., 1972).
1971:	The Paris Conference (Fourth International Congress of Human Genetics) agreed upon a uniform system of human chromosome identification and formed the first Cytogenetic Standing Committee (SC) (Chair: John Hamerton). The Paris Conference (1971) report provided a way in which structural rearrangements and variants could be described in terms of their band composition, and proposed a basic system for designating individual chromosomes, chromosome regions, and bands.
1975:	The Paris Conference, 1971, Supplement (1975), was published, which included heteromorphic chromosomes of the Hominoidea, and chromosome registers.
1976:	The Mexico City Conference (Fifth International Congress of Human Genetics) elected an International Standing Committee on Human Cytogenetic Nomenclature (ISCN SC) with a mandate to propose ways in which human chromosome nomenclature could be improved (Chair: Jan Lindsten).

1977:	The ISCN SC ceased labelling the reports geographically and unified the conference reports of Denver, London, Chicago, and Paris into one document entitled "An International System for Human Cytogenetic Nomenclature (1978)," abbreviated as ISCN 1978.
1978:	The introduction of high-resolution banding (Dutrillaux, 1975; Yunis, 1976) demonstrated that a new nomenclature was required (Francke and Oliver, 1978; Viegas-Pequignot and Dutrillaux, 1978; Yunis et al., 1978). A working group was established under the direction of Bernard Dutrillaux.
1981:	At the Jerusalem Conference (Sixth International Congress of Human Genetics), David Harnden was appointed Chair of the ISCN SC. "An International System for Human Cytogenetic Nomenclature – High Resolution Banding (1981)" known as ISCN 1981 was published.
1985:	A revision of the International System for Human Cytogenetic Nomenclature was prepared in 1984, and published as ISCN 1985, without major revision except to correct errors and make minor amendments.
1986:	A new ISCN SC was elected at the Seventh Congress of Human Genetics in Berlin (Chair: Uta Francke).
1991:	A subcommittee under the direction of Felix Mitelman produced a nomenclature for cancer cytogenetics. The report of this subcommittee was adopted by the ISCN SC and published as "ISCN 1991: Guidelines for Cancer Cytogenetics." A new ISCN SC was elected at the Eighth International Congress of Human Genetics in Washington, DC (Chair: Felix Mitelman).
1995:	The ISCN SC reviewed and updated the ISCN 1985 nomenclature in light of developments in the field, including advances in the use of *in situ* hybridization techniques. All revisions and the guidelines for cancer cytogenetics were incorporated into a single document, which was published as ISCN 1995.
1996:	At the Ninth International Congress of Human Genetics in Rio de Janeiro, a new ISCN SC was elected (Chair: Patricia A. Jacobs). It was agreed no further changes were needed to ISCN 1995.
2001:	The Tenth International Congress of Human Genetics was held in Vienna and a new ISCN SC was elected (Chair: Niels Tommerup).

2005:	Following a review of ISCN 1995, primary changes in ISCN 2005 included the addition of new idiograms at the 300- and 700-band level that reflected the actual size and position of bands. The *in situ* hybridization nomenclature was modernized, simplified, and expanded. New examples reflecting unique situations were added, and a basic nomenclature for recording array comparative genomic hybridization results was introduced (Chair: Lisa Shaffer).
2009:	ISCN 2009: The primary change in neoplasia (Chapter 11) was the introduction of either **idem** or **sl/sdl** in the nomenclature to describe clonal evolution. Nomenclature for *in situ* hybridization was further clarified and additional examples provided. The basic microarray nomenclature was revised and expanded to accommodate all platform types, with more examples provided. In addition, a nomenclature for multiplex ligation-dependent probe amplification (MLPA) was introduced.
2012:	Jean McGowan-Jordan was elected as the new Chair of the ISCN SC.
2013:	ISCN 2013: The primary changes to the new edition of ISCN included additional nomenclature examples, inclusion of some definitions such as chromothripsis and duplication, and the use of the genome build when describing microarray results. The ISCN SC deleted Section 14.4 on MLPA and introduced a new Chapter 15 for nomenclature that can be used for any region-specific assay (RSA) such as quantitative fluorescence polymerase chain reaction (QF-PCR), real-time polymerase chain reaction (PCR), and beadbased multiplex techniques in addition to MLPA.
2014:	Various approaches to describing chromosome abnormalities characterized by DNA sequencing were considered and discussed during a special joint session with members of the Human Genome Variation Society (HGVS) Sequence Variant Description Working Group.
2016:	The ISCN SC incorporated into ISCN 2016 a new chapter on sequence nomenclature and new examples for microarray and region-specific assays, including the requirement to incorporate the genome build in the HGVS standard format whenever nucleotide numbers are specified. Changes in the main text compared to the previous edition were marked in the margin, for the first time. The decision to modify the name of the ISCN nomenclature scheme to reflect changes in technology under its purview was made by the use of the term “Cytogenomic” replacing “Cytogenetic.”

2020:	ISCN 2020: Due to the increased use of technologies such as microarray and sequencing that orientated chromosomes by nucleotide number from pter to qter, the ISCN SC standardized this approach across all technologies, including banded chromosomes. Standardization in the positioning of sex chromosome abnormalities before those affecting autosomes for all technologies was also made. It was decided to adopt a nomenclature for inherited abnormalities that clarified whether the rearrangement is inherited intact or partially as a derivative. The ISCN SC identified the need for specific nomenclature for the analysis of polar bodies, and to improve the existing nomenclature based on sequencing technology. For the first time, ISCN 2020 was made available online, together with an ISCN Forum where the cytogenomic community could submit ISCN queries or make suggestions for improvement to the nomenclature. Following publication of ISCN 2020, Ros Hastings was nominated as the Chair of the ISCN SC.
2023:	A new nomenclature for genome mapping (OGM) was created and published (Moore et al., 2023).
2024:	The ISCN SC completed a major review of ISCN 2020 and eliminated some of the inconsistencies between the different technologies' nomenclature. Historic information not directly related to the nomenclature was shortened. The meiotic chromosome chapter, fiber fluorescence *in situ* hybridization (FISH) ISCN, reverse FISH ISCN, and unnecessary repetition have been removed for the ISCN 2024 edition. The chapters have been restructured so that the generic rules are now unified in Chapter 4. More complex ISCN examples were added to the microarray, sequencing, and neoplasia chapters. Nomenclature for targeted karyotype and microarrays, methylation-specific assays, as well as expansion and contraction repeats has been added to the RSA Chapter 10. Each chapter was revised by two members of the ISCN SC before a full review by the entire committee. The rules have been listed (a, b, c, etc.) and examples have been numbered (i, ii, iii, etc.). OGM nomenclature was also incorporated into ISCN 2024. Some of the ISCN examples do not represent observed data but are provided to demonstrate the nomenclature principles.

2 Normal Chromosomes

2.1 Introduction

Human chromosome nomenclature has evolved from meetings at international conferences (Denver 1960, London 1963, Chicago 1966, Paris 1971, Paris 1975, Stockholm 1977, Paris 1980, Memphis 1994, Vancouver 2004, Vancouver 2008, Seattle 2012, San Diego 2014, Gothenburg 2019 and Glasgow 2023). The present report, which summarizes the current nomenclature, incorporates and supersedes all previous ISCN recommendations.

2.2 Chromosome Number and Morphology

2.2.1 Non-Banding Techniques

In the construction of the karyogram[1] the autosomes are numbered from 1 to 22 in order of decreasing length (for historical reasons chromosome 21 is listed before chromosome 22, despite it being smaller). The sex chromosomes are referred to as X and Y.

When chromosomes are stained by methods that do not produce bands, they can be arranged into seven readily distinguishable groups, defined as A to G, based on descending order of size, and the ratio of the length of the short arm to the long arm with respect to the centromere (London Conference, 1963). Satellites are not always visible on all chromosomes in the D and G groups as the number and size of these structures are variable. The following parameters were used to describe non-banded chromosomes:

- The length of each chromosome, expressed as a percentage of the total length of a normal haploid set, *i.e.*, the sum of the lengths of the 22 autosomes and of the X chromosome;
- The arm ratio of the chromosomes, expressed as the length of the longer arm relative to the shorter arm; and
- The centromeric index, expressed as the ratio of the length of the shorter arm to the whole length of the chromosome. The latter two indices are, of course, related algebraically.

Group A (1–3)	Large metacentric chromosomes distinguished from each other by size and centromere position
Group B (4–5)	Large submetacentric chromosomes
Group C (6–12, X)	Medium-sized metacentric or submetacentric chromosomes. The X chromosome resembles the longer chromosomes in this group
Group D (13–15)	Medium-sized acrocentric chromosomes with satellites
Group E (16–18)	Relatively short metacentric or submetacentric chromosomes
Group F (19–20)	Short metacentric chromosomes
Group G (21–22, Y)	Short acrocentric chromosomes with satellites. The Y chromosome has no satellites

The definition of metacentric, submetacentric, and acrocentric traditionally relates to the ratio of the chromosome arms in unbanded preparations (Levan et al., 1964; Al-Aish, 1969).

[1] The terms *karyogram*, *karyotype*, and *idiogram* have often been used indiscriminately. The term *karyogram* should be applied to a systematized array of the chromosomes prepared either by drawing, digitized imaging, or by photography, with the extension in meaning that the chromosomes of a single cell can typify the chromosomes of an individual or even a species. The term *karyotype* should be used to describe the normal or abnormal, constitutional or acquired, chromosomal complement of an individual, tissue or cell line. We recommend that the term *idiogram* be reserved for the diagrammatic representation of a karyotype.

2.2.2 Banding Techniques

Numerous technical procedures have been reported that produce banding patterns on metaphase chromosomes. The chromosomes are visualized as consisting of a continuous series of light and dark bands, so that, by definition, there are no "interbands." Bands that stain darkly with one method may stain lightly with other methods. The methods first published for demonstrating bands along the chromosomes are:

- **Q-bands** (Fig. 1): Caspersson et al. (1972)
- **G-bands** (Fig. 2): Seabright (1971)
- **R-bands** (Fig. 3): Dutrillaux and Lejeune (1971)

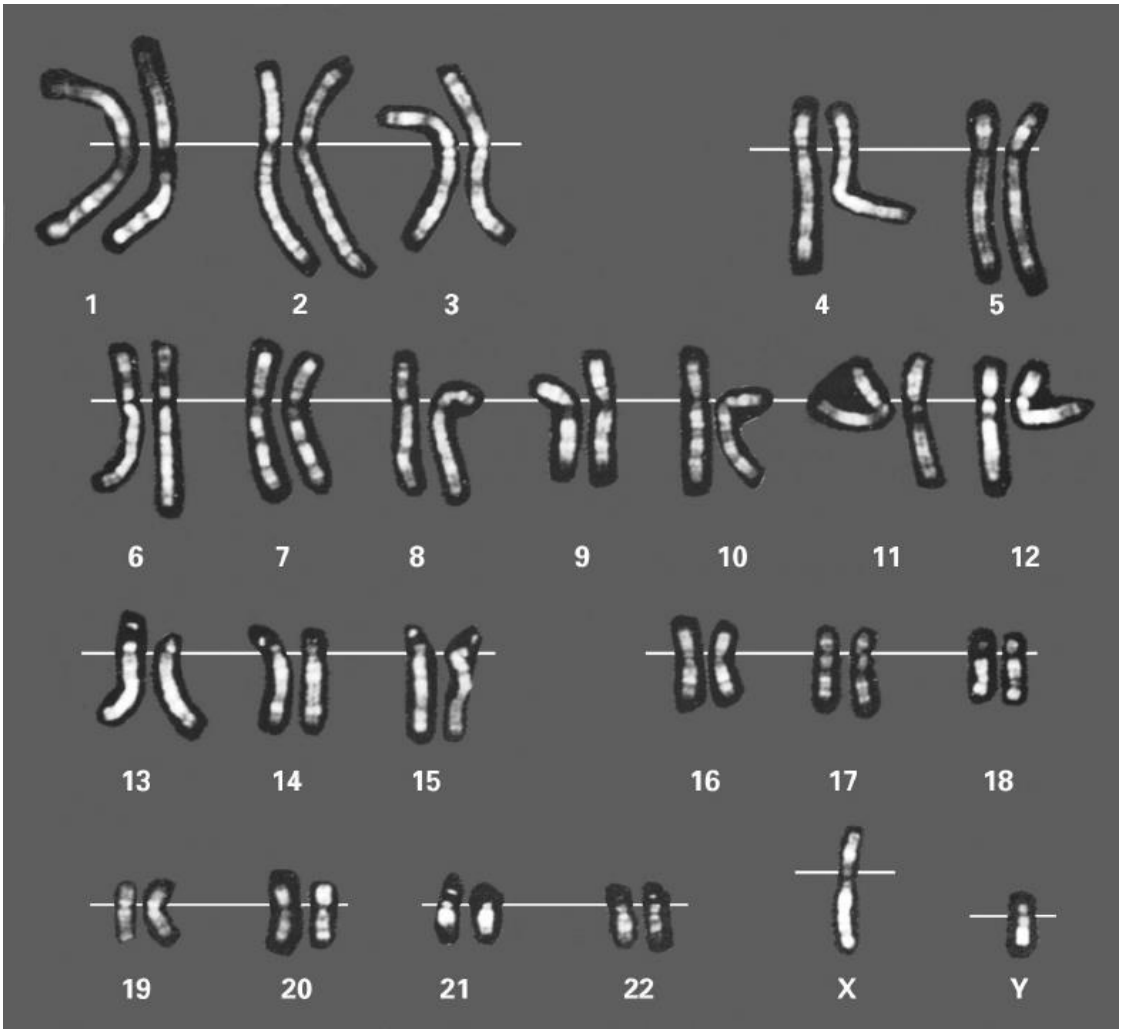


Fig. 1. *Q-banded human karyogram (courtesy of Dr. E. Magenis).*

The banding techniques fall into two principal groups:

1. Those resulting in bands distributed along the length of the whole chromosome, such as G-, Q-, and R-bands, including techniques that demonstrate patterns of DNA replication, and
2. Those that stain specific chromosomal structures and hence give rise to a restricted number of bands (Table 1). These include methods that reveal constitutive heterochromatin (**C-bands**) (Fig. 4), telomeric bands (**T-bands**), and nucleolus organizing regions (**NORs**). For the banding technique acronyms, refer to Table 2.
   The patterns obtained with the various C-banding methods do not permit identification of every chromosome in the somatic cell complement but can be used to identify specific chromosomes (Table 1). The C-bands on chromosomes 1, 9, 16, and Y are morphologically variable. The shortarm regions of the acrocentric chromosomes also demonstrate variations in size and staining intensity of the Q-, G-, R-, C-, T- bands and NOR staining. These variations are heritable benign features of the particular chromosome.

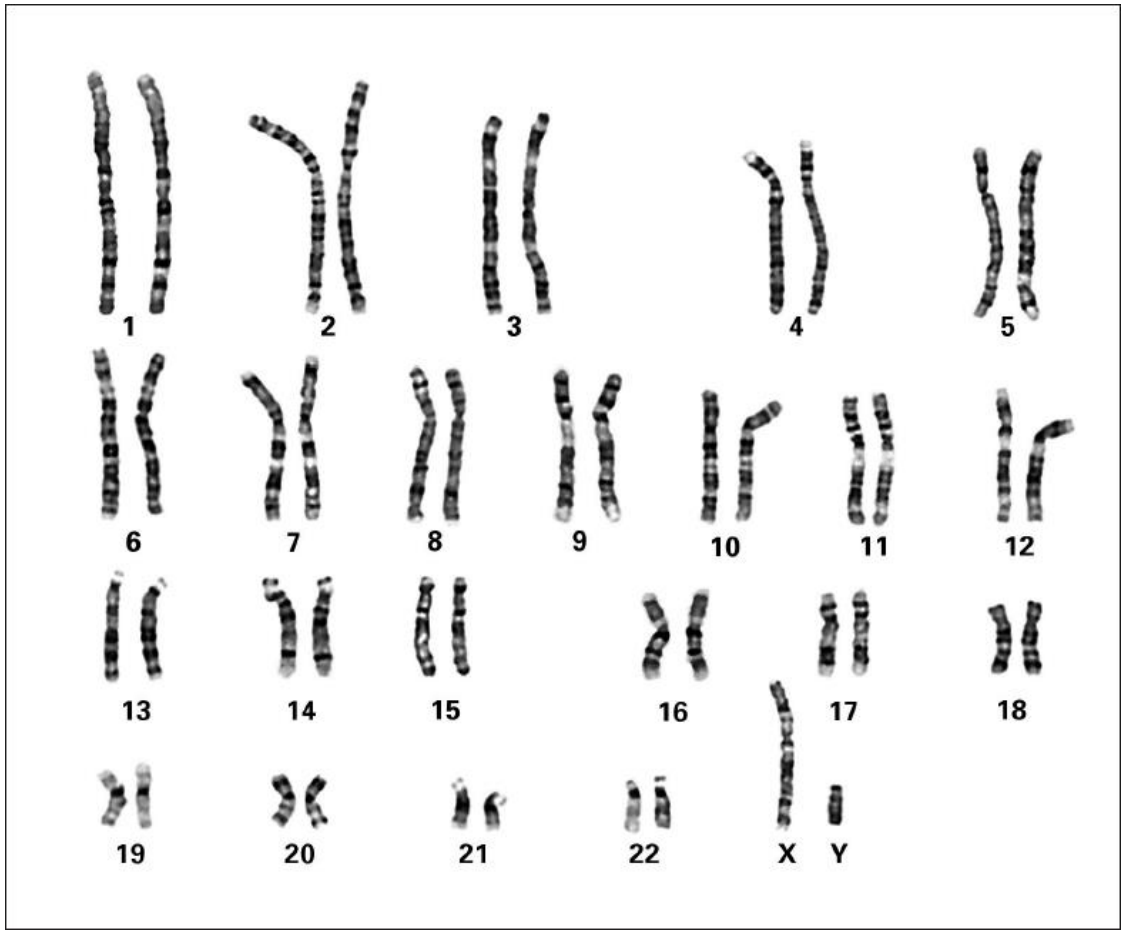


Fig. 2. *G-banded human karyogram (courtesy of N.L. Chia).*

2.2.3 X- and Y-Chromatin

Inactive X chromosomes, as well as the heterochromatic segment on the long arm of the Y chromosome, appear as distinctive structures in interphase nuclei, for which the terms **X-chromatin** (Barr body, sex chromatin, X-body) and **Y-chromatin** (Y-body), respectively, should be used.

2.3 Chromosome Band Nomenclature

2.3.1 Identification and Definition of Chromosome Bands, Landmarks and Regions

Bands are defined as parts of a chromosome that are clearly distinguishable from their adjacent segments by appearing darker or lighter with one or more banding techniques. The bands are large structures of differing size, that may include hundreds of genes.
Landmarks are defined as consistent and distinct morphologic features important in identifying the chromosome. Landmarks include the ends of the chromosome arms, the centromere, and certain bands. (See Table 12 in Appendix)
Regions are defined as an area of a chromosome lying between two adjacent landmarks.

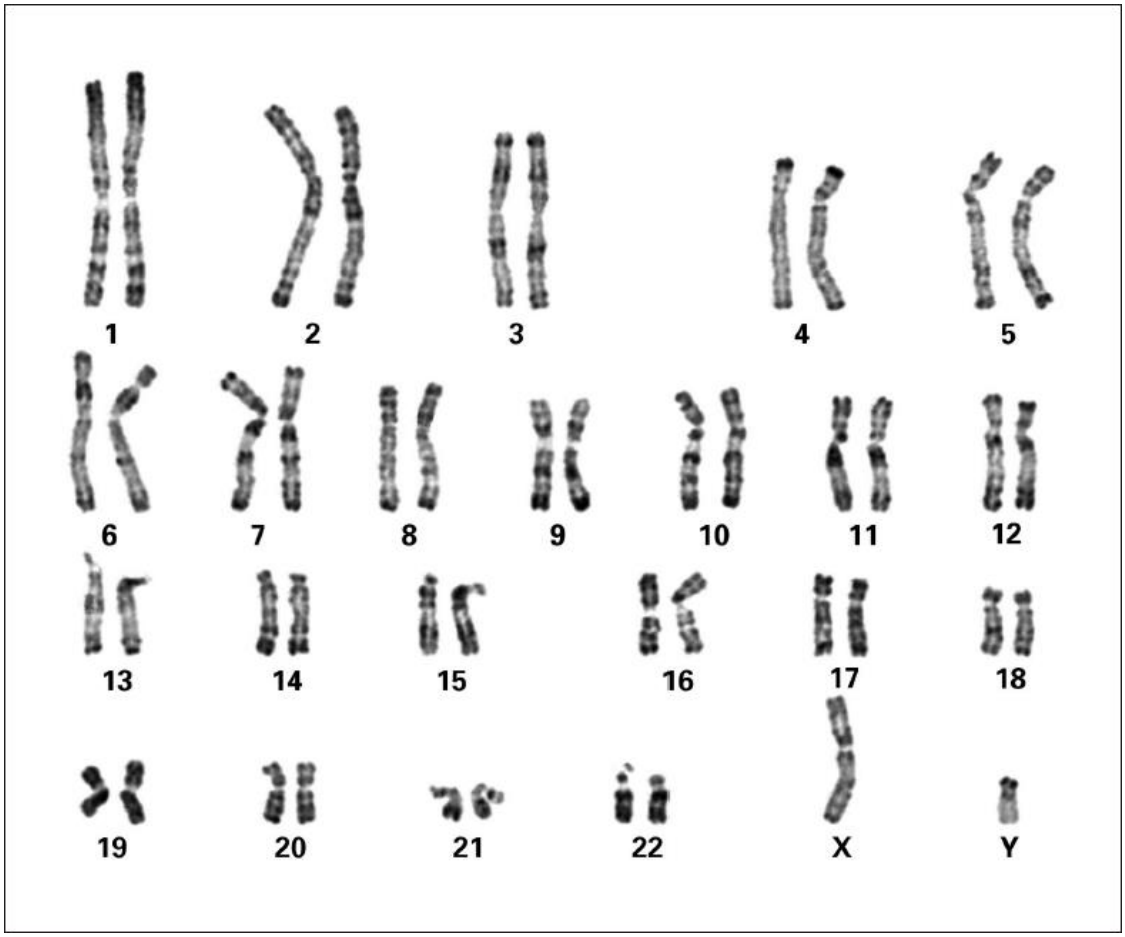


Fig. 3. *R-banded human karyogram (courtesy of Dr. M. Prieur).*

The bands are allocated to various regions along the chromosome arms, and the regions are delimited by specific landmarks. The bands and the regions are numbered consecutively from the centromere outward along each chromosome arm.

2.3.2 Designation of Regions, Bands and Subbands

a. The symbols **p** and **q** are used to designate, respectively, the **short** and **long** arms of each chromosome.
b. The **centromere** (**cen**) itself is designated 10; the part facing the short arm is p10, the part facing the long arm is q10 (not shown in the idiograms in the Appendix). The two regions adjacent to the centromere are labeled as 1 in each arm; the next, more distal regions as 2, and so on. The heterochromatic regions adjacent to the centromere carry band designations of 11, 11.1 or 11.11 depending on the level of resolution. A band used as a landmark is considered as belonging entirely to the region distal to the landmark and is accorded the band number of 1 in that region.
c. In designating a particular band, four items are required:

- The chromosome number

- The arm symbol
- The region number, and
- The band number within that region
- These items are given in order without spacing or punctuation. For example, 1p31 indicates chromosome 1, short arm, region 3, band 1.

d. Whenever an existing band is subdivided, a **decimal point** (**.**) is placed after the original band designation and is followed by the number assigned to each subband.

e. The subbands are numbered sequentially from the centromere outward. For example, if the original band 1p31 is subdivided into three equal or unequal subbands, the subbands are labeled 1p31.1, 1p31.2, and 1p31.3, subband 1p31.1 being proximal and 1p31.3 distal to the centromere.

f. If a subband is subdivided, additional digits, but no further punctuation, are used; *e.g.*, subband 1p31.1 might be further subdivided into 1p31.11, 1p31.12, *etc*. In principle a band can be subdivided into any number of new bands at higher resolution.

Table 1. Examples of heteromorphisms with various stains[a].

Technique	Chromosome									
	1	2	3	4	5	6	7	8	9	10
G[b]	q12 inv(p13q21)	inv(p11.2q13)	inv(p11.2q12)			p11.1			q12 inv(p12q13)	inv(p11.2q21.2)
C[c]	qh								qh	
G11	qh		cen		q11.1		p11.1		qh	q11.1
R or T	p36.3	q37		p16	p15.3 q35		p22	q24.3	q34	q26
NOR										
Q[d]			cen	cen						
DA-DAPI[e]	qh								qh	

Technique	Chromosome													
	11	12	13	14	15	16	17	18	19	20	21	22	X	Y
G[b]			p	p	p	q11.2 inv(p11.2q12.1)					p	p		inv(p11.2q11.2)
C[c]			p	p	p	qh	p11				p	p		q12
G11			p	p	p		p11.1			q11.1	p	p		q12
R or T	p15 q13	p13	p12 q34	p12 q32	p12	p13.3 q24	q25		p13.3 q13.1	q13	p12 q22	p12 q11.2 q13		
NOR			p12	p12	p12						p12	p12		
Q[d]			p11.2 p13 cen	p11.2 p13	p11.2 p13						p11.2 p13	p11.2 p13		
DA-DAPI[e]					p11.2	qh								q12

[a] cen = centromere, h = heterochromatin, inv = inversion, p = short arm, q = long arm.
[b] Only the most commonly seen heteromorphisms are listed.
[c] All centromeres show constitutive heterochromatin variation.
[d] Only the brilliant and intensity-variable Q-bands are listed.
[e] DA-DAPI = Distamycin A and 4′,6-diamidino-2-phenylindole.

2.4 High-Resolution Banding

The nomenclature for high-resolution preparations of prophase and prometaphase chromosomes described in ISCN 1981 is an extension of the nomenclature for the banding patterns for metaphase chromosomes established at the Paris Conference (1971) and in ISCN 1978.

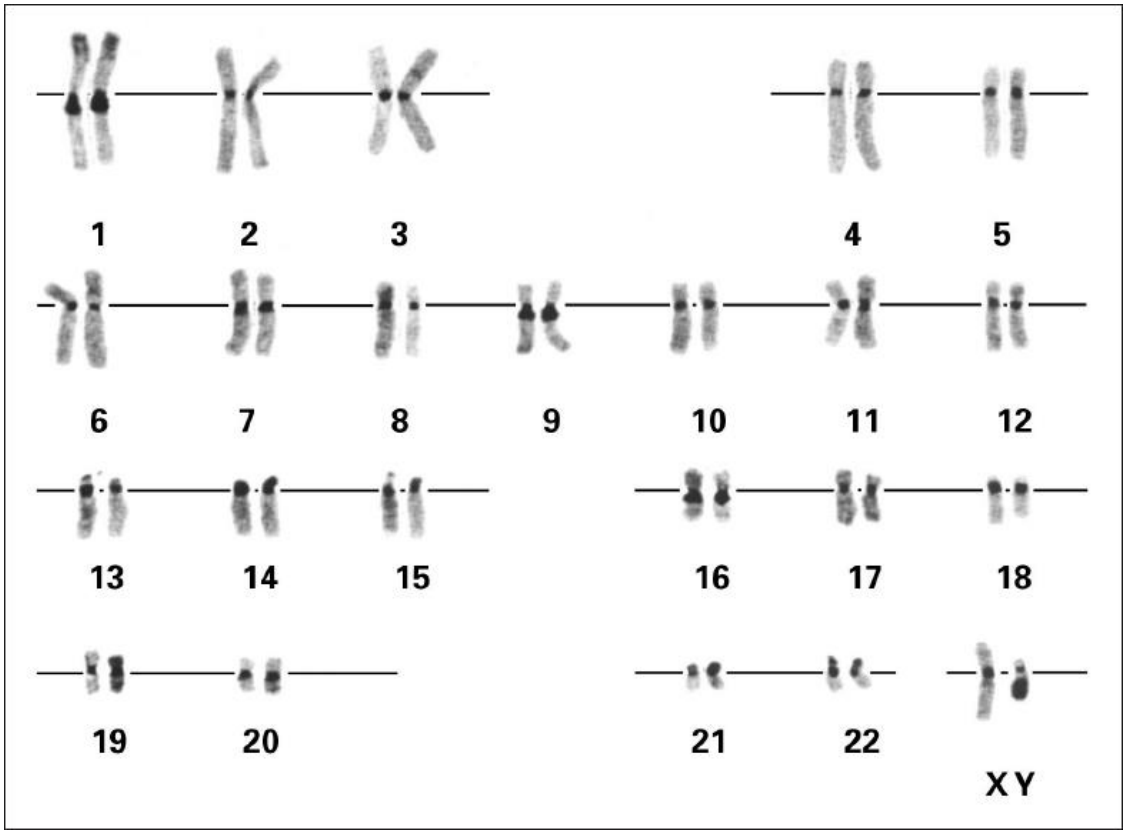


Fig. 4. *C-banded human karyogram. The chromosomes were not preidentified with other banding techniques (courtesy of Dr. N. Mandahl).*

Table 2. Examples of the banding technique acronyms. In the acronym, the first letter denotes the type of banding, the second letter the general technique and the third letter the stain.

Q	Q-bands
QF	Q-bands by fluorescence
QFQ	Q-bands by fluorescence using quinacrine
QFH	Q-bands by fluorescence using Hoechst 33258
G	G-bands
GT	G-bands by trypsin
GTG	G-bands by trypsin using Giemsa
GTL	G-bands by trypsin using Leishman
GTW	G-bands by trypsin using Wright
GAG	G-bands by acetic saline using Giemsa
C	C-bands
CB	C-bands by barium hydroxide
CBG	C-bands by barium hydroxide using Giemsa
R	R-bands
RF	R-bands by fluorescence
RFA	R-bands by fluorescence using acridine orange
RH	R-bands by heating
RHG	R-bands by heating using Giemsa
RB	R-bands by BrdU
RBG	R-bands by BrdU using Giemsa
RBA	R-bands by BrdU using acridine orange
DA-DAPI	DAPI-bands by Distamycin A and 4′,6-diamidino-2-phenylindole

High-resolution banding techniques can be applied to chromosomes in different stages of the cell cycle, *e.g.*, prophase, prometaphase, or interphase (by methods that induce premature chromosome condensation). Furthermore, the number of discernible bands depends not only on the state of condensation but also on the banding technique used. The level of resolution is determined by the number of bands seen in a haploid set (22 autosomes plus either X or Y). The standard idiograms provide schematic representations of chromosomes corresponding to approximately 300, 400, 550, 700 and 850 **bands per haploid set** (**bphs**) (see Chia, 2009; Francke, 1981, 1994 and Fig. 15 in the Appendix). These resolution labels are not intended to convey the actual number of bands, for example the 700 bphs is actually 759 bphs in males and 786 bphs in females (Chia, 2009; Thomas Liehr, personal communication). Although larger numbers of bands can be visualized, designating the idiograms as 550 to 850 bands is sufficient for practical purposes.

The idiograms were designed differently for the applications of ISCN and Genome Browsers resulting in some discrepancies. The 700-band level is the best fit to the GRCh38 idiograms. However, two loci are more detailed in GRCh38 than in the ISCN: 6p24 and 9q34.1. On the other hand, the ISCN 850-band level is more detailed than GRCh38 idiograms at five loci: 1q32, 2p21, 5q13.2, 6p22.3 and 6q21.

In G-banded preparations, new subbands appear to arise by subdivision of darkly stained Gbands on less extended chromosomes, while in R-staining preparations the dark R-bands appear to split. Therefore, in assigning subband numbers, arbitrary decisions were made for the purposes of nomenclature only and they should not be interpreted as statements about chromosome physiology. Examples of G- and R-banded chromosomes at successive stages of resolution are shown in the Appendix (see Fig. 16a, b). In addition, G- and R-banded metaphase chromosomes at approximately the 550-band level and their diagrammatic representation are illustrated in a detachable foldout on the inside of the back cover.

2.5 Variation in Heterochromatic Segments, Satellite Stalks and Satellites

Variation refers to the differences in size or staining of chromosomal segments in the population (see Wyandt and Tonk, 2008, and Table 1). The following sections outline a means to describe these variations; however, to avoid misinterpretation, these benign variants are **not** included in ISCN descriptions. Rather, they should be reserved for report text descriptions in which the variation may be useful to distinguish between two or more distinct cell lines or clones, *e.g.*, chimerism or transplant. **Note:** it is essential that a balanced or unbalanced rearrangement involving the satellites is excluded before assuming this is a benign variant (described in Sections 2.2.2, 2.5.1 and 2.5.2).

2.5.1 Variation in Length

Variation in length of **heterochromatic segments** (**h**), **stalks** (**stk**) or **satellites** (**s**) should be distinguished from increases or decreases in arm length as a result of other structural alterations by placing a **plus** (**+**) or **minus** (**–**) sign after the symbols **h**, **stk** or **s** following the appropriate chromosome and arm designation.

16qh+	Increase in length of the heterochromatin on the long arm of chromosome 16
Yqh–	Decrease in length of the heterochromatin on the long arm of the Y chromosome
21ps+	Increase in length of the satellite on the short arm of chromosome 21
22pstk+	Increase in length of the stalk on the short arm of chromosome 22
13cenh+pat	Increase in length of the centromeric heterochromatin of the chromosome 13 inherited from the father
1qh–,13cenh+,22ps+	Decrease in length of the heterochromatin on the long arm of chromosome 1, increase in length of the centromeric heterochromatin on chromosome 13, and large satellites on chromosome 22
15cenh+mat,15ps+pat	Increase in length of the centromeric heterochromatin on the chromosome 15 inherited from the mother and large satellites on the chromosome 15 inherited from the father
14cenh+pstk+ps+	Increase in length of the centromeric heterochromatin, the stalk, and the size of satellites on the same chromosome 14

2.5.2 Variation in Number and Position

The same nomenclature symbols as described above are used to describe variation in position of heterochromatic segments, satellite stalks, and satellites and should not be included in the ISCN but can be described in the text of the report.

22pvar	Variable presentation of the short arm of chromosome 22
17ps	Satellites on the short arm of chromosome 17
Yqs	Satellites on the long arm of the Y chromosome
9phqh	Heterochromatin in both the short and the long arms of chromosome 9
9ph	Heterochromatin only in the short arm of chromosome 9
1q41h	Heterochromatic segment in chromosome 1 at band 1q41

Duplicated chromosome structures are indicated by repeating the appropriate designation:

21pss	Double satellites on the short arm of chromosome 21
14pstkstk	Double stalks on the short arm of chromosome 14

Likewise, the common population inversion variants (see Table 1) are specified by their euchromatic breakpoints and should not be reported in the ISCN.

inv(9)(p12q13)	Pericentric inversion on chromosome 9
inv(2)(p11.2q13)	Pericentric inversion on chromosome 2
inv(Y)(p11.2q11.2)pat	Pericentric inversion on the Y chromosome inherited from the father

2.6 Euchromatic Variants

There are several euchromatic duplications and deletions involving both G-positive and G-negative bands that are phenotypically neutral (see Wyandt and Tonk, 2008; Behrend et al., 2023). The most common euchromatic variants occur at 4p16, 8p23.1, 9p12, 9q12, 9q13, 15q11.2 and 16p11.2, but these must be distinguished from the clinically significant (likely pathogenic/pathogenic) variants such as dup(8)(p23.1p23.1) and del(15)(q11.2q11.2). Only clinically significant (likely pathogenic/ pathogenic) euchromatic variants should be reported in the ISCN.

2.6.1 Copy Number Variants and Structural Variants

Benign and likely benign copy number variants (CNVs) and structural variants (SVs) are **NOT** reported in the ISCN. However, if the CNV or SV is suggestive of a structural rearrangement(s) at a chromosome level, then these should be reported, as there may be reproductive implications. Followup studies may be required.

Laboratories should report clinically significant variants in the ISCN according to the laboratory policy and current guidelines.

2.6.2 Fragile Sites

Fragile sites (**fra**) associated with a specific disease or phenotype are referred to in Section 5.5.7.

Fragile sites associated with specific chromosome bands can occur as normal variants with no phenotypic consequences. These fragile sites are inherited in a co-dominant Mendelian fashion and may result in chromosome abnormalities such as deletions, multiradial figures, and acentric fragments. While there may be several different types of fragile sites inducible by culturing cells in media containing different components, all of these will be covered by a single nomenclature.

fra(10)(q25.2)	A fragile site on chromosome 10 in 10q25.2
fra(10)(q22.1),fra(10)(q25.2)	Two fragile sites on chromosome 10
fra(10)(q22.1),fra(10)(q25.2)	Two fragile sites on different homologues
fra(10)(q25.2),fra(16)(q22.1)	Two fragile sites on different chromosomes

3 Symbols and Abbreviated Terms

All symbols and abbreviated terms used in the description of chromosomes and chromosome abnormalities are listed below. Section references are given within parentheses for terms that are defined in greater detail in the text.

ace	Acentric fragment (5.5.12, 12.2.1)
add	Additional material of unknown origin (5.1, 5.5.1)
amp	Denotes an amplified signal (4.5.3, 7.1.1, 7.4)
arr	Microarray (4.4.5, 4.5.3, 8, 8.1.1, 8.3)
arrow (→ or –>)[(1)]	From – to, in detailed system (5.4.2.2)
b	Break (12.1.1, 12.2.1)
bphs	Bands per haploid set (2.4, 5.4.1, 6.1)
brackets, angle (< >)	Surround the ploidy level (5.7, 6.3.7, 8.2.6)
brackets, square ([ ])	Surround number of cells, level of mosaicism or genome build (4.2.1, 4.4.5, 4.5.3, 5.1, 6.2, 6.3.1, 6.3.5, 7.1.1, 7.3.1, 8.1.1, 9.3, 10.2, 11.2.2, 11.2.3)
c	Constitutional anomaly (4.2.1, 5.1, 6.4)
caret (^)	Denotes 'or' in HGVS nomenclature (11.2.3)
cen	Centromere (2.3.2, 5.4.2.2)
cha	Chromoanasynthesis (8.2.7.1, 8.2.7.1.2, 9.4.2.7.1, 9.4.2.7.1.2)
chi	Chimera (4.5.2, 4.5.3, 5.1)
chr	Chromosome (12.2.1)
chrb	Chromosome break (12.2.1)
chre	Chromosome exchange (12.2.1)
chrg	Chromosome gap (12.2.1, 12.3)
cht	Chromatid (8.3, 12.1.1, 12.1.2)
chtb	Chromatid break (12.1.1, 12.3)
chte	Chromatid exchange (12.1.1, 12.3)
chtg	Chromatid gap (12.1.1, 12.3)
colon, single (:)	Break, in detailed system (5.4.2.2, 5.5.2, 5.5.6)
colon, double (::)	Break and reunion, in detailed system and for fusion genes (4.4.6.1, 5.4.2.2, 7.1.1, 9.3, 10.2.2, 11.2.3.1, 11.4.2.4)
comma (,)	Separates chromosome numbers, sex chromosomes, and chromosome abnormalities (4.2.1, 4.3, 4.4.5, 5.1, 5.4.2.2, 5.4.3.1, 5.4.3.2, 6.2, 6.3.6, 7.3.1, 8.1.1, 9.3);

	Separates non-tandem duplication (7.2.1) Separates probe designations (7.2.1, 7.3.1); Separates thousand and million in nucleotide position in the short system (4.4.5)
con	Connected signals (7.3.1, 7.3.4, 7.3.4.3)
cp	Composite karyotype (6.2, 6.3.5)
cpx	Chromoplexy (8.2.7.1, 9.4.2.7.1, 9.4.2.7.1.3)
cth	Chromothripsis (8.2.7.1, 8.2.7.1.1, 9.4.2.7.1, 9.4.2.7.1.1)
cx	Complex rearrangements – used in neoplasia, microarray or sequencing (8.2.7, 9.4.2.7, 9.4.2.7.1)
decimal point (.)	Denotes subbands (2.3.2)
del	Deletion (5.1, 5.5.2, 9.3, 9.4.2.2, 11.2.3.2, 11.4.2.1, 12.1.2)
delins	Sequence change with nucleotides of the reference sequence replaced by other nucleotides (11.2.3.2)
der	Derivative chromosome (5.1, 5.4.2.2, 5.4.3, 5.4.3.1, 5.5.1, 5.5.2, 5.5.3, 5.5.5, 5.5.11, 5.5.12, 5.5.13, 5.5.16.2, 5.5.18.2, 5.5.18.3, 9.3, 11.4.2.3, 12.3)
dic	Dicentric (5.4.1, 5.5.4, 5.5.16.2, 5.5.18.3, 12.3)
dim	Diminished (7.2.5)
dinh	Derived from chromosome abnormality of parental origin (4.2.1, 4.6, 5.1, 8.2.3)
dmat	Derived from chromosome abnormality of maternal origin (4.2.1, 4.6, 5.1, 6.4, 8.2.3, 9.4.2.6)
dmin	Double minute (4.3, 5.5.3, 5.5.12, 12.2.1)
dn	Designates a chromosome abnormality that has not been inherited (*de novo*) (4.2.1, 8.2.3, 9.4.2.6)
dpat	Derived from chromosome abnormality of paternal origin (4.2.1, 4.6, 5.1, 6.4, 8.2.3, 9.4.2.6)
dup	Duplication (5.1, 5.4.3.2, 5.5.5, 9.3, 9.4.2.3, 11.2.3.2, 11.4.2.2)
e	Exchange (12.1.1, 12.1.2, 12.2.1)
end	Endoreduplication (5.7)
enh	Enhanced (7.2.5)
equal (=)	Denotes a normal reference sequence in HGVS (11.2.3)
fis	Fission, at the centromere (5.5.6)
fra	Fragile site (2.6.2, 5.5.7)
g	Gap (12.1.1, 12.2.1)
g.	Genome with reference to the genomic sequence (11.2.3)
gom	Gain of methylation (10.2.3)
GRCh	Genome Reference Consortium human; human genome build or assembly (4.4.5, 8.1.1, 9.3, 9.4, 11.2.3)
greater than (>)	Greater than (5.5.12, 7.4)
h	Heterochromatin, constitutive (2.5.1)

hmz	Homozygous, homozygosity; used when one or two copies of a genome are detected, but previous, known heterozygosity has been reduced to homozygosity through a variety of mechanisms, *e.g.*, loss of heterozygosity (LOH) (8.2.6, 8.2.7)
hsr	Homogeneously staining region (5.5.3, 5.5.8)
htz	Heterozygous, heterozygosity (8.2.6)
hyphen (-)	Hyphen, designation with a chromosome band at low resolution (5.4.1)
i	Isochromosome (5.5.11)
idem	Denotes the stemline karyotype in a subclone (6.2, 6.3.4)
ider	Isoderivative chromosome (5.5.3)
idic	Isodicentric chromosome (5.5.4, 5.5.11)
inc	Incomplete karyotype (5.1, 6.2, 6.3.6,)
inh	Inherited (4.2.1, 4.6, 5.1, 8.2.3, 9.4.2.6)
ins	Insertion (5.4.1, 5.5.1, 5.5.5, 5.5.9, 5.5.9.1, 5.5.9.2, 9.3, 9.4.2.4); insertion of nucleotides (11.2.3.2, 11.4.2.5)
inv	Inversion (5.4.3.2, 5.5.10, 9.3, 12.1.2); inverted in orientation relative to the reference sequence (11.2.3.2, 11.4.2.6)
ish	*In situ* hybridization; when used without a prefix applies to metaphase or prometaphase chromosomes of dividing cells (7.1.1, 7.2, 7.2.1)
lom	Loss of methylation (10.2.3)
mar	Marker chromosome (4.3, 5.4.3.1, 5.5.3, 5.5.12, 12.2.2, 12.3)
mat	Maternal origin (4.2.1, 4.6, 5.1, 6.4, 8.2.3, 9.4.2.6)
met	Normal methylation pattern (10.2.3, 10.7)
min	Minute acentric fragment (12.2.1, 12.3)
minus (–) sign	Loss (5.1, 5.3.1.2); Decrease in length (2.5.1, 5.1); Locus absent from a specific chromosome (7.2.1, 9.3)
mos	Mosaic (4.5.2, 4.5.3, 5.1)
mr	Multiradial (12.1.1)
multiplication (×) sign	Number of copies or signals (4.4.3, 7.2.1, 7.3.1, 10.2.1, 10.2.3); Multiple copies of rearranged chromosomes (5.1, 5.5.12, 5.6); Aberrant polyploidy clones in neoplasia (6.3.4, 6.3.7); Multiple copies of a chromosome or chromosomal region (4.4.3, 5.5.12, 5.6, 8.1.1)
neo	Neocentromere (5.5.13)
nuc	Nuclear or interphase (7.1.1, 7.3.1)
nuc	ish Interphase fluorescent *in situ* hybridization (7.1.1, 7.3, 7.3.1)
ogm	Genome Mapping (4.4.5, 4.5.3, 9)
or	Alternative interpretation (4.2.1, 5.1, 5.4.1)
p	Short arm of chromosome (2.3.2)
parentheses ( )	Surround structurally altered chromosomes and breakpoints (4.4.3, 5.4.1, 5.4.2.1, 5.4.2.2, 5.4.3.1, 5.5.3, 5.5.16); Surround chromosome numbers, X, and Y, loci, probes, gene names in normal

	and abnormal results (7, 8, 9, 10); Surround coordinates (or nucleotide positions) in abnormal result (8, 9, 10, 11)
pat	Paternal origin (4.2.1, 4.6, 5.1, 6.4, 8.2.3, 9.4.2.6)
PB1	1st polar body (8.3, 8.3.2, 8.3.4)
PB2	2nd polar body (8.3, 8.3.3, 8.3.5)
pcc	Premature chromosome condensation (12.2.1)
pcd	Premature centromere division (12.2.1)
pcp	Partial chromosome paint (7.2.8)
period (.)	Separates various techniques (4.6, 7.1.1, 9.4.2.5, 9.4.2.8, 11.2.2, 11.2.3)
Ph	Philadelphia chromosome (5.5.3)
pipe (|)	Denotes a modification in the DNA sequence (*e.g.*, a state of change such as methylation) (10.2.3)
plus sign, single (+)	Additional normal or abnormal chromosomes (2.5.1, 5.1, 5.3.1.2, 5.5.12, 5.5.16.2, 5.5.18.3); Denotes an increase in length (2.5.1, 5.1); Denotes a locus present on a specific chromosome (7.2.1, 9.3)
plus sign, double (++)	Two tandem hybridization signals or hybridization regions on a specific chromosome (7.2.1)
ps	Satellited short arm of chromosome (2.5.1, 2.5.2)
psu	Pseudo- (5.5.4)
pter	Terminal end of the short arm of a chromosome (5.4.2.2)
pvz	Pulverization (12.2.1)
q	Long arm of chromosome (2.3.2)
qdp	Quadruplication (5.5.14)
qr	Quadriradial (12.1.1, 12.3)
qs	Satellited long arm of chromosome (2.5.2)
qter	Terminal end of the long arm of a chromosome (5.4.2.2)
question mark (?)	Questionable identification of a chromosome or chromosome structure (4.2.1, 4.5.3, 5.1, 5.4.1, 5.5.1, 5.5.3, 9.4.2.4, 11.2.3.1); Questionable identification of copy number or level of mosaicism (4.5.3, 8.2.5, 9.4.2.7.1.2) Unknown nucleotide position (11.2.3.1, 11.4.2.1)
r	Ring chromosome; a defined structure with chromosome ends fused (4.3, 5.5.3, 5.5.12, 5.5.16, 5.5.16.2, 11.4.2.4, 12.3)
rec	Recombinant chromosome (5.4.3, 5.4.3.2, 5.5.15) rob Robertsonian translocation (5.5.18.3)
rsa	Region-specific assay (4.4.5, 4.5.3, 10, 10.1, 10.2)
rsa-ms	Methylation region-specific assay (10.2.3, 10.7)
s	Satellite (2.5.1, 2.5.2)
sce	Sister chromatid exchange (12.1.1)
sdl	Sideline (6.2, 6.3.4)

semicolon (;)	Separates altered chromosomes and breakpoints in structural rearrangements involving more than one chromosome (4.2.1, 5.4.1, 5.5.3, 9.3, 9.4.2.5); Separates probes on different derivative chromosomes (7.2.1)
sep	Separated signals (7.3.1, 7.3.4, 7.3.4.3)
seq	Sequencing (4.4.5, 4.5.3, 11, 11.2.2)
sl	Stemline (6.2, 6.3.4)
slant line, single (/)	Separates cell lines, clones or contiguous probes (4.5.3, 5.1, 6.2, 7.1.1, 11.2.3)
slant line, double (//)	Separates recipient and donor cell lines (4.5.3, 6.2, 7.6)
sseq	Shallow next-generation sequencing (8.1.1, 8.3, 11.2.2)
stk	Satellite stalk (2.5.1, 2.5.2)
subtel	Subtelomeric region (7.2.6)
sup	Additional (supernumerary) sequence not attached to other chromosomal material (11.2.3.2)
t	Translocation (5.5.18, 9.3, 9.4.2.5, 11.4.2.7)
tas	Telomeric association (5.5.17)
ter	Terminal (end of chromosome) or telomere (5.4.2.2, 11.2.3.1)
tilde (~)	Denotes intervals and boundaries of a chromosome segment or number of chromosomes, fragments, or markers or nucleotides (4.2.1, 4.5.3, 5.1, 5.4.1, 9.3, 9.4.2.4, 9.4.2.5) Denotes a range of number of copies of a chromosomal region when the exact number cannot be determined (4.2.1, 4.5.3, 8.1.1)
tr	Triradial (12.1.1, 12.3)
trc	Tricentric chromosome (5.5.4, 5.5.16.2, 5.5.19)
trp	Triplication (5.5.20)
U	Undisclosed normal sex complement (5.2)
underlining	Used to distinguish homologous chromosomes (4.4.2, 5.1, 5.5.3, 5.5.18.1, 7.2.2)
underscore (_)	Used to indicate range of nucleotide positions (4.4.5, 8.1.1, 9.3, 11.2.3.1) Chromosomal region between bands in ogm (instead of an arrow) (9.4.2.3)
umat	Maternal uniparental disomy (8.2.3, 8.2.6)
upat	Paternal uniparental disomy (8.2.3, 8.2.6)
VAF	Variant allele frequency (4.5.3, 9, 9.3)
var	Variant or variable region (2.5.2, 11.2.3)
wcp	Whole chromosome paint (7.2.1, 7.2.7, 7.2.8)

(1) Note: In ogm ISCN an underscore is used in the detailed system (karyotype format).

4 General Rules

4.1 Introduction

a. ISCN provides a unified nomenclature to describe the chromosome complement and aberrations. This nomenclature is improved regularly for existing technologies and expanded as new technological approaches are developed. Over time, redundancies and inconsistencies between chapters have appeared, whilst rules have been dispersed throughout different chapters in the ISCN. ISCN 2024 provides an overview of the general rules applying to all technologies in Chapter 4. Terms and recommendations related to specific technologies and applications are described in detail in the relevant chapters.
b. Some of the examples in this and subsequent chapters do not represent observed abnormalities but are provided to demonstrate the nomenclature principles.

4.2 General Principles

a. The current version of ISCN must always be used. As ISCN guidelines may differ between versions, it is recommended that either the interpretive text or the test details of the report include a statement on the version of ISCN used to write the nomenclature description. This is particularly relevant for follow-up samples.
b. A summary of the general principles applicable to cytogenomic reporting of the various methodologies is given in Table 3.

Table 3. The following general principles are applicable to multiple chapters and techniques as indicated.

	Karyotype	Neoplasia	ish	arr	ogm	rsa	seq
Different band resolutions may be used within the same karyotype string	+	+					
Sex chromosome abnormalities listed first (X before Y) followed by the autosomes in chromosomal order	+	+	+	+	+	+	+
For each chromosome, numerical abnormalities are listed before structural changes	+	+	+	+	+	+	+
Numerical abnormalities are listed in autosomal order and for each autosome gains are listed before losses	+	+	+	+	+	+	+
Breakpoint band designations from pter to qter of the rearranged chromosome	+	+	+	+	+	+	+
For duplication or deletion within the same chromosome band, the band containing the breakpoint is repeated for karyotype format ISCN	+	+	+		+		+
For duplication or deletion within the same chromosome band, the band containing the breakpoint is given only once for microarray format ISCN				+	+	+	+
Multiple structural changes presented in alphabetical order	+	+	+		+		+
For each homologous chromosome, constitutional abnormalities are listed before the same acquired anomaly	+	+	+			+	
Largest cell line/unrelated clone is listed first; normal cells are always listed last	+	+	+				
Number of cells in each cell line or DNA proportion shown in square brackets for mosaic	+		+	+	+	+	
Related clones listed in order of increasing complexity, irrespective of size		+					
Number of cells shown in square brackets for neoplasia (both single or multiple clones)		+	+				
Express abnormalities relative to the appropriate ploidy level	+	+	+	+	+	+	+
Multiplication sign for number of signals or copies outside the parenthesis when identical for all probes/loci			+	+	+	+	
Genome build required when nucleotides designated				+	+	+	+
Nucleotide numbers given either with or without commas to indicate thousands and millions for structural anomalies				+	+	+	+
Nucleotide span separated by an underscore				+	+	+	+
Inheritance indicated only once when several techniques are used	+	+	+	+	+	+	+
Separate results of different techniques with periods (.)	+	+	+	+	+	+	+

+, applicable.

c. The same general rules for designating chromosome aberrations are followed in the description of constitutional and neoplastic chromosome aberrations.
d. Abnormal findings and/or clinically significant results, based upon the laboratory's reporting protocols, must be included in the ISCN. Additionally, normal sex chromosomes may be reported for the purpose of:

- clarity of the sex complement is required (see Sections 8.2.2, 8.2.3, 11.4.2.1);
- chimerism (Sections 4.5.3, 8.2.6);
- when part of a targeted assay (see Chapter 10).

e. Abnormal results are reported using two different formats, karyotype format and microarray format (see Section 4.7). The karyotype format is described using either the abbreviated, short, and detailed systems, while the microarray format is expressed using either the abbreviated, short, and extended systems (see Section 4.7).

4.2.1 Chromosome Abnormality Description Rules

a. The number of chromosomes is specified first, followed by a **comma** (**,**), the sex chromosome complement, followed by a comma and then the chromosome abnormality. There are no spaces before or after a comma (see Section 4.4.1).
b. If a sex chromosome has a structural abnormality, the normal chromosome, if present, is listed first.
c. The total number of analyzed metaphases is **not** specified in constitutional samples, unless there is evidence of clinically significant mosaicism. The number of metaphases must always be given in the karyotype of neoplastic samples, even when the result is normal, or the abnormality is present in all metaphases.
d. Absolute cell numbers are given in **square brackets** (**[ ]**).
e. For neoplastic samples, constitutional chromosome anomalies are indicated by the letter **c** immediately after the constitutional abnormality designation (see also Sections 5.1 and 6.4). When associated with the sex chromosomes, the letter **c** refers to the whole sex complement (see Section 5.3.1.2).

i. 48,XX,+8,+21c[20]Karyotype of a neoplastic sample with acquired trisomy 8 in a female individual with constitutional trisomy 21.
ii. 46,XXYc,–X[10]/47,XXYc[2]Karyotype of a neoplastic sample with acquired loss of one X chromosome in ten metaphases in an individual with Klinefelter syndrome.

f. For clarity, rearrangements are written with breakpoints the first time they are listed in the ISCN description. It is not necessary to repeat the breakpoints subsequently *e.g.*,

- *constitutional:* 47,XXX,t(11;22)(q23;q11.2)[10]/46,XX,t(11;22)[10]
  neoplasia: 46,XX,t(9;22)(q34;q11.2)[10]/47,XX,t(9;22),+der(22)[10]

g. **Inherited (inh)** aberrations for which the parental origin has not been established or disclosed may be indicated as 46,XX,t(5;6)(q34;q23)inh

- When it is known from which parent the aberration is inherited, the abbreviation for **maternal** (**mat**) or **paternal** (**pat**) is used immediately following the designation of the abnormality, *e.g.*, 46,XX,t(5;6)(q34;q23)mat,inv(14)(q12q31)pat
- If only part of an aberration (*e.g.*, one derivative chromosome from a parental balanced translocation) has been inherited, the abbreviation **dmat**, **dpat** or **dinh** is used to distinguish it from the complement in the parent, *e.g.*, 46,XX,der(5)t(5;6)(q34;q23)dmat,inv(14)(q12q31)pat

h. If it is known that the parents' chromosomes are normal with respect to the abnormality, the abnormality may be designated ***de novo*** (**dn**), *e.g.*, 46,XY,t(5;6)(q34;q23)mat,inv(14)(q12q31)dn
i. Alternative interpretations of an aberration are provided with the term **or**. **Note**: there is a space before and after the term **or** (see Section 4.4.1).

. 46,XX,add(19)(p13.3 or q13.3)A female karyotype shows additional material of unknown origin attached to either 19p13.3 or 19q13.3 (see Section 5.5.1).

i. 46,Y,del(X)(q22) or i(X)(p10)A male karyotype shows a deletion of the long arm of the X chromosome with a breakpoint in Xq22 or an isochromosome of the short arm of the X chromosome. **Note:** the different structural rearrangements give rise to karyotypically similar abnormal X chromosomes.
ii. 46,XX,t(12;14)(q15;q24) or t(12;14)(q13;q22)The two alternative interpretations of the t(12;14) give rise to karyotypically similar chromosomes in this female

karyotype. **Note:** the breakpoints are in either of these two ISCN descriptions, which is a different situation to t(12;14)(q13~15;q22~24), where the breakpoint localizations are less certain and a variety of breakpoint combinations are possible (see example iv in j below).

j. When there is uncertainty over the breakpoint localization or chromosome number, a **tilde** (**~**) is used to denote intervals and to express uncertainty about breakpoint localizations and/or the range of chromosome numbers.

. 45~48,XX,+8[cp10]The chromosome number is within the interval 45 to 48 in this female karyotype of a neoplastic sample where the only clonal abnormality identified is trisomy 8.

i. 46,XX,del(1)(q21~24)A female karyotype shows an apparently terminal deletion of the long arm of chromosome 1 and a breakpoint within the segment 1q21 to 1q24, *i.e.,* the breakpoint may be in band 1q21, 1q22, 1q23 or 1q24.

ii. 46,XY,dup(1)(p34~32p22)A male karyotype shows duplication in the short arm of chromosome 1; the distal breakpoint is in 1p34, 1p33 or 1p32 and the proximal breakpoint is in band 1p22.

iii. 46,XX,t(3;12)(q27~29;q13~15)A female karyotype where both breakpoints in this translocation are uncertain; in chromosome 3 the breakpoint may be in bands 3q27, 3q28 or 3q29 and in chromosome 12 in bands 12q13, 12q14 or 12q15.

iv. ogm[GRCh38] t(6;7)(q21;q32.1)(108,976,886~108,982,237;128,310,022~128,316,239)Genome mapping identified a reciprocal translocation between chromosomes 6 and 7. The chromosomes and breakpoints are separated by a **semicolon** (**;**) as are the nucleotides. **Note:** this nomenclature uses the short system (karyotype format) (see Section 4.7) and the **tilde** (**~**) demonstrates the region of uncertainty in the breakpoints at the nucleotide level.

k. A **question mark** (**?**) indicates uncertain identification of a chromosome or chromosome structure. It is placed either before the uncertain item, or it may replace a chromosome, region, band or subband designation.

. 45,XX,–?21A female karyotype with a missing chromosome, likely to be chromosome 21.

i. 47,XX,+?8A female karyotype with an additional chromosome, likely to be chromosome 8.

ii. 46,XY,?del(1)(p36.1)A male karyotype where the deletion is uncertain, but if present it is a terminal deletion from chromosome 1, band p36.1 to 1pter.

iii. 46,XX,del(19)(?q)A female karyotype where there is a deletion, likely to be in the long arm of chromosome 19.

iv. 46,XX,del(20)(q?)A female karyotype with a deletion in the long arm of chromosome 20, but neither the region nor the band can be identified.

v. 46,XX,del(1)(q?2)A female karyotype with a deletion in the long arm of chromosome 1, probably in region 1q2.

vi. 46,XY,del(1)(q?23)A male karyotype where it is uncertain whether the breakpoint in the long arm of chromosome 1 is in region 1q2. If so, the breakpoint is in band 1q23.

vii. 46,XX,del(1)(q2?)A female karyotype with a deletion in the long arm of chromosome 1 in region 1q2, and it is not possible to determine the band within that region.

viii. 46,XY,del(1)(q2?3)A male karyotype with a deletion in the long arm of chromosome 1 in region 1q2, probably in band 1q23.

ix. 46,XY,t(5;6)(q31.1;q22.?1)A male karyotype with a translocation between chromosomes 5 and 6. The breakpoint in chromosome 5 is within 5q31.1 and the breakpoint in the long arm of chromosome 6 is in the region of 6q22 and probably in subband 6q22.1 but this is uncertain.

x. 46,XX,der(1)?t(1;3)(p22;q13)A female karyotype where the der(1) has probably resulted from a t(1;3) with proposed breakpoints in bands 1p22 and 3q13.

xi. 46,XY,der(5)ins(5;?)(q32;?)A male karyotype with a derivative chromosome from an insertion of unidentified chromosomal material into the long arm of chromosome 5 at band 5q32.

xii. 46,XY,–5,+der(?)t(?;5)(?;q13)A male karyotype with loss of a chromosome 5 and gain of a derivative chromosome of an unknown origin that is composed partly of chromosome 5 long arm material. **Note:** the unknown chromosome (**?**) contains the centromere and so is listed before chromosome 5 in the description of the translocation.

xiii. 46,XX.ish X(DXZ1×2),der(7)ins(7;Y)(q3?;p11.?2p11.?2)(SRY+)*In situ* hybridization using probes for the X chromosome pericentromeric alphoid repeat sequence and the *SRY* gene shows a signal for the SRY probe in region 7q3 of one chromosome 7, and the band cannot be determined. The breakpoints of the inserted Y chromosome segment are uncertain but are possibly in Yp11.2, which contains the *SRY* gene. The DXZ1 signal pattern is given as this is an XX male.

4.3 Order of Cytogenomic Abnormalities

a. For karyotype, the normal sex chromosomes are listed before any abnormality. When there is an abnormal X chromosome in a male individual, the normal Y chromosome is listed first. When clarity of the sex complement is required, the normal Y chromosome may be listed in microarray and genome mapping, and it appears in the ISCN description before the abnormal X chromosome (see example ii).

i. 46,Y,t(X;10)(q27;p13)A male constitutional karyotype. The normal Y chromosome is listed before the translocation involving the X chromosome.

ii. ogm[GRCh38]
(Y)×1,Xq25(126023321×1,126228413_126535347×0,126556900×1)matGenome mapping shows with an interstitial deletion of Xq25 involving loss of nucleotides between 126,228,413 and 126,535,347 of maternal origin in a male. The normal Y chromosome is described so the sex chromosome constitution is clear, *i.e.,* the individual is male and not a female with a single X chromosome. **Note**: to avoid confusion, commas to separate millions and thousands are not used in the nucleotides in the extended system (microarray format) (see Section 4.7).

b. Sex chromosome aberrations are specified first. (X chromosome abnormalities are presented before those involving the Y chromosome), followed by abnormalities of the autosomes listed in numerical order irrespective of the aberration type. Each abnormality is separated by a **comma** (**,**).

i. 50,X,+X,–Y,+10,+14,+17,+21[5]Karyotype of a neoplastic sample in a male. The numerical abnormality of the X chromosome is listed before that of the Y chromosome.

ii. 47,X,t(X;13)(q27;q12),inv(10)(p13q22),+21A female karyotype shows a reciprocal translocation between the X chromosome at Xq27 and chromosome 13 at 13q12, an inversion of chromosome 10 between 10p13 and 10q22 and trisomy 21. The sex chromosome abnormality is presented first, followed by the autosomal abnormalities in chromosome number order, irrespective of whether the aberrations are numerical or structural.

iii. 47,Y,t(X;13)(q27;q12),inv(10)(p13q22),+21The same karyotype as in the previous example in a male. The normal Y chromosome is listed before the abnormal X chromosome.

iv. 46,t(X;18)(p11.1;q11.2),t(Y;1)(q11.2;p13)[10]Karyotype of a neoplastic sample in a male. The abnormality involving the X chromosome is listed before that of the Y chromosome.

v. 48,X,t(Y;12)(q11.21;p12),del(6)(q11),+8,t(9;22)(q34;q11.2),+17,–21,+22[10]Karyotype of a neoplastic sample in a male. The translocation involving the Y chromosome is presented first, followed by all autosomal abnormalities in consecutive chromosome number order.

vi. arr[GRCh38] Xp22.33(23,934_1,604,049)×3,9p24.3p23(56,537_9,401,480)×1Microarray shows an apparently terminal gain of the X chromosome involving Xp22.3 and an interstitial loss of chromosome 9 at 9p24.3 to 9p23. The abnormalities are given in chromosome order.

c. For each homologous chromosome, numerical abnormalities are listed before structural changes and constitutional abnormalities are listed before the same acquired abnormality.

i. 46,XY,+13,der(13;14)(q10;q10)A male karyotype in which the abnormalities are presented in chromosome order (13 before 14) with the chromosome 13 numerical abnormality before the structural abnormality.

ii. 46,XY,der(13;21)(q10;q10),+21A male karyotype in which the numerical abnormality of chromosome 21 is listed after the structural abnormality of chromosome 13 and 21 following the chromosome order rule.

iii. 47,X,inv(X)(p21q26),+3,inv(3)(q21q26.2),–7,+10,–20,del(20)(q11.2q13.1),+21[10]Karyotype of a neoplastic sample in a female shows pericentric inversion of the X chromosome, gain of chromosome 3, an inversion 3, monosomy 7, trisomy 10, monosomy 20, an interstitial deletion within the long arm of chromosome 20, and trisomy 21. The normal X chromosome is listed first followed by the abnormal X chromosome with an inversion. The extra chromosome 3 is presented before the inversion of chromosome 3, and the monosomy 20 before the deletion of chromosome 20. **Note**: the karyotype can also be written to show gain of the inverted chromosome 3, and therefore trisomy is implied, *i.e.*, 47,X,inv(X)(p21q26),+inv(3)(q21q26.2),–7,+10,–20,del(20)(q11.2q13.1),+21[10]

iv. 50,XXYc,+X,+21c,+21[10]Karyotype of a neoplastic sample in a XXY male shows an acquired gain of an X chromosome and acquired gain of chromosome 21, both are listed after the respective constitutional gain.

d. Multiple structural changes of homologous chromosomes are presented in alphabetical order according to the abbreviated term of the abnormality.

i. 50,XX,+1,+del(1)(p13),+dup(1)(q21q32),+inv(1)(p31q41),+8,r(10)(p12q25),–21[10]Karyotype of a neoplastic sample in a female shows four abnormalities involving

different chromosome 1 homologues, one aneuploidy and three different structural abnormalities. The numerical change is presented first, followed by the structural aberrations listed in alphabetical order, *i.e.*, **del**, **dup**, **inv**.

e. Multiple changes within the same chromosome are presented from **pter** to **qter** (irrespective of alphabetical order), consistent with the public databases of current genome builds on UCSC or Ensembl Genome Browsers (www.genome.ucsc.edu or www.ensembl.org).

i. 46,XX,der(8)ins(8;?)(p23;?)del(8)(q22)A female karyotype shows two abnormalities involving one chromosome 8 described using the short system (karyotype format). Chromosome 8 is described as a derivative chromosome with the structural aberrations listed from the distal short (p) arm to the distal long (q) arm, rather than in alphabetical order, following the **pter** to **qter** rule. The ISCN description using the detailed system (karyotype format) would be 46,XX,der(8)(8pter→8p23::?::8p23→8q22:) (see Section 4.7).

ii. arr[GRCh38] 8p23.3p23.1(176,814_7,691,960)×1,8p23.1p21.3(12,556,004_20,026,406)×3Microarray shows an apparently terminal single copy loss of the short arm of chromosome 8 involving the segment 8p23.3 to 8p23.1 and an interstitial single copy gain of the segment segment 8p23.1 to 8p21.3.

f. Unidentified structural rearrangements are given after the other numerical and structural abnormalities in the following order: unidentified **ring chromosomes** (**r**), **marker chromosomes** (**mar**), and **double minutes** (**dmin**). The number of double minutes is not included in the chromosome count (see Section 5.5.12).

i. 52,XX,+7,+12,+13,+17,+r,+mar,12~20dmin[10]A female karyotype with 52 chromosomes in a neoplastic sample. The **ring chromosome** (**r**) is listed before the **marker** (**mar**) and the **double minutes** (**dmin**) are given after a marker chromosome.

g. Derivative chromosomes whose centromere is unknown (see Section 5.5.3) are placed after all identified abnormalities but before unidentified ring chromosomes, marker chromosomes, and double minutes.

i. 52,XX,+12,+13,+17,+der(?)t(?;6)(?;q16),+r,+mar,5~9dmin[10]A female karyotype with 52 chromosomes in a neoplastic sample. Abnormalities are given in chromosome order, and derivative chromosomes that can be partly identified are given before ring chromosomes, marker chromosomes and double minutes of unknown origin.

4.4 Nomenclature Rules

4.4.1 Spaces

Spaces are not given in the ISCN description except for the following three scenarios:

a. A space is always present between the abbreviations for the technique used (+/– genome build) and the result.

i. 46,XY.ish 4p16.3(D4F26,WHS,D4S96)×2

ii. nuc ish (TP73×1,ANGPTL×2)[107/200]

iii. arr (X)×1

iv. arr[GRCh38] 5q22.1q31.1(110,670,174_131,637,624)×3
v. ogm (X)×1[0.6]
vi. ogm[GRCh38] 22q11.2(18,730,698_21,689,521)×1

b. There is a space between two abbreviations when no period or a comma is present.

i. nuc ish (KAL1,D21S65)×2
ii. 47,XY,+mar dn[14]/46,XY[16]
iii. 45,XY,psu dic(14;21)(q31;q22.1)

c. A space is added before and after **chi**, **con**, **mos**, **or**, and **sep**.

i. nuc ish (MYH11,CBFB)×3(MYH11 con CBFB)×2[100/200]*In situ* hybridization of 200 nuclei shows colocalization of *MYH11* and *CBFB* in 100 nuclei and a normal hybridization signal pattern in 100 nuclei. The number of normal nuclei is inferred from the denominator.
ii. 46,XY,add(1)(q42) or dup(1)(q42q44)An abnormal chromosome 1 in a male individual has arisen by an unknown mechanism as shown by the use of add(1) or by a duplication involving bands 1q42 to 1q44.

4.4.2 Identification of Homologous Chromosomes

a. To distinguish homologous chromosomes when both are involved in an abnormality (numerical or structural), one of the numerals may be **underlined** (_).

i. 46,XY,t(5;8)(q23;q24),t(5;11)(p12;p11.1)A male karyotype with different translocations involving both chromosome 5 homologues. Single underlining may be used to distinguish between the homologues. As these are different homologues, the t(5;8) is listed before the t(5;11) following the chromosome order rule, *i.e.*, the partner chromosome determines the numerical order.

4.4.3 Number of Signals or Copies

a. A **multiplication** (×) sign can be used to describe two or more copies of a structurally rearranged chromosome. The number of copies (×2, ×3, *etc*.) should be placed after the abnormality. The **multiplication** (×) sign should not be used to denote multiple copies of normal chromosomes (see exception for targeted chromosome analysis in Section 10.2.1).

i. 47,XY,+5,del(5)(q13q33)×2[15]Karyotype of a neoplastic sample shows an interstitial deletion of the long arm of two chromosome 5 homologues. The remaining chromosome 5 is apparently normal.

b. In *in situ* hybridization a **multiplication** (×) sign and the number of signals seen is given **outside** the **parentheses** (**( )**) when the number of copies for each probe is the same. If the copy number differs between probes within the same hybridization, the **multiplication** (×) sign is given for each probe **inside** the parentheses.

i. nuc ish (RB1,D21S259/D21S341/D21S342)×2*In situ* hybridization shows two signals for the RB1 probe and the D21S259/D21S341/D21S342 contig. The ×2 applies to all probes and is given outside the parenthesis. **Note:** D21S259 could be given on its own in the ISCN description and the other chromosome 21 contig probes must then be given in the text of the report.

ii. nuc ish (MYC×2,IGH×3)[90/200]*In situ* hybridization in a neoplastic sample using a D8Z2/MYC/IGH probe set shows three signals for IGH probe and two signals for the MYC probe. The multiplication (×) sign is associated individually with each probe. **Note:** cell numbers must be given for neoplastic samples. The control probe, D8Z2, need not be given as both MYC and control probes show a normal signal pattern (see Chapter 7).

iii. 46,XX.rsa (X,13,18,21)×2Apparently normal female karyotype and normal copy number of chromosomes X, 13, 18, and 21 using a regionspecific assay (*e.g.,* QF-PCR).

4.4.4 Breakpoint Designation

a. The location of a breakpoint(s) is specified by the band in which that break has occurred, *e.g.*, 17p13.1

- If a break can be localized to a band and not a subband, then the band may be specified, *e.g.*, 17p13
- Likewise, if a breakpoint can be localized only to a region but not to a particular band, then the region number may be specified, *e.g.*, 17p1

b. In the *detailed system (karyotype format)* the aberrations are listed according to the breakpoints of the derivative chromosome from **pter** to **qter** and are not separated by a comma (see Section 4.7). If a rearrangement is confined to a single chromosome, the chromosome number is not repeated in the band description. If more than one chromosome is involved, the bands and chromosome ends are identified with the appropriate chromosome numbers (see Section 5.4.2.2).

i. 46,XY,der(9)(pter→p23::p13→p23::p13→q22::q33→qter)A male karyotype shows a derivative chromosome 9 from an intrachromosomal rearrangement. The chromosome number is not repeated before each breakpoint because all the breakpoints are within chromosome 9.

ii. 46,XY,der(7)(7pter→7q22::2q21→2qter)A male karyotype shows chromosomes 2 and 7 are involved in this derivative chromosome. The chromosome number is reported for each breakpoint in the brackets.

c. A mixture of the short and detailed systems (karyotype format) can be used in the ISCN description but are not intermixed to describe abnormalities of a single chromosome.

. 46,XX,der(2)t(2;5)(p23;q35),der(8)(22qter→22q12::8q22→8q13::8p22→8q13::8p22 →8p23::17q21→17qter)[10]Karyotype of a female neoplastic sample shows a derivative chromosome 2 and a derivative chromosome 8. The derivative chromosome 2 is written using the short system (karyotype format) and is derived from a translocation between 2p23 and 5q35. The derivative chromosome 8 is written using the detailed system (karyotype format) and involves multiple rearrangements involving chromosomes 8, 17, and 22, in addition to a pericentric inversion of chromosome 8 (see Section 5.5.10 for more examples involving inversions). **Note:** when using the detailed system (karyotype format), derivative chromosomes are written from **pter** to **qter** with respect to the orientation of the segment containing the centromere.

d. For interstitial deletions or duplications where both breakpoints are within the same chromosome band, both breakpoints are given when describing the aberration using the

karyotype format but the breakpoint is only given once when using the microarray format (see Table 4 and Section 4.7).

4.4.5 Nucleotide Position

a. The genomic coordinates that are used in cytogenomic nomenclature for **microarrays** (**arr**), **region-specific assays** (**rsa**), **genome mapping** (**ogm**) and **sequencing** (**seq**) are defined in the translation tables provided by NCBI (hg38/GRCh38): http://hgdownload.cse.ucsc.edu/goldenPath/hg38/database/cytoBand.txt.gz
b. When nucleotide coordinates are used to define an abnormal result, the **genome build** (*e.g.*, **[GRCh38]**) must be specified within the ISCN. The genome build follows immediately after the technique with no space, as illustrated in Chapters 8–11. There is a space between the **genome build** in **square brackets [GRCh38]** and the remainder of the ISCN description.
c. The genome build is not included in the ISCN if the nucleotide coordinates are not reported, *e.g.*, when describing normal results or when using the abbreviated system (microarray format) to describe whole chromosome aneuploidy (see Sections 4.7 and 8.2.2). The genome build should be provided in the report.
d. The nucleotide numbers are given either with or without commas to indicate thousands and millions, but the use of **commas (,)** is recommended to improve readability. **Note:** commas are not used in the extended system (microarray format) since they confound the copy number (see Sections 4.7 and 8.1.1).
e. The span of abnormal nucleotides is separated by an **underscore** (_), in line with the Human Genome Variation Society (HGVS) recommendations (www.HGVS.org/varnomen) for molecular genetic nomenclature.
f. Band designations of only the abnormal genomic regions are shown. Abnormal regions of the sex chromosomes are listed first (X before Y) followed by autosomes, which are listed from lowest to highest number chromosome. **Note:** conventional cytogenetic banding assignments are those derived from banded chromosomes, while the microarray/sequencing banding assignments are those derived from genome browsers. These are not always concordant (see Section 2.4).

i. 46,X,der(Y)t(Y;20)(q11.23;q13.2).arr[GRCh38] Yq11.23q12(24,741,599_57,191,562)×0,20q13.2q13.33(53,224,067_63,743,732)×3A derivative Y chromosome from an unbalanced translocation involving Yq11.23 and 20q13.2 by conventional karyotype. There is no normal Y chromosome in this individual. Microarray shows an apparently terminal loss of part of the long arm of the Y chromosome and gain of an apparently terminal segment of the long arm of chromosome 20. **Note:** when the abnormality involves one of the sex chromosomes, the normal sex chromosome is listed first in the ISCN description followed by the abnormal sex chromosome (see Sections 4.2.1 and 4.3).

g. In complex microarray or genome mapping results, as may be the case in neoplastic studies, the laboratory may choose to display results using ISCN in a tabular form instead of in a string (see Section 8.2.7, Tables 9, 10 and 11 for examples). The information in the table must include the chromosomes and bands corresponding to the abnormality, the type of abnormality (*e.g.*, loss, gain, amplification, translocation,

inversion or region of homozygosity), the genomic coordinates of the abnormality, and the proportion of the sample with the abnormality where applicable. When the tabular form is used the genome build is designated in the table.

h. A mixture of the abbreviated, short and extended systems (microarray format) and the abbreviated, short and detailed systems (karyotype format) can be used in the ISCN description but are not intermixed to describe a single abnormality (see examples in Chapters 8, 9, 10 and 11).

4.4.6 Gene Symbols

a. Although gene symbols are usually italicized, they are not italicized in the ISCN description.

4.4.6.1 Gene Fusions

a. The gene fusion definition has been harmonized between ISCN, the Human Genome Organisation (HUGO) Gene Nomenclature Committee, Variant Interpretation for Cancer Consortium (VICC) Gene Fusion Specification, and HGVS (Bruford et al., 2021). Gene fusions occur when two or more genes join and result in a chimeric transcript and/or a novel interaction between a rearranged regulatory element with the expressed product of a partner gene (a regulatory fusion).

b. A **double colon** (**::**) is used in the ISCN description to identify fusion genes in rsa and ogm nomenclature only.

4.5 Clones, Mosaicism and Chimeras

4.5.1 Clones

a. A clone is a cell population derived from a single progenitor.

b. When several cells have the same or a closely related abnormal chromosome complement, the clonal origin may be inferred. A clone is therefore not necessarily completely homogeneous.

- There must be at least two metaphases with the same chromosome gain or structural rearrangement for the abnormality to be accepted as clonal.
- The same chromosome loss must occur in at least three metaphases to be accepted as clonal. However, identical losses in two metaphases with the same clonal chromosome gain or structural aberration(s) may also be considered clonal and included in the nomenclature at the laboratory's discretion.

iii. 46,XY,del(5)(q13q33),–7,+8[2]/46,XY[18]A neoplastic clone with an interstitial deletion of 5q13 to 5q33, monosomy 7 and trisomy 8 in two metaphases. The monosomy 7 can be included in the ISCN description as both metaphases have the same structural rearrangement and chromosome gain.

c. Clonality may need to be defined operationally. The criteria for acceptance will depend on, *e.g.*, the number of metaphases examined, the nature of the aberration involved, the type of culture, and the time cells spend *in vitro* prior to harvest.

d. Where *in situ* preparations are analyzed in neoplasia, the abnormality must meet the above criteria and be from either different primary cultures, or from well-separated areas or different cell colonies on the same culture.
e. When the same abnormal clone has been found in an initial and follow-up study, even in a single metaphase, it should be reported in the karyotype.
. 46,XX,t(9;22)(q34;q11.2)[1]/46,XX[19]A neoplastic clone with a translocation between chromosomes 9 and 22. The t(9;22) was seen in the initial sample.

4.5.2 Mosaicism and Chimerism

a. **Mosaicism (mos)** is the presence of two or more cell lines derived from the same zygote.
- Mosaicism may occur pre- or post-zygotically.

b. **Chimerism** (**chi**) is the presence of two or more cell lines originating from different zygotes.
- Chimerism may occur by fusion of gametes or embryos or may occur as a result of organ or stem cell transplantation.

c. In microarray nomenclature **mos** is not used.
d. Where *in situ* preparations are analyzed in constitutional samples, the abnormality must meet the following criteria and be from either different primary cultures, or from well-separated areas or different cell colonies on the same culture:
- There must be at least two metaphases with the same chromosome gain or structural rearrangement for the abnormality to be accepted as clonal.
- The same chromosome loss must occur in at least three metaphases to be accepted as clonal. However, identical losses in two metaphases with the same clonal chromosome gain or structural aberration(s) may also be considered clonal and included in the nomenclature at the laboratory's discretion.

4.5.3 Nomenclature for Clones, Mosaics and Chimeras

a. The karyotype designations of different clones or cell lines are separated by a **slant line** (/). The exception is that karyotypes of chimeras due to stem cell transplantation are separated by a **double slant line** (//).
b. **Square brackets ([ ])**, placed after the karyotype description, are used to designate the absolute number of metaphases in each cell line or clone.
c. Multiple clones in neoplastic samples are given in order of size if they are unrelated and in order of complexity if they are cytogenetically related.
d. Multiple cell lines with constitutional abnormalities are given according to their size; the largest first, then the second largest, and so on. Likewise, the largest cell line in chimeras is presented first and where discernable, in SNP microarray and genome mapping.
e. The normal cell line is always listed last even if it is the largest.
i. mos 45,X[15]/47,XXX[10]/46,XX[23]Sex chromosome mosaicism in a female with the largest abnormal cell line listed first and the normal cell line last.
f. The exception is chimerism from stem cell transplants where the donor cell line is listed last.

g. When the metaphase numbers are the same, the XX cell line is always listed before the XY when neither shows an abnormality.

h. To distinguish between **mosaic** (**mos**) and **chimeric** (**chi**) cell lines, the respective abbreviation may be used preceding the karyotype designation, with a space following the abbreviation.

i. The use of **mos** or **chi** is optional. In most instances the abbreviation will be given only in the initial ISCN description in a report, *e.g.*, mos 45,X[10]/46,XX[10] and chi 46,XX[10]/46,XY[10]

i. 45,X[10]/46,XX[20]Mosaic karyotype with one cell line having one X chromosome in ten metaphases and a second cell line with a normal diploid female pattern in 20 metaphases.

ii. chi 46,XY[25]/46,XX[10]An XY/XX chimera with the larger cell line listed first.

iii. 46,XX[5]//46,XY[25]Incomplete engraftment in a female recipient following stem cell transplant with male donor cells.

j. In neoplasia, individual neoplastic clones and, if present, constitutional cell lines are listed in the following order irrespective of clone size or complexity:

- abnormal clones with an acquired abnormality,
- cell lines with a constitutional abnormality,
- the normal cell line, if present.

iv. 45,XY,–21[5]/47,XY,+21c[10]/46,XY[10]Neoplastic sample with acquired loss of chromosome 21 in an individual with mosaic Down syndrome.

v. 47,XY,t(8;14)(q11.2;q32),+21c[5]/47,XY,+21c[7]/46,XY[10]A neoplastic clone with a translocation between chromosomes 8 and 14 in an individual with mosaic Down syndrome.

k. When the number of abnormal metaphases in constitutional cell lines or neoplastic unrelated clones is *equivalent*, or the complexity of clones in cytogenetically related neoplastic clones is *equivalent*, their order in the ISCN description is determined by the sequential application of the following rules (see also Section 6.3.3 for neoplasia examples):

- Where abnormalities in different clones/cell lines involve chromosomes of a different number, the **chromosome order** rule applies, X before Y, followed by autosomes in increasing number, *e.g.*,
  Constitutional cell lines: 47,XXX[25]/47,XX,+21[25]/46,XX[10]
  Unrelated neoplastic clones: 47,XX,+8[25]/47,XX,+21[25]
  Related neoplastic clones: 45,XY,–5,t(7;11)(p15;p15)[10]/45,XY,–7,t(7;11)(p15;p15)[15]
- When the same chromosome is involved, gains are listed before losses before structural change, *e.g.*,
  Constitutional cell lines: 45,X[25]/46,X,i(X)(q10)[25]/46,XX[25]
  Unrelated neoplastic clones: 47,XY,+5[25]/46,XY,del(5)(q13q33)[25]/46,XY[10]
  Related neoplastic clones: 47,XX,t(9;22)(q34;q11.2),+19[5]/45,XX,t(9;22),–19[10]
- Structural abnormalities of the same number chromosome are listed **alphabetically,** *e.g.*,
  Constitutional cell lines: 46,X,del(X)(q13)[25]/46,X,i(X)(q10)[25]/46,XX[25]
  Unrelated neoplastic clones: 46,XX,add(7)(q34)[10]/46,XX,del(7)(q22)[10]
  Related neoplastic clones: 46,XX,del(7)(q22),+8[10]/46,XX,i(7)(q10),+8[12]

- Where the same type of abnormality is detected on the same chromosome, the **pter to qter** rule applies, *e.g.*,
  Constitutional cell lines: 46,XY,del(5)(p15.31)[10]/46,XY,del(5)(p15.2)[10]
  Unrelated neoplastic clones: 46,XX,del(13)(q13q14)[10]/46,XX,del(13)(q14q22)[10]/46,XX[2]
  Related neoplastic clones: 46,XY,del(5)(q13q31),–7[3]/46,XY,del(5)(q13),–7[17]

l. When a single abnormal metaphase is detected with one technique and confirmed by a different method (*e.g., in situ* hybridization) and thus shown to be clonal, it is reported in the ISCN description. When additional abnormalities are seen in a single metaphase, but not proven to be present with another method, they should not be listed in the nomenclature but, if appropriate, may be discussed in the interpretation.

. 46,XX,del(20)(q11.2q13.3)[1]/46,XX[19].nuc ish (D20S108)×1[40/200]A neoplastic clone with an interstitial deletion of 20q11.2 to 20q13.3 seen in one metaphase and confirmed by interphase *in situ* hybridization. **Note:** the abnormal *in situ* hybridization interphase result must be above the laboratory reporting threshold.

i. 47,XX,+8[1]/46,XX[19].nuc ish (D8Z2)×1[30/200]Karyotype shows an additional chromosome 8 in one metaphase and is confirmed as a mosaic trisomy 8 by interphase *in situ* hybridization.

m. In chimerism **secondary to stem cell transplant**, the recipient clone(s) are listed first, followed by the donor clone(s).

. 46,XY[3]//46,XX[17]Karyotype shows three metaphases from the male recipient and 17 metaphases from the female donor.

i. //46,XX[20]Karyotype shows that all 20 metaphases are derived from the female donor.

ii. 46,XY[20]//Karyotype shows that all 20 metaphases are derived from the male recipient.

iii. 46,XY,t(9;22)(q34;q11.2)[4]//46,XX[16]Karyotype shows four male recipient metaphases with a 9;22 translocation and 16 apparently normal female donor metaphases.

iv. 46,XX[5]//45,XX,der(13;14)(q10;q10)c[15]Karyotype shows five metaphases from the female recipient and 15 metaphases from the donor. The donor cells can be distinguished by the presence of a constitutional Robertsonian translocation involving chromosomes 13 and 14.

n. If present in cytogenomic results (**arr, ogm, rsa, seq**), clonality/mosaicism must be indicated in the ISCN description as follows (see Chapters 8–11):

- An estimate of the proportion of the sample with the abnormality, or the **variant allele frequency** (**VAF**) of the abnormality is reported in **square brackets** (**[ ]**) immediately following the abnormality.
- If it is not possible to determine the level of mosaicism, a **question mark** (**?**) may be used in **square brackets** (**[ ]**) in place of the **VAF** or sample proportion.
- Alternatively where the level of mosaicism cannot be determined, a **tilde** (**~**) may be used to indicate a range of copy numbers.
- **Amplification** (**amp**) may be used when there are too many signals to allow enumeration and the amplification meets the clinical criterion for gene amplification in the disease under investigation.
- The abbreviation **mos** is not used in ISCN for molecular cytogenomic results.

v. arr[GRCh38] 17p13.3~p13.1(158,756_7,281,077)×1[0.7~0.9]SNP microarray of a neoplastic sample shows loss of a segment of the short arm of chromosome 17 with a range of deletion breakpoints between 17p13.3 and 17p13.1, as indicated by using **tilde** (**~**) in the breakpoint designation. There is similarly a range in the proportion of the sample within this region from 70% to 90%.

vi. arr[GRCh38] 7p11.2(54,290,345_55,087,100)amp[?]Microarray of a neoplastic sample shows **amplification** (**amp**) of a region in 7p11.2. The exact copy number is too large to be enumerated accurately by microarray and the proportion of the sample with the amplification cannot be determined.

vii. ogm[GRCh38] t(1;17)(p36.23;p13.3)(8,781,440;2,208,744)(RERE::SMG6)[VAF0.3],del(6)(q12q23.3)(63,771,696_135,674,891)[0.5],del(12)(p13.1)(pter_12,722,843)[0.5]Genome mapping shows a reciprocal translocation between chromosomes 1 and 17 resulting in a *RERE::SMG6* fusion gene with a VAF of 30%. There is an interstitial deletion of 6q and an apparently terminal deletion of 12p, both losses are in 50% of this neoplastic sample.

4.6 Multiple Techniques

a. Where multiple techniques are reported in the nomenclature, the karyotype (if undertaken) is always listed first. The order of the subsequent techniques is at the discretion of the laboratory. Subsequent techniques are separated by a **period** (**.**) to designate the beginning of the next result. Alternatively, multiple techniques can be listed on separate lines without a **period** (**.**).

b. If an alternative technique clarifies the karyotype and, in retrospect, the abnormality can be visualized with banding, the karyotype may be amended to reflect this new information.

c. If the abnormality is cryptic and cannot be visualized by banding, the abnormality is **not** listed in the banded karyotype.

i. 46,XX,del(4)(q32q35).arr[GRCh38] 4q32.2q35.1(163,146,681_183,022,312)×1.ogm[GRCh38] del(4)(q32.2q35.1)(163,146,681_183,022,312)
or
46,XX,del(4)(q32q35)
arr[GRCh38] 4q32.2q35.1(163,146,681_183,022,312)×1
ogm[GRCh38] del(4)(q32.2q35.1)(163,146,681_183,022,312)Karyotype shows a large interstitial deletion in the long arm of chromosome 4 in a female. The breakpoints are further delineated by microarray and genome mapping. **Note:** the nucleotides are likely to be different for microarray and genome mapping platforms. They are the same for this example as they are given only to demonstrate the nomenclature.

ii. 46,XX.arr[GRCh38] 22q11.21(18,339,130_21,086,225)×1.ish del(22)(q11.2q11.2)(TBX1-,SHANK3+)An interstitial deletion of the long arm of chromosome 22, which is detected by chromosome microarray and confirmed by metaphase *in situ* hybridization. The microdeletion is not visible in the karyotype and is therefore not shown in the karyotype nomenclature.

d. When the same structural abnormality is seen with different techniques or in different clones/subclones/cell lines, breakpoints do not need to be repeated unless their use clarifies or extends the breakpoints.

i. 46,XX,t(4;18)(q31.1;q21.1).ish t(4;18)(wcp4+,wcp18+;wcp18+,wcp4+)A female karyotype with a reciprocal translocation 4;18 confirmed by *in situ* hybridization using painting probes for chromosomes 4 and 18. Breakpoints of the translocation are not repeated in the *in situ* hybridization result.

ii. 45,XY,der(7)t(7;15)(q36.2;q11.1),–15.arr[GRCh38] 7q36.2q36.3(154,257,444_159,128,556)×1.ish der(7)t(7;15)(wcp7+,RP11–324E12–,wcp15+)A male karyotype with a derivative chromosome 7 with one normal chromosome 7 and one normal chromosome 15. Due to unbalanced segregation, the derivative 15 is not present, hence the chromosome number of 45 and –15 in the karyotype nomenclature. Breakpoints are not repeated in the *in situ* hybridization result.

iii. 47,XX,inv(6)(p21q25),+12[17]/47,XX,inv(6),+mar[11]/46,XX[2].ish der(8)(D8Z2+,MYC–)[10]A female karyotype of a neoplastic sample. The breakpoints of the inv(6) are not repeated in the sideline. The marker is confirmed to be derived from chromosome 8 by *in situ* hybridization.

e. When several techniques are used, the abbreviation **mat, pat, inh, dmat, dpat** or **dinh** is given in the nomenclature of the technique where the inheritance was first identified. The inheritance abbreviation is not given in the ISCN description of subsequent technologies.

i. 46,XY,t(1;18)(p31;q22)pat.ish t(1;18)(wcp18+,wcp1+;wcp18+,wcp1+)A paternally inherited translocation between the short arm of chromosome 1 and the long arm of chromosome 18, seen with karyotype and *in situ* hybridization in a male individual. The abbreviation **pat** is only given once.

ii. 46,XY.ish del(22)(q11.2q11.2)(TBX1–)matA maternally inherited interstitial deletion of the proximal part of the long arm of chromosome 22 in this male sample. The abbreviation **mat** is given in the *in situ* hybridization part of the ISCN description as the del(22) is not visible on conventional karyotype.

iii. arr[GRCh38] 7q35(145,733,219_146,772,842)×1mat.ish del(7)(q35q35)(RP11–79M8–)A maternally inherited interstitial loss in 7q35 detected by chromosome microarray and confirmed by *in situ* hybridization. The abbreviation **mat** is associated with the technique performed first.

iv. 46,XX,der(13)t(13;20)(q34;p13)dmat.ish der(13)(163C9–,dj1061L1+)An unbalanced translocation between the distal long arm of chromosome 13 and the distal short arm of chromosome 20, inherited from a balanced maternal t(13;20). The subtelomeric region of 13q is deleted and replaced with the subtelomeric region of the chromosome 20 short arm.

4.7 ISCN Formats

a. The ISCN description uses two different formats depending on the technique used and/or the structural information given by the assay:

- **Karyotype format** based on chromosome bands, *e.g.*, banded chromosome analysis (*i.e.*, conventional karyotype), *in situ* hybridization, genome mapping, region-specific assays (RSA) and sequencing or
- **Microarray format** based on molecular cytogenomic techniques, *e.g.*, microarray, genome mapping, RSA, and sequencing.

b. The karyotype format is described using the abbreviated, short, and detailed systems, while the microarray format is expressed using the abbreviated, short, and extended systems.

c. For interstitial deletions or duplications where both breakpoints are within the same chromosome band, both breakpoints are given when describing the aberration using the karyotype format (see Section 4.7.1), but the breakpoint is only given once when using the microarray format (see Table 4 and Section 4.7.2).

i. Interstitial deletion of chromosome 12.

- Karyotype: 46,XY,del(12)(q22q22)
- *In situ* hybridization: ish del(12)(q22q22)(RP11–917O5+,RP11–850P15–,RP11–541G9+)
- Microarray: arr[GRCh38] 12q22(93,201,112_95,156,540)×1
- Sequencing:
  - *Karyotype format ISCN:*
    seq[GRCh38] del(12)(q22q22)
    NC_000012.12:g.93201112_95156540del
  - *Microarray format ISCN*:
    seq[GRCh38] 12q22(93,201,112_95,156,540)×1
- Genome mapping:
  - *Karyotype format ISCN*:
    ogm[GRCh38] del(12)(q22q22)(93,201,112_95,156,540)
  - *Microarray format ISCN*:
    ogm[GRCh38] 12q22(93,201,112_95,156,540)×1

ii. Paracentric inversion of chromosome 12.

- *In situ* hybridization: ish inv(12)(q22)(RP11–490G8+)(q22)(RP11–850P15+)
- Sequencing:
  - *Karyotype format ISCN*:
    seq[GRCh38] inv(12)(q22q22)
    NC_000012.12:g.93,201,112_95,156,540inv
- Genome mapping:
  - *Karyotype format ISCN*:
    ogm[GRCh38] inv(12)(q22q22)(93,201,112_95,156,540)

Table 4. ISCN for breakpoints within a chromosome band for each technique

Abnormality	Cytogenetic		Molecular Cytogenetic				
	karyotype	ish	arr[1]	ogm[1]		seq[1]	
			microarray format	karyotype format	microarray format	karyotype format	microarray format
del(12)(q22q22)	q22q22	q22q22	q22	q22q22	q22	q22q22	q22
dup(12)(q22q22)	q22q22	q22q22	q22	q22q22	q22	q22q22	q22
inv(12)(q22q22)	N/A	Separate listing[2]	N/A	q22q22	N/A	q22q22	N/A

[1] For further arr examples see Chapter 8; for ogm see Chapter 9; for seq see Chapter 11.
[2] See Section 7.2.4.

4.7.1 Karyotype Format

a. The karyotype format describes the abnormality using chromosome bands (short and detailed systems).

- The abbreviated system defines each abnormality by only the chromosome number. It is applicable for *in situ* hybridization of sex determination and whole chromosome enumeration and targeted chromosome analysis.
  - ish 7(D7Z1)×1[20]/7(D7Z1)×2[15] (see Chapter 7).
    rsa (21)×3[25]/(21)×2[5] (see Chapter 10).
- The short system defines each abnormality by their breakpoints. However, with genome mapping the short system includes the nucleotides without indicating the copy number, *i.e.*,
  - 46,XX,del(5)(q13) (see Chapter 5).
    ish del(15)(q11.2q11.2)(SNRPN–,D15S10–) (see Chapter 7).
    ogm[GRCh38] del(17)(q11.2q11.2)(29,069,481_30,273,120)[0.5] (see Chapter 9).
- The detailed system (karyotype format only) defines each abnormality in terms of its band composition from **pter** to **qter**. However, with genome mapping the detailed system includes the nucleotides without indicating the copy number, *i.e.*,
  - 46,XX,del(5)(pter→q13:) (see Chapter 5).
    46,XX.ish del(15)(pter→q11.2::q12→qter)(D15S11+,SNRPN–,D15S10–,GABRB3+) (see Chapter 7).
    nuc ish (KMT2A)x2(5′KMT2A sep 3′KMT2A)×1[200] (see Chapter 7).
    ogm[GRCh38]
    der(2)(pter_p24.1::p12_p11.2::p24.1_p12::p11.2_qter)(pter_19,795,841~19,799,854::80,780,708_87,576,955::19,795,841~19,799,854_80,780,709::87,576,956_qter) (see Chapter 9).

4.7.2 Microarray Format

a. The microarray format describes the abnormality using nucleotides (short and extended systems) and copy number. When describing normal results or whole chromosome aneuploidy or chromosome arm aneuploidy the abbreviated system is used that does not include the nucleotides. The abbreviations **pter** and **qter** are not used in the ISCN microarray format.
b. The abbreviated system (microarray format only) describes the abnormality/abnormalities with no breakpoints and no nucleotides, *i.e.*,
   arr (X,1–22)×3 (see Chapter 8).
   ogm (X,21)×3 (see Chapter 9).
   seq (13)×3 (see Chapter 11).
c. The short system includes the breakpoints and nucleotides involved in the abnormality and copy number, *i.e.*,
   arr[GRCh38] 22q11.21(18,730,698_21,689,521)×1 (see Chapter 8).
   ogm[GRCh38] 22q11.21(18,730,698_21,689,521)×1 (see Chapter 9).
   seq[GRCh38] 10p15.3(49,086_2,944,634)×1dn (see Chapter 11).
d. The extended system (microarray format only) describes the abnormality in detail including the flanking normal nucleotides, *i.e.*,
   arr[GRCh38] 22q11.21(18889117×2,18929329_21111370×1,21116218×2) (see Chapter 8).
   ogm[GRCh38] 22q11.21(18855621×2,18858640_21290760×1,21294586×2) (see Chapter 9).
   seq[GRCh38] 10p15.3(46696_1737263×1,3067438×2)dn (see Chapter 11).

5 Karyotype

5.1 General Principles

a. For general rules that are also applicable to karyotype analysis, see Chapter 4.
b. Symbols and abbreviations used to designate chromosome abnormalities are listed in Chapter 3.
c. In the description of a karyotype based on banded chromosomes, the total number of chromosomes is listed first, followed by a **comma** (**,**), and then followed by the sex chromosomes.
d. In the description of chromosome abnormalities, sex chromosome aberrations are given first, and X before Y, followed by abnormalities of the autosomes listed in numerical order. Each abnormality is separated by a **comma** (**,**) and listed in order, *e.g.*, 48,XY,+18,+21 (see a summary below and Section 4.3).

- Constitutional abnormalities are listed before acquired abnormalities of the same chromosome.
- The normal sex chromosome is listed first in the ISCN description when the other sex chromosome is abnormal (see Section 4.3).
- For each chromosome numerical abnormalities are given before structural changes. Gains are given before losses and before structural abnormalities.
- Where abnormalities are on the same chromosome homologue they are given in **pter** to **qter** order as they lie on the abnormal chromosome. The orientation of the abnormal chromosome is determined by the segment with the centromere.
- Abnormalities on the same chromosome homologue involving the same chromosome band are given in alphabetical order according to the abbreviated term of the abnormality, *e.g.*, **additional material** (**add**) before **deletion** (**del**); deletion before **derivative** (**der**); derivative before **duplication** (**dup**) *etc*.
- Structural changes involving both homologous chromosomes are given in alphabetical order according to the abbreviated term of the abnormality.

e. A normal diploid cell line, when present, is always listed last.
f. A **plus** (+) sign or a **minus** (–) sign may be used to indicate gain or loss of chromosomes (see Section 5.3).

- The **plus** (+) sign or **minus** (–) sign is given before a structurally normal or abnormal autosome to indicate autosomal aneuploidy in constitutional and in neoplastic samples.
- The **plus** (+) sign or **minus** (–) sign is given to describe acquired sex chromosome aneuploidy in neoplastic samples.
- The **plus** (+) sign or **minus** (–) sign are **not** used to indicate constitutional numerical sex chromosome abnormalities *i.e.,* all sex chromosomes comprising the constitutional

sex chromosome complement are given after the chromosome number, without indicating copy gain or loss (see examples in Section 5.3.1).

g. In the situations described below, the **plus** (+) sign and the **minus** (–) sign may be used in the interpretive comments but are **NOT** used in the ISCN description.

- To indicate an increase or decrease in the length of a chromosome arm (p or q) the **plus** (+) or **minus** (–) signs may be placed after the arm abbreviation, *e.g.*, 4p+, 5q– in the text.
- For benign variable chromosome features (see Section 2.5.1), to indicate an increase or decrease in arm length by placing a **plus** (+) or **minus** (–) sign after the appropriate abbreviation, *e.g.*, ps+. Heterochromatic variants are **not** included in the ISCN description but may be included in the text (see Chapter 2).

h. The **multiplication** (×) sign can be used to describe multiple copies of a rearranged chromosome but is not used to denote multiple copies of normal chromosomes (see Sections 4.4.3 and 5.6).

i. To distinguish homologous chromosomes, one of the numerals may be **underlined** (_) (see Section 4.4.2).

j. Uncertainty in chromosome, in band designation or in the type of aberration may be indicated by a **question mark** (**?**) or a **tilde** (**~**) (see Section 4.2.1). The term **or** is used to indicate alternative interpretations of an aberration (see Section 4.2.1).

k. The number of metaphases examined is indicated in **square brackets** (**[ ]**), where there is constitutional mosaicism and for all ISCN descriptions of neoplastic samples.

l. The karyotype designations of different clones or cell lines are separated by a **slant line** (/) (see Section 4.5.3).

m. **Mosaic** (**mos**) cell lines originate from the same zygote and **chimeric** (**chi**) cell lines originate from different zygotes (See Section 4.5). In constitutional cases, **mos** or **chi** may precede the karyotype designation and are followed by a space before the total chromosome number. The use of the abbreviations **mos** or **chi** is optional.

n. To describe more than one cell line (see Sections 4.5.3 and 6.3.3) the following applies:

- Where there is an abnormality in more than one cell line, these are given according to their size; the largest is given first and a normal cell line, if present is listed last, *e.g.*, mos 45,X[15]/47,XXX[10]/46,XX[23].
- When the different cell lines are found in **equal numbers**, the order is determined by the sequential application of the following rules:
  - A numerical abnormality is listed first before a structural abnormality.
  - Cell lines with gains of the same chromosome are given before cell lines with loss of the same chromosome and losses are given before structural aberrations of the same chromosome.
  - When both cell lines have numerical abnormalities, alterations of sex chromosomes are given first, followed by autosome number in chromosome order, *e.g.*, 47,XX,+X[25]/47,XX,+21[25].
- For rules to describe chimerism secondary to stem cell transplant see Section 4.5.3.
- To describe a constitutional chimera where the number of metaphases are different for the cell lines, the largest cell line is listed first, *e.g.*, chi 46,XY[25]/46,XX[10].
- To describe a constitutional chimera where cell lines are of **equal numbers** the XX cell line is listed before the XY cell line, *e.g.*, chi 46,XX[10]/46,XY[10].

o. When it is known that a chromosome aberration is inherited, the term **inh** is used. When the parent of origin is known, it can be designated **maternal** (**mat**) or **paternal** (**pat**). If only part of a parental aberration is inherited, the abbreviation **dmat**, **dpat** or **dinh** is used (see Section 4.2.1).
p. The same rules are followed to designate the type of chromosome aberrations in the description of constitutional and acquired chromosome aberrations. Specific terms and recommendations related to abnormalities seen in neoplasia are described in Chapter 6.
q. When an acquired abnormality is found in an individual with a constitutional chromosome anomaly, the constitutional aberration is indicated by the letter **c** immediately after the constitutional abnormality designation (see Sections 4.2.1, 5.3.1.2 and 6.4).
r. In the interest of clarity, complex rearrangements necessitating descriptions using the detailed system (karyotype format) should be written out in full the first time they are used in the report. The short system (karyotype format) version may be used subsequently.
s. The breakpoints of a rearranged chromosome(s) need not be repeated in any subsequent description of the same rearrangement or derivative of it.
t. In neoplasia an **incomplete** karyotype (**inc**) is used when the chromosome quality is too poor to allow complete chromosome analysis. The karyotype is thus likely to contain unidentified structural or numerical changes in addition to the abnormalities listed (see Section 6.3.6).

5.2 Normal Results

The normal karyotype is designated as follows:

i. 46,XXKaryotype shows an apparently normal female.
ii. 46,XYKaryotype shows an apparently normal male.
iii. 46,UKaryotype shows no evidence of an abnormality, and the sex chromosomes are not disclosed (*i.e.*, U replaces XX or XY).

5.3 Numerical Abnormalities

5.3.1 Sex Chromosome Numerical Abnormalities

5.3.1.1 Constitutional

i. 45,XKaryotype shows one X chromosome (Turner syndrome).
ii. 47,XXXConstitutional karyotype shows three X chromosomes.
iii. 47,XYYKaryotype shows one X chromosome and two Y chromosomes.
iv. 48,XXXYKaryotype shows three X chromosomes and one Y chromosome.
v. 45,X[13]/46,XY[17]Karyotype shows mosaicism with two cell lines. One X chromosome is seen in 13 metaphases, and a normal diploid male pattern of one X chromosome and one Y chromosome is seen in 17 metaphases.
vi. mos 47,XXY[10]/46,XY[20]A mosaic karyotype shows one cell line with two X chromosomes and one Y chromosome in ten metaphases and a second cell line with a

normal diploid male pattern of one X chromosome and one Y chromosome in 20 metaphases.

vii. 47,XXY[15]/45,X[15]A mosaic karyotype shows one cell line with two X chromosomes and one Y chromosome in 15 metaphases, and a second cell line with one X chromosome and no Y chromosome in 15 metaphases. **Note:** when the number of metaphases is equal in each cell line, the cell line with an extra sex chromosome is listed first following the rule gains before losses (see Sections 4.5.3 and 5.1).

viii. 45,X[25]/47,XXX[12]/46,XX[13]A mosaic karyotype shows two abnormal cell lines. One cell line with one X chromosome in 25 metaphases, and a second cell line with three copies of the X chromosome in 12 metaphases. Thirteen metaphases show a normal female karyotype. **Note:** the largest abnormal cell line is listed first, and the normal cell line is listed last.

ix. 47,XXX[25]/45,X[12]/46,XX[13]A mosaic karyotype shows two abnormal cell lines. One cell line with three copies of the X chromosome in 25 metaphases, and a second cell line with one X chromosome in 12 metaphases. Thirteen metaphases show a normal female karyotype. **Note:** the largest abnormal cell line is listed first, and the normal cell line is listed last.

5.3.1.2 Neoplasia

i. 46,Xc,+X[10]Karyotype shows an acquired clonal gain of one X chromosome in a neoplastic sample of an individual with Turner syndrome. **Note**: the **plus** (+) sign is given to designate the acquired clonal gain of a sex chromosome. For use of the letter (**c**) to describe constitutional abnormalities in neoplastic samples see Sections 4.3 and 6.4.

ii. 45,X,–X[8]Karyotype shows an acquired clonal loss of one X chromosome in a neoplastic sample in a female. **Note**: the **minus** (–) sign is given to designate the acquired clonal loss of a sex chromosome in a neoplastic sample.

iii. 44,Xc,–X[10]Karyotype shows an acquired clonal loss of the X chromosome in a neoplastic sample from a female individual with Turner syndrome.

iv. 45,X,–Y[20]/46,XY[5]Karyotype shows an acquired clonal loss of the Y chromosome in 20 metaphases and a normal male karyotype in five metaphases in a neoplastic sample.

v. 45,Y,–X[10]Karyotype shows an acquired clonal loss of the X chromosome in a neoplastic sample.

vi. 47,XX,+X[10]Karyotype shows an acquired clonal gain of one X chromosome in a neoplastic sample.

vii. 48,XY,+X,+Y[15]Karyotype shows an acquired clonal gain of one X chromosome and one Y chromosome in a neoplastic sample.

viii. 48,XXYc,+X[5]Karyotype shows an acquired clonal gain of one X chromosome in a neoplastic sample from an individual with Klinefelter syndrome. **Note**: the letter **c** for the constitutional anomaly refers to the whole sex complement, *i.e.*, in this example it indicates that XXY is the constitutional sex complement.

ix. 46,XXYc,–X[20]Karyotype shows an acquired clonal loss of one X chromosome in a neoplastic sample from an individual with Klinefelter syndrome. **Note:** an acquired

abnormality is presented in relation to the constitutional karyotype (see Sections 4.3 and 6.4).

x. 47,XXX?c[10]Karyotype shows three X chromosomes in a neoplastic sample in a female. **Note:** the **question mark** (**?**) indicates that it is unclear if the extra X is constitutional or acquired (see Section 4.2.1).

xi. 46,Xc,+21[15]Karyotype of a neoplastic sample with an acquired clonal gain of chromosome 21 in an individual with Turner syndrome.

xii. 48,XY,+X,+mar c[6]Karyotype of a neoplastic sample with an acquired clonal gain of the X chromosome and a constitutional marker. For constitutional markers, there is a space between **mar** and **c** (see Section 4.4.1).

5.3.2 Autosomal Numerical Abnormalities

i. 47,XX,+21The constitutional karyotype shows trisomy 21.

ii. 48,XX,+13,+21The constitutional karyotype shows trisomy 13 and trisomy 21.

iii. 45,XX,–22The constitutional karyotype shows monosomy 22.

iv. 46,XX,+8,–21The constitutional karyotype shows trisomy 8 and monosomy 21.

v. 48,XY,+21c,+21[10]Karyotype shows an acquired gain of chromosome 21 in a neoplastic sample from an individual with Down syndrome.

vi. 46,XY,+21c,–21[10]Karyotype shows acquired loss of one chromosome 21 in a neoplastic sample in an individual with Down syndrome. **Note**: +21 is listed before –21 following the rule that a constitutional abnormality is listed before an acquired abnormality of the same chromosome (see Sections 5.1 and 6.4).

vii. 47,XY,+8[15]/46,XY[5]Karyotype shows gain of chromosome 8 in 15 metaphases and a normal male karyotype in five metaphases in a neoplastic sample.

5.4 Structural Abnormalities

5.4.1 Specification of Chromosomes and Breakpoints

a. In single chromosome rearrangements, the abbreviation identifying the type of rearrangement is listed before the chromosome involved in the change. The chromosome involved is specified within **parentheses** (**( )**) and is followed by the breakpoint in a second set of **parentheses** (**( )**).

b. The location of a breakpoint(s) is specified by the band in which the break has occurred. Where the breakpoint appears to be at the interface between two bands the breakpoint is assigned to the higher of the two band numbers, *i.e.*, the number of the band more distal to the centromere.

c. A breakpoint may appear to be in either of two consecutive bands. A similar situation may occur when breakpoints at or near an interface between two bands are studied with different banding techniques. In this event, the breakpoint can be specified by both band numbers separated by the term **or**, *e.g.*, 1q23 **or** 1q24, indicating a break in either band 1q23 or band 1q24 (see Section 4.2.1).

d. If a breakpoint can be localized to a region but not a particular band then it may be specified giving only the region, *e.g.*, 1p3. If the band but not subband is discernable

then it may be given as, *e.g.*, 1p34. If the subband is identifiable then it is specified in the breakpoint description, *e.g.*, 1p34.1

- Some bands at 300 **bands per haploid set** (**bphs**) do not resolve into separate bands and are designated with a **hyphen** (-), *e.g.*, 20q11.2–13.1

e. Alternatively, uncertainty of breakpoints may be indicated by a **question mark** (**?**), *e.g.*, 1p1? (see Section 4.2.1) or by a **tilde** (**~**), *e.g.*, 1p34~p35 (see Section 4.2.1).

f. Breakpoint(s) of rearrangement(s) reported in the ISCN description may be at different levels of resolution reflecting the banding resolution, and hence the precision of the karyotype. The overall banding resolution is reported in accordance with the national guidelines as applicable and **not** included in the ISCN description.

g. If two or more chromosomes are involved in a rearrangement, chromosome numbers and breakpoint positions are separated by a **semicolon** (**;**).

h. If the rearrangement involves a single chromosome the breakpoints are not separated by a **semicolon** (**;**), *e.g.*, inv(2)(p23q11.2), del(4)(p15.3p16.1), r(18)(p11.2q23)

i. If one of the rearranged chromosomes is a sex chromosome, then it is listed first. When both X and Y chromosomes are involved in a rearrangement, the X chromosome is listed before the Y chromosome. Otherwise, the chromosome having the lowest number is always specified first, *e.g.*, t(X;3) (p22.1;p21.3) and t(2;5)(p23;p13.3)

j. An exception to the rule (i) above is an interchromosomal **insertion** (**ins**) in which part of one chromosome is inserted at a point of breakage in another chromosome. The **recipient** chromosome is specified **first**, regardless of whether it is a sex chromosome or an autosome with a number higher or lower than that of the donor chromosome, *e.g.*, ins(5;2)(p14;q22q32) and ins(3;X)(q21;p22.1p11.23) (see Section 5.5.9).

k. Normal chromosomes that are replaced by structurally altered chromosomes are not recorded in the ISCN description as missing. In the description of karyotypes containing dicentric chromosomes or derivative chromosomes resulting from whole-arm translocations, the abnormal chromosomes by convention replace both normal chromosomes involved in the formation of the dicentric chromosome or derivative chromosome. Thus, in these situations the two missing chromosomes are not specified (see Sections 5.5.4 and 5.5.18.2).

i. 46,XX,inv(3)(q21q26.2)[15]Karyotype of a neoplastic sample shows an inversion of one chromosome 3 replacing one normal chromosome 3 homologue in a female. There is no need to indicate that one chromosome 3 is missing, *i.e.*, the karyotype must **not** be written 46,XX,–3,+inv(3)(q21q26.2)[15]

ii. 46,Y,t(X;8)(p22.3;q24.1)Karyotype shows a balanced translocation between the X chromosome and chromosome 8 in a male. **Note:** the normal sex chromosome, in this example the Y chromosome, is listed first.

iii. 45,XX,dic(13;15)(q22;q24)Karyotype shows a translocation between chromosomes 13 and 15 involving bands 13q22 and 15q24 resulting in a dicentric (**dic**) chromosome in a female. **Note:** it is apparent from the total chromosome number in the ISCN description that the dicentric chromosome replaces the two normal chromosomes (see Section 5.5.4).

iv. 46,XY,der(1)t(1;3)(p22;q13.1)Karyotype shows an abnormal chromosome 1 that results from an unbalanced segregation of a translocation between chromosomes 1 and 3 in a male. The der(1) replaces a normal chromosome 1 and there is no need to indicate the missing normal chromosome. The description implies that the karyotype contains one normal chromosome 1, a derivative chromosome 1 and two normal chromosomes 3.

v. 46,XX,der(1)ins(1;?)(p22;?)Karyotype shows material of unknown origin is inserted in chromosome 1 within band 1p22 in a female. The homologous chromosome 1 is normal.

vi. 46,XY,–10,+der(17)t(10;17)(q22;p12)Karyotype shows an additional abnormal chromosome 17 that is a derivative of a translocation involving chromosomes 10 and 17, and two normal chromosomes 17 in a male. In this situation the missing chromosome 10 must be indicated.

5.4.2 Karyotype Format for Designating Structural Chromosome Abnormalities

a. There are two systems within the karyotype format for designating structural abnormalities, the short system (karyotype format) and the detailed system (karyotype format) (see Section 4.7).
b. The short and detailed systems (karyotype format) may be combined in the ISCN description, but each derivative must be described using only a single system.

i. 46,XX,inv(9)(p23q22),der(11)(11pter→11q12::5q11.2→5q23::8q24.1→8qter)A female karyotype with a pericentric inversion of chromosome 9 written with the short system (karyotype format) and a derivative 11 written with the detailed system (karyotype format). The abnormal chromosome 11 has resulted from a complex translocation involving chromosomes 5, 8 and 11, t(5;8;11;5)(q23;q24.1;q12;q11.2)

5.4.2.1 Short System (Karyotype Format) for Designating Structural Chromosome Abnormalities

a. In the short system (karyotype format), structural abnormalities are defined by their breakpoints. The breakpoints are specified within **parentheses** (**()**) immediately following the abbreviation of the type of rearrangement and the chromosome(s) involved. The breakpoints are identified by band designations and are listed in the same order as the chromosomes.
b. Arrows are not used in the short system (karyotype format).
c. For very complex abnormalities, the short system (karyotype format) may lack clarity compared to the detailed system (karyotype format), although the short system (karyotype format) will provide information on all breakpoints involved in the generation of an abnormal chromosome.

5.4.2.2 Detailed System (Karyotype Format) for Designating Structural Chromosome Abnormalities

a. Structurally altered chromosomes are defined by their band composition. The conventions used in the short system (karyotype format) are maintained in the detailed system (karyotype format), except in the detailed system (karyotype format) the

description of the band composition of the rearranged chromosome(s) is specified in the **parentheses** (**()**) with the breakpoints.

b. In the detailed system (karyotype format) the ISCN description starts at the end of the short arm and proceeds to the end of the long arm (**pter** to **qter**), with the bands being identified in the order in which they occur in the rearranged chromosome.

- The aberrations are listed according to the breakpoints of the rearranged chromosome from **pter** to **qter** and not separated by a **comma** (**,**).
- If the rearrangement is confined to a single chromosome, the chromosome number is not repeated in the band description.
- The terminal end of a single chromosome arm may be designated using the abbreviation **ter** preceded by the arm designation, *i.e.*, **qter** and **pter**
- If more than one chromosome is involved, the bands and/or terminal ends are identified with the appropriate chromosome numbers (see Section 4.4.4).
- If the abnormality involves different chromosomes, then the chromosome number precedes **pter** or **qter**, *i.e.*, 3pter and 7qter
- When the breakpoint of the chromosome(s) is not at the terminal end then the chromosome band designation should be used.

c. A **single colon** (**:**) is used to indicate a chromosome *break* and a **double colon** (**::**) to indicate *break* and *reunion*. To avoid an unwieldy description, an **arrow** (→ or –>), meaning *from – to*, is employed. The end of a chromosome arm may be designated either by its band designation or by **terminal** (**ter**), preceded by the arm designation, *i.e.*, **pter** indicates the end of the short arm and **qter** the end of the long arm. When it is necessary to indicate the **centromere**, the abbreviation **cen** can be used.

d. A **derivative** chromosome (**der**) is described according to the number and orientation of the chromosome providing the centromere.

e. The description of a derivative chromosome begins at the end of the chromosome replacing the short arm of the original chromosome, even if the translocated segment is from a long arm or a chromosome with a higher or lower chromosome number.

i. 46,XY,der(5)(qter→q13::q10→q13::p15→p13)[20]The karyotype of a neoplastic sample with a structurally altered chromosome 5 in 20 metaphases in a male. There is a deletion of 5pter to 5p15 and of 5p13 to 5p10 (5q10 is present). **Note:** the orientation of the derivative chromosome 5 is determined by the segment 5q10 to 5q13 because it contains the centromere. The ISCN description begins at 5qter because the segment 5qter to 5q13 replaces the chromosome 5 short arm.

ii. 46,XX,der(8)(10qter→10q11.2::7q11.2→7q32::8p21→8q22::3p12→3pter)The karyotype shows a derivative chromosome 8 in a female. The derivative chromosome consists of part of chromosomes 10, 7, 8 and 3. The derivative 8 is described from **pter** to **qter** and is composed of 10qter to 10q11.2; a chromosome 7 segment from 7q11.2 to 7q32; a segment of chromosome 8 involving 8p21 to 8q22 including the centromere, and a chromosome 3 segment from 3p12 to 3pter. **Note:** the orientation of the derivative chromosome 8 is determined by the segment 8p21 to 8q22 that contains the centromere. The ISCN description begins at 10qter to 10q11.2 because this is the most distal part of the material replacing the chromosome 8 short arm.

f. Unbalanced segregation rearrangements will lead to at least one derivative chromosome, and in these situations the use of the abbreviation **der** to describe the derivative

chromosome is recommended. It will usually not be possible to adequately describe all the complex rearrangements in the short system. The detailed system (karyotype format) can be used to describe any abnormality. However, the karyotype must be described in words to ensure complete clarity.

5.4.3 Derivative and Recombinant Chromosomes

a. **Derivative** (**der**) and **recombinant** (**rec**) chromosomes are structurally rearranged chromosomes that result from different mechanisms.

5.4.3.1 Derivative Chromosomes

a. A **derivative chromosome (der)** is a structurally rearranged chromosome generated by a *de novo* mechanism or by *meiotic* malsegregation of an inherited balanced anomaly. It is characterized by:
- more than one rearrangement within a single chromosome, *e.g.*, an inversion and a deletion of the same chromosome, or deletions in both arms of a single chromosome, or
- rearrangements involving two or more chromosomes, *e.g.*, the unbalanced product(s) of a translocation, or
- an undetermined mechanism.

b. The term **derivative chromosome** (**der**) refers to the chromosome(s) that has an intact centromere or neocentromere (for examples see Sections 5.5.3 and 5.5.13).

c. In the short system (karyotype format), the **derivative chromosome** is specified in **parentheses** (**()**) followed by the aberrations involved in the generation of the derivative chromosome. These are listed according to the breakpoints of the derivative chromosome from **pter** and **qter** and not separated by a **comma** (**,**).

d. An abnormal chromosome, in which no part can be identified, is referred to as a **marker** chromosome (**mar**) (see Section 5.5.12).

e. In the detailed system (karyotype format), the abbreviations designating the abnormalities are omitted and only the band composition of the derivative chromosome is specified.

As an illustration of how the derivative chromosomes can be written, a balanced reciprocal translocation between chromosomes 2 and 5, 46,XX,t(2;5)(q21;q31) is represented by the pachytene diagram in Figure 5. The derivative chromosomes from this translocation are designated der(2) and der(5). Table 5 gives the possible unbalanced gametes resulting from adjacent-1 and adjacent-2 segregation. The table also shows four of the 12 possible 3:1 segregation products together with the designations of the karyotypes resulting from the fertilization between each unbalanced gametic type and a normal gamete. The karyotype designation needs to be written in full only once in the ISCN description after that it may be described without the breakpoints. A suggested abbreviation for the first designated karyotype in Table 5 is 46,XX,der(5)t(2;5)dmat

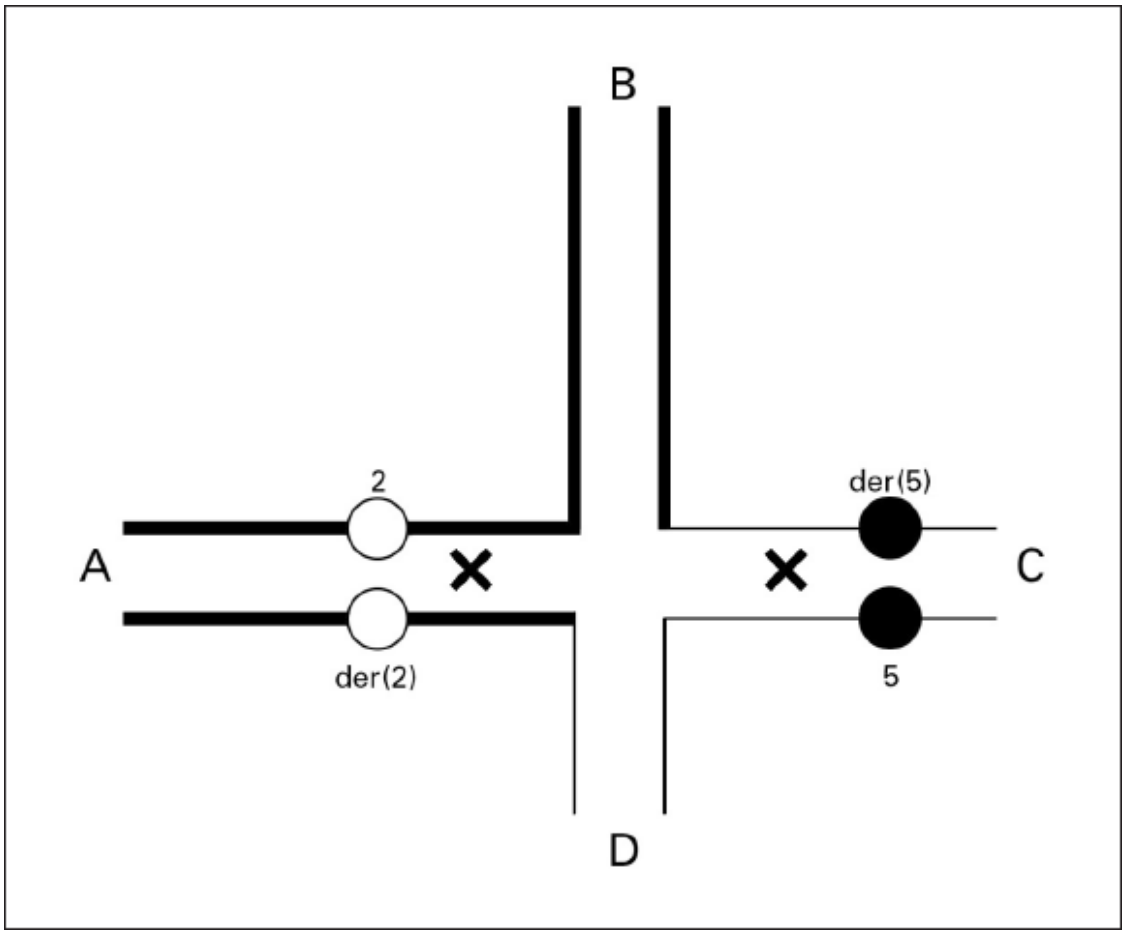


Fig 5. *Pachytene diagram of a t(2;5)(q21;q31) reciprocal translocation heterozygote used to specify the disjunctional possibilities and derivative chromosome combinations given in Table 5. Letters A, B, C, and D designate chromosome ends (telomeres). For the sake of simplicity only those two of the four chromatids that are involved in crossing-over (see Table 5) are indicated. Crosses mark the positions of crossing-over.*

Table 5. Possible unbalanced gametes derived from segregation of a balanced reciprocal translocation of maternal origin. The pachytene configuration is given in Figure 6.

Segregation pattern	Schematic segregants	Chromosomal complement of gametes	Karyotype of potential female zygotes
Adjacent-1	AB CB	2, der(5)	46,XX,der(5)t(2;5)(q21;q31)dmat
	AD CD	der(2), 5	46,XX,der(2)t(2;5)(q21;q31)dmat
Adjacent-2[a]	AB AD	2, der(2)	46,XX,+der(2)t(2;5)(q21;q31)dmat,–5
	CD CB	5, der(5)	46,XX,–2,+der(5)t(2;5)(q21;q31)dmat
	AB AB	2, 2	46,XX,+2,–5
	AD AD	der(2), der(2)	46,XX,der(2)t(2;5)(q21;q31)dmat,+der(2)t(2;5),–5
	CB CB	der(5), der(5)	46,XX,–2,der(5)t(2;5)(q21;q31)dmat,+der(5)t(2;5)
	CD CD	5, 5	46,XX,–2,+5
3:1[b]	AB CD CB	2, 5, der(5)	47,XX,+der(5)t(2;5)(q21;q31)dmat
	AD	der(2)	45,XX,der(2)t(2;5)(q21;q31)dmat,–5
	AD CD CB	der(2), 5, der(5)	47,XX,t(2;5)(q21;q31)mat,+5
	AB	2	45,XX,–5
	AB AD CD	2, der(2), 5	47,XX,+der(2)t(2;5)(q21;q31)dmat
	CB	der(5)	45,XX,–2,der(5)t(2;5)(q21;q31)dmat
	AB AD CB	2, der(2), der(5)	47,XX,+2,t(2;5)(q21;q31)mat
	CD	5	45,XX,–2

[a] Adjacent-2 disjunction minimally results in the first two unbalanced gametic types shown (AB AD, CD CB). Crossing-over in the interstitial segments between centromeres and points of exchange is necessary for the origin of the remaining four types.

[b] A further eight segregants can occur if there is crossing-over in the interstitial segments, making a total of 12 types of gametes with three chromosomes derived from the translocation quadrivalent.

5.4.3.2. Recombinant Chromosomes

a. A **recombinant chromosome (rec)** is a structurally rearranged chromosome with a new segmental composition resulting from *meiotic* crossing-over between a displaced segment and its normally located counterpart in certain types of structural heterozygotes, *e.g.*, inversion or insertion heterozygotes.
b. **rec** is inferred from the parental karyotype and is not to be used in the description of acquired chromosome abnormalities nor those resulting from malsegregation.
c. In a **recombinant chromosome (rec)** there is a duplication and deletion of material. In the ISCN description the **duplication** (**dup**) is explicitly stated, and the deletion is inferred. See Figure 6 for a diagrammatic representation of a parental pericentric **inversion** (**inv**) of chromosome 2, 46,XX,inv(2)(p21q31)
d. The aberrations following the abbreviation **rec** are not separated by a **comma** (**,**):

i. 46,XX,rec(2)dup(2p)inv(2)(p21q31)dmatKaryotype describes the recombinant chromosome 2 with a duplication from 2pter to 2p21 and a deletion from 2q31 to 2qter.

ii. 46,XX,rec(2)dup(2q)inv(2)(p21q31)dmatKaryotype describes the recombinant chromosome 2 with a duplication from 2q31 to 2qter and a deletion from 2pter to 2p21.

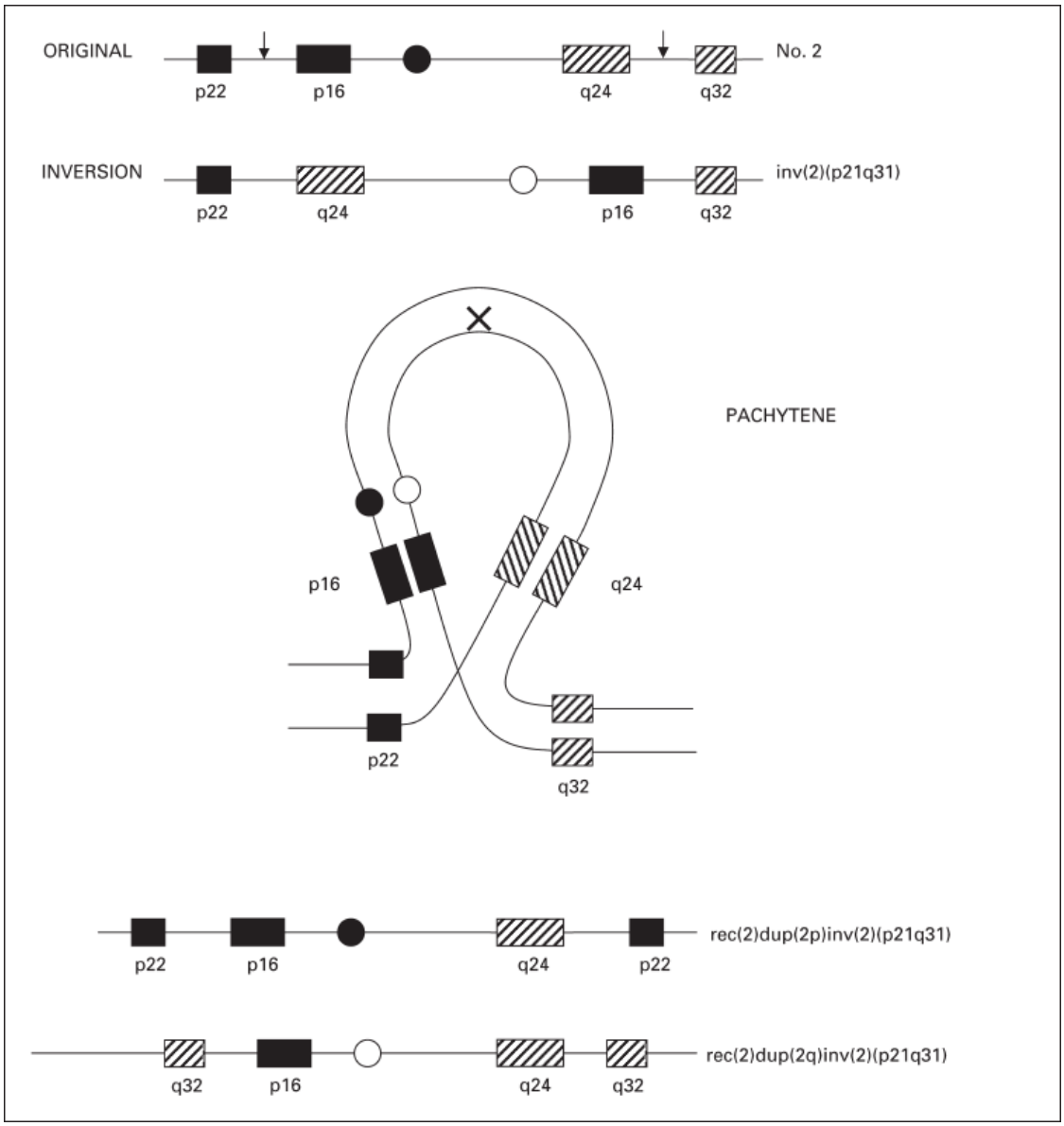


Figure 6. *Diagram of an inv(2)(p21q31)mat pericentric inversion heterozygote. Bands delimiting the breakpoints (arrows on original) are shown as black boxes on the short arm and as hatched boxes on the long arm. In the pachytene diagram, the cross indicates crossing-over within the inversion loop. For the sake of simplicity only those two of the four chromatids that are involved in crossing-over and give rise to the recombinant chromosomes are indicated.*

5.5 Specification of Structural Rearrangements

The types of structural rearrangements are listed below in alphabetical order and examples of constitutional and neoplastic structural rearrangement are given. The short system (karyotype format) is provided first, and when appropriate, an alternative detailed system (karyotype format) description is also provided.

5.5.1 Additional Material of Unknown Origin

a. The abbreviation **add** is used to indicate additional material of unknown origin that replaces the terminal segment of the chromosome. The abbreviation is recommended where the mechanism and origin of the segment cannot be ascertained.

b. Depending on the size of the additional material of unknown origin, it may result in no change, or an increase or a decrease in the length of the chromosome. Designations such as 1p+ or 1p– may be used in the text to describe such abnormal chromosomes but is not used in the ISCN description (see Section 5.1).

i. 46,XX,add(19)(p13.3)
or
46,XX,add(19)(?::p13.3→qter)Karyotype shows additional material attached to band 19p13.3 and replacing 19pter to 19p13.3, but neither the origin of the extra segment nor the type of rearrangement is known.

ii. 46,XY,add(12)(q13)
or
46,XY,add(12)(pter→q13::?)Karyotype shows additional material of unknown origin replacing the segment 12q13 to 12qter

c. When additional material of unknown origin is attached to both arms of a chromosome and/or replaces more than one segment in a chromosome, the abbreviation **der** is used (see Section 5.5.3).

i. 46,XX,der(5)add(5)(p15.3)add(5)(q23)
or
46,XX,der(5)(?::p15.3→q23::?)Karyotype shows additional material of unknown origin attached at band 5p15.3 in the short arm and replacing the segment 5p15.3 to 5pter. There is also additional material at band 5q23 that replaces the segment 5q23 to 5qter in the long arm.

d. The abbreviation, **add**, applies only to the terminal addition of unknown material and its use is not appropriate for insertions. The abbreviation **ins** is used to describe unknown material *inserted* into a chromosome arm and the **question mark** (**?**) is used to describe the unknown segment (see Section 5.5.9).

i. 46,XX,der(5)ins(5;?)(q13;?)
or
46,XX,der(5)(pter→q13::?::q13→qter)Karyotype shows insertion of material of

unknown origin into the long arm of chromosome 5 at band 5q13. For this example **der** is used as the abbreviation **add** would imply that the unknown material has replaced 5q13 to 5qter

5.5.2 Deletions

a. The abbreviation **del** is used to denote both **terminal** and **interstitial deletions**. A deletion is a loss of a chromosome segment, the extent of which is apparent from the description of the breakpoints. **Note:** designations such as 5q– or del(5q), that may be useful abbreviations in the text, must not be used in the ISCN description (see Section 5.1).

b. With an interstitial deletion where the two breaks occur within the same arm, the breakpoints are specified from **pter** to **qter**. Terminal deletions are reported using a single breakpoint.

i. 46,XX,del(5)(q13)
or
46,XX,del(5)(pter→q13:)Karyotype shows a terminal deletion with a **break** (**:**) in band 5q13. The remaining chromosome consists of the entire short arm of chromosome 5 and the part of the long arm between the centromere and band 5q13. **Note:** the number of metaphases must be given if this is a neoplastic sample.

ii. 46,XX,del(4)(p15.2)
or
46,XX,del(4)(:p15.2→qter)Karyotype shows a terminal deletion with a **break** (**:**) in band 4p15.2. The remaining chromosome consists of the part of the short arm of chromosome 4 between band 4p15.2 to the centromere, and then to the end of the entire long arm.

iii. 46,XX,del(5)(q13q33)[20]
or
46,XX,del(5)(pter→q13::q33→qter)[20]Karyotype of a neoplastic sample with an interstitial deletion of chromosome 5 involving the segment 5q13 to 5q33. The detailed system (karyotype format) shows **breakage and reunion** (**::**) of 5q13 and 5q33.

iv. 46,XX,del(5)(q13q13)
or
46,XX,del(5)(pter→q13::q13→qter)Karyotype shows an interstitial deletion of a small segment within band 5q13, *i.e.*, both breakpoints are in band 5q13.

v. 46,XY,del(5)(q?)[20]Karyotype shows deletion of the long arm of chromosome 5 in a neoplastic sample, but it is unclear whether it is a terminal or an interstitial deletion, and the breakpoints are unknown.

vi. 46,Y,del(X)(p21p11.4)Karyotype shows interstitial deletion of the segment between bands Xp21 and Xp11.4.

vii. 46,XY,del(20)(q11.2–13.1q13.3)Karyotype at 300 band resolution shows an interstitial deletion with the proximal breakpoint in band 20q11.2–13.1 and distal breakpoint at 20q13.3. **Note:** metaphase numbers are given if this is a neoplastic sample.

c. Multiple deletions of the same chromosome are expressed using the abbreviation **der** (see Section 5.5.3).

5.5.3 Derivative Chromosomes

a. A **derivative** chromosome (**der**) is a structurally rearranged chromosome generated either by a rearrangement involving two or more chromosomes or by multiple aberrations within a single chromosome. The abbreviation always refers to chromosome(s) with the intact centromere.
b. A derivative chromosome generated by **more than one rearrangement within a chromosome** is specified in **parentheses** (**()**), followed by the ISCN description of the abnormality. The rearrangements are given according to the breakpoints of the derivative chromosome from **pter** to **qter**.
c. The detailed system (karyotype format) is more informative in the following examples.

i. 46,XY,der(9)del(9)(p12)del(9)(q31)
or
46,XY,der(9)(:p12→q31:)Karyotype shows a derivative chromosome 9 resulting from terminal deletions in both the short and long arms with breakpoints in bands 9p12 and 9q31.

ii. 46,XY,der(9)inv(9)(p23p13)del(9)(q22q33)
or
46,XY,der(9)(pter→p23::p13→p23::p13→q22::q33→qter)Karyotype shows a derivative chromosome 9 resulting from an inversion in the short arm with breakpoints in 9p23 and 9p13, and an interstitial deletion of the long arm with breakpoints in 9q22 and 9q33.

d. A derivative chromosome resulting from **one rearrangement** involving **two or more chromosomes** is specified in **parentheses** (**()**), followed by the description of the abnormality.

i. 46,Y,der(X)t(X;8)(p22.3;q24.1)
or
46,Y,der(X)(8qter→8q24.1::Xp22.3→Xqter)A male karyotype with a derivative X chromosome from a translocation between Xp22.3 and 8q24.1. **Note:** the normal sex chromosome, in this example the Y chromosome, is listed first.

ii. 46,XX,der(1)t(1;3)(p22;q13.1)
or
46,XX,der(1)(3qter→3q13.1::1p22→1qter)Karyotype shows a derivative chromosome 1 from a translocation of the chromosome 3 segment 3q13.1 to 3qter to the short arm of chromosome 1 at band 1p22. This results in an unbalanced karyotype with loss of the segment 1pter to 1p22 and gain of 3q13.1 to 3qter. The der(1) replaces a normal chromosome 1 and there is no need to indicate the missing chromosome (see Section 5.4.1). There are two normal chromosomes 3.

iii. 45,XY,der(1)t(1;3)(p22;q13.1),–3The derivative chromosome 1 (same as above) replaces a normal chromosome 1, but there is only one normal chromosome 3, hence –3 is given in the ISCN description. The der(3) resulting from the t(1;3) is presumed to be lost, but this assumption is not stated in the karyotype.

iv. 47,XY,+der(4)t(4;11)(q21;q23),t(4;11)[10]Karyotype of a neoplastic sample shows a balanced translocation between the long arms of chromosomes 4 and 11. There is an additional copy of the derivative chromosome 4 from this translocation. The additional derivative chromosome 4 is listed before the translocation following the chromosome order rule (see Section 4.3). **Note:** the breakpoints do not need to be repeated because the chromosome abnormalities are generated by the same rearrangement (see Sections 4.2.1, 5.1 and 5.6).

v. 46,XY,der(3)ins(16;3)(p12;p21p13)dmatKaryotype shows a derivative 3 from a balanced maternal insertion of bands 3p21p13 into chromosome 16 at band 16p12. There is one normal chromosome 3. The net imbalance in the proband is a loss of region 3p21p13. **Note**: correlation and interpretation of the clinical history must be made and the ISCN description written in accordance with known parental rearrangements. Therefore, 46,XY,del(3)(p21p13)dmat should not be used.

e. The term **Philadelphia chromosome** is a historical description of the derivative chromosome 22 generated by the translocation t(9;22)(q34;q11.2). The abbreviation **Ph** (formerly Ph^1) may be used in text, but not in the ISCN description, where der(22)t(9;22)(q34;q11.2) must be given. Similarly, the derivative chromosome 9 resulting from the t(9;22) is designated der(9)t(9;22)(q34;q11.2).

f. **A derivative chromosome generated by more than one rearrangement** involving **two or more chromosomes** is specified in **parentheses** (**()**), followed by all aberrations involved in the generation of the derivative chromosome. The aberrations are listed from **pter** to **qter** of the derivative chromosome according to the rules governing the order of chromosome anomalies (see Section 4.3) and are not separated by **commas** (**,**).

i. 46,XX,der(1)t(1;3)(p32;q21)t(1;11)(q25;q13)
or
46,XX,der(1)(3qter→3q21::1p32→1q25::11q13→11qter)Karyotype shows a derivative chromosome 1 generated by two unbalanced translocations. One unbalanced translocation between chromosome 1 at 1p32 and chromosome 3 at 3q21, and a second unbalanced translocation between the same chromosome 1 at 1q25 and chromosome 11 at 11q13.

ii. 46,XY,der(1)t(1;3)(p32;q21)t(3;7)(q28;q11.2)
or
46,XY,der(1)(7qter→7q11.2::3q28→3q21::1p32→1qter)Karyotype shows a derivative chromosome 1 resulting from an unbalanced translocation between chromosome 1 at 1p32 and chromosome 3 at 3q21, and an unbalanced translocation between chromosome 3 at 3q28 and chromosome 7 at 7q11.2. The detailed system (karyotype format) describes the derivative chromosome 1 from 7qter to 1qter as the aberrations are listed from **pter** to **qter,** according to the orientation of the segment that contains the centromere (see Sections 4.3 and 5.4.2.2).

iii. 46,XY,der(1)t(1;3)(p32;q21)dup(1)(q25q42)
or

46,XY,der(1)(3qter→3q21::1p32→1q42::1q25→1qter)Karyotype shows a derivative chromosome 1 resulting from an unbalanced translocation between chromosome 1 at 1p32 and chromosome 3 at 3q21; there is also duplication of the chromosome 1 long arm segment from 1q25 to 1q42.

iv. 46,XY,der(9)del(9)(p12)t(9;13)(q34;q11)
or
46,XY,der(9)(:9p12→9q34::13q11→13qter)Karyotype shows a derivative chromosome 9 generated by a terminal short arm deletion with the breakpoint at 9p12, and by an unbalanced translocation with chromosome 13 at 13q11 and the long arm of the same chromosome 9 at 9q34.

v. 46,XX,der(1)t(1;11)(p32;q13)t(1;3)(q25;q21)
or
46,XX,der(1)(11qter→11q13::1p32→1q25::3q21→3qter)Karyotype shows a derivative chromosome 1 generated by two unbalanced translocations. One unbalanced translocation between chromosome 1 at 1p32 and chromosome 11 at 11q13, and a second unbalanced translocation between the same chromosome 1 at 1q25 and chromosome 3 at 3q21. **Note:** the detailed system (karyotype format) describes the derivative chromosome 1 from 11qter to 3qter as the aberrations are listed according to the orientation of the segment that contains the centromere, from **pter** to **qter** (see Sections 4.3 and 5.4.2.2).

vi. 47,XY,+der(8)r(8;17;1)(p23q13;q12q25;p36.3p32)
or
47,XY,+der(8)(::8p23→8q13::17q12→17q25::1p36.3→1p32::)Karyotype shows a supernumerary ring chromosome determined to be a derivative chromosome 8 as it has the chromosome 8 centromere. The ring is generated by breakage and joining of the chromosome 1 segment from 1p36.3 to 1p32 to the chromosome 8 segment from 8p23 to 8q13 that is then joined to the chromosome 17 segment from 17q12 to 17q25. For additional examples of ring chromosomes, see Section 5.5.16. **Note:** for ring chromosomes, the chromosome that provides the centromere is listed first (see Section 5.5.16.2).

vii. 46,XX,der(1)del(1)(p34p22)ins(1;17)(p34;q25q11.2)
or
46,XX,der(1)(1pter→1p34::17q25→17q11.2::1p22→1qter)Karyotype shows a derivative chromosome 1 resulting from insertion of chromosome 17 from 17q25 to 17q11.2 between chromosome 1 bands 1p34 and 1p22. There is a deletion of 1p34 to 1p22. In such situations, when there are two breakpoints in the recipient chromosome, the breakpoint closest to **pter** is listed as the point of insertion. The orientation of the inserted segment relative to **pter** and **qter** of the derivative chromosome is reversed in its new position.

viii. 46,XY,der(7)ins(7;?)(q22;?)t(2;7)(q21;q22)
or
46,XY,der(7)(7pter→7q22::?::2q21→2qter)Karyotype shows a derivative chromosome 7 in which material of unknown origin has replaced the segment 7q22 to 7qter, and the segment 2q21 to 2qter from the long arm of chromosome 2 is attached to unidentified chromosomal material. The breakpoint in the derivative chromosome is specified as the point of insertion of the unknown material. **Note:** as the breakpoint on the chromosome

7 is the same, 7q22, for the insertion and the translocation, the abnormalities are given in alphabetical order, *i.e.*, **ins** before **t** (see Section 5.1).

ix. 47,XX,t(6;9;22)(p21;q34;q11.2),+der(22)t(6;9;22)[15]Karyotype of a neoplastic sample shows a three-way translocation between chromosomes 6, 9, and 22 with an additional derivative chromosome 22 from this three-way translocation (see Section 4.2.1). The derivative chromosome refers to the rearrangement from which it is derived, in this example it is t(6;9;22). **Note**: the derivative 22 is **not** described as a der(22)t(9;22) as this would imply there is a second **different** translocation.

x. 46,XX,der(8)t(8;17)(p23;q21)inv(8)(p22q13)t(8;22)(q22;q12)
or
46,XX,der(8)(17qter→17q21::8p23→8p22::8q13→8p22::8q13→8q22::22q12→22qter)A female karyotype with a derivative chromosome 8 resulting from two translocations and a pericentric inversion. One translocation involves the short arm of chromosome 8 with a breakpoint at 8p23 and the long arm of chromosome 17 at 17q21. The other translocation involves the long arm of chromosome 8 with a breakpoint at 8q22 and the long arm of chromosome 22 at 22q12. The pericentric inversion has breakpoints at 8p22 and 8q13. As the derivative 8 has no 8p telomere to follow the **pter** to **qter** description rule, the **pter** region of the derivative chromosome replacing the normal 8p is described first. In this example, the normal 8pter region is replaced by the 17qter region due to the t(8;17) translocation.

xi. 46,XY,der(5)t(5;11)(p10;p10)t(5;8)(q31;q23),der(8)t(5;8),der(11)t(5;11)
or
46,XY,der(5)(11pter→11p10::5p10→5q31::8q23→8qter),der(8)(8pter→8q23::5q31→5qter),der(11)(5pter→5p10::11p10→11qter)Karyotype with two different balanced translocations involving the same chromosome 5 homologue: a whole-arm translocation between the short arms of chromosomes 5 and 11 and one translocation between the long arms of the same chromosome 5 and chromosome 8. **Note:** the abnormal chromosome 5 is involved in two rearrangements, therefore it is designated as a derivative chromosome. The other derivative chromosomes (der(8) and der(11)) are also included in the ISCN description as the rearrangement is balanced.

g. An **isoderivative chromosome**, abbreviated to **ider**, designates an isochromosome formation for one of the arms of a derivative chromosome. The breakpoints are assigned to the centromeric bands p10 and q10 according to the morphology of the isoderivative chromosome (see Section 5.5.11).

i. 46,XX,ider(22)(q10)t(9;22)(q34;q11.2)[20]
or
46,XX,ider(22)(9qter→9q34::22q11.2→22q10::22q10→22q11.2::9q34→9qter)[20]Karyotype of a neoplastic sample shows an isochromosome for the long arm of the derivative chromosome 22 from a t(9;22).

ii. 46,XY,ider(9)(p10)ins(9;12)(p13;q22q13)[12]
or
46,XY,ider(9)(9pter→9p13::12q22→12q13::9p13→9p10::9p10→9p13::12q13→12q22::9p13→9pter)[12]Karyotype of a neoplastic sample shows an isochromosome for the short arm of a derivative chromosome 9 resulting from an insertion of the segment 12q13 to 12q22 at band 9p13. Band 12q22 is closer than band 12q13 to 9pter

h. When a derivative chromosome is **dicentric** and contains one or more additional abnormalities, the two centromere containing chromosomes are given within **parentheses** (**()**), separated by a **semicolon** (**;**), followed by the specification of the aberrations.

i. 45,XX,der(5;7)t(5;7)(q22;p13)t(3;7)(q21;q21)
or
45,XX,der(5;7)(5pter→5q22::7p13→7q21::3q21→3qter)Karyotype shows a dicentric derivative chromosome with centromeres from chromosomes 5 and 7. Breakage and reunion occurs at band 5q22 in the long arm of chromosome 5 and at band 7p13 in the short arm of chromosome 7. In addition, the segment 3q21 to 3qter is translocated onto the long arm of chromosome 7 at band 7q21. **Note**: in the detailed system (karyotype format) the terminal end of a chromosome arm may be designated using the abbreviation **ter** preceded by the arm designation, *i.e.*, 3qter instead of 3q29 in this example (see also example ii below).

ii. 45,XY,der(5;7)t(3;5)(q21;q22)t(3;7)(q29;p13)
or
45,XY,der(5;7)(5pter→5q22::3q21→3q29::7p13→7qter)Karyotype shows a dicentric derivative chromosome with centromeres of chromosomes 5 and 7. An acentric chromosome 3 segment (3q21→3q29) is inserted between the long arm of chromosome 5 and the short arm of chromosome 7. **Note**: when the terminal band of a chromosome is involved in a breakpoint and the end of that chromosome is not the end of the derivative chromosome, then the band designation should be used, *e.g.,* 3q29 in this example.

iii. 45,XY,der(5;7)t(3;5)(q21;q22)t(3;7)(q29;p13)del(7)(q32)
or
45,XY,der(5;7)(5pter→5q22::3q21→3q29::7p13→7q32:)The same dicentric derivative chromosome as in the previous example but with an additional terminal deletion of the long arm of chromosome 7 at band 7q32.

iv. 45,XX,der(8;8)(q10;q10)del(8)(q22)t(8;9)(q24.1;q12)
or
45,XX,der(8;8)(:8q22→8q10::8q10→8q24.1::9q12→9qter)Karyotype with a derivative chromosome composed of the long arms of chromosome 8 with material from chromosome 9 translocated to one arm of chromosome 8 at 8q24.1. There is a deletion at 8q22 to 8qter in the other long arm. There are two normal chromosomes 9.

i. When the centromere of the derivative chromosome is not known, but more distal parts of the chromosome can be recognized, the abnormal chromosome may be designated **der(?)** (see Section 4.2.1). Where the chromosome containing the centromere is known then that chromosome is described first (see example iv).

i. 47,XY,+der(?)t(?;9)(?;q22)
or
47,XY,+der(?)(?→cen→?::9q22→9qter)Karyotype shows translocation of 9q22 to 9qter onto a derivative chromosome of unknown origin that has the centromere.

ii. 47,XX,+der(?)t(?;9)(?;p13)ins(?;7)(?;q11.2q32)[20]
or
47,XX,+der(?)(9pter→9p13::?→cen→?::7q11.2→7q32::?)[20]Karyotype of a neoplastic sample shows a derivative chromosome of unknown origin. The segment of

chromosome 9 distal to band 9p13 translocated onto a centric segment of unknown origin, and 7q11.2 to 7q32 is translocated onto the other end of this centric segment. There is also additional material of unknown origin joined to 7q32 on the derivative chromosome.

iii. 47,XX,+der(?)t(?;9)(?;p13)hsr(?)[20]
or
47,XX,+der(?)(9pter→9p13::?→cen→?::hsr→?)[20]Karyotype of a neoplastic sample shows a derivative chromosome of unknown origin. The segment of chromosome 9 distal to band 9p13 translocated onto a centric segment of unknown origin and a **homogeneously staining region** (**hsr**) is present on the other end of the centric segment.

iv. 47,XY,+der(8)ins(8;?)(p22;?)t(8;9)(q24;q22)[10]
or
47,XY,+der(8)(8pter→8p22::?::8p22→8q24::9q22→9qter)[10]Karyotype in a neoplastic sample shows a derivative chromosome 8 with an insertion of unknown material in 8p22 and an unbalanced translocation between chromosome 8 at 8q24 and chromosome 9 at 9q22. The chromosome 8 segment (8p22 to 8q24) has the centromere.

j. Derivative chromosomes whose centromeres are unknown should be placed after all identified abnormalities but before unidentified **ring chromosomes** (**r**), **marker chromosomes** (**mar**) and **double minutes** (**dmin**) (see Section 4.3), *e.g.,* 50,XX,+X,+der(?)t(?;9)(?;q22),+r,+mar,>20dmin[20]

k. There is usually no need to indicate which homologue is involved in a derivative chromosome because this will be apparent from the karyotype description. If both homologues are involved, this will result in two derivative homologous chromosomes.

l. When homologous chromosomes cannot be distinguished within the ISCN description, one of the numerals may be **underlined** (_). This may be helpful when the two homologous chromosomes are involved in identical aberrations resulting in two identical derivative chromosomes (see Section 4.4.2).

i. 46,XX,der(9)del(9)(p12)t(9;22)(q34;q11.2),der(9)t(9;12)(p13;q22)inv(9)(q13q22)[20]
or
46,XX,der(9)del(9)(p12)t(9;22)(q34;q11.2),der(9)t(9;12)(p13;q22)inv(9)(q13q22)[20]
Karyotype of a neoplastic sample shows two derivative chromosomes 9. One der(9) has a terminal deletion of the short arm and a translocation with chromosome 22 involving 9q34 and 22q11.2. The other der(9) has a translocation between 9p13 and 12q22, and a paracentric inversion in the long arm of chromosome 9. There are two normal chromosomes 12, two normal chromosomes 22, but no normal chromosome 9.

ii. 46,XX,der(1)t(1;3)(p34.3;q21),der(1)t(1;3)(p34.3;q21)[15]Karyotype of a neoplastic sample shows two homologous chromosomes 1, as identified by C-band polymorphism, are involved in apparently identical translocations.

iii. 46,XX,der(1)t(1;3)(p34.3;q21)[20]/46,XX,der(1)t(1;3)(p34.3;q21)[10]Karyotype of a neoplastic sample shows the two chromosome 1 homologues involved in apparently identical translocations in different metaphases. The two abnormalities represent two different cell lines; the homologous chromosomes 1 in each cell line are normal. The two homologous chromosomes 1 are identified as being different by C-banding.

iv. 46,XX,der(1)t(1;1)(p31;q32)In this unbalanced translocation between both chromosome 1 homologues, underlining can be used to distinguish between the two

different derivatives. The detailed system (karyotype format) is recommended for a clearer description of the rearrangement (see examples iv and v below that clarify the two different derivatives from the balanced translocation where the homologue without the centromere is underlined).

v. 46,XX,der(1)t(1;1)(p31;q32)
or
46,XX,der(1)(1pter→1q32::1p31→1pter)Same translocation as above in which the underlined homologue has a break at 1q32. In this example the der(1) is not underlined. The underlined homologue does not have the centromeric segment, *i.e.,* has the breakpoint at 1p31. **Note:** the chromosome number is given in the detailed system (karyotype format) to show that both homologues are involved.

vi. 46,XX,der(1)t(1;1)(p31;q32)
or
46,XX,der(1)(1qter→1q32::1p31→1qter)The derivative chromosome 1 is not underlined in this example and represents the homologue with a breakpoint in 1p31. The underlined homologue does not have the centromeric segment, *i.e.,* has the breakpoint at 1q32. **Note:** the chromosome number is given in the detailed system (karyotype format) to show that both homologues are involved.

m. Complex rearrangements may give rise to several derivative chromosomes. The breakpoints in the derivative chromosomes generated by the *same* rearrangement need not be repeated in the description of each individual derivative chromosome.

i. 47,XX,t(9;22)(q34;q11.2),+der(22)t(9;22)[10]Karyotype of a neoplastic sample shows t(9;22) and an additional Ph chromosome. The breakpoints in the extra der(22) do not need to be repeated.

ii. 46,XX,der(1)t(1;3)(p32;q21)inv(1)(p22q21)t(1;11)(q25;q13),der(3)t(1;3),der(11)t(1;11)Karyotype shows a balanced complex rearrangement with three derivative chromosomes. The breakpoints of the t(1;3) and the t(1;11), that both contribute to the der(1), are not repeated in the description of der(3) and der(11).

iii. 47,XY,der(9)t(9;22)(q34;q11.2),+22,ider(22)(q10)t(9;22)[20]
or
47,XY,der(9)(9pter→9q34::22q11.2→22qter),+22,ider(22)(9qter→9q34::22q11.2→22q10::22q10→22q11.2::9q34→9qter)[20]Karyotype of a neoplastic sample shows a derivative chromosome 9 and an isochromosome for the long arm of the derivative chromosome 22 derived from a t(9;22). There are also two normal copies of chromosome 22, hence the +22 in the ISCN description. **Note:** the breakpoints in the short system (karyotype format) do not need to be repeated for the derivative chromosome 22 as they were given in the description of the t(9;22) (see Section 4.2.1).

n. Complex karyotypes involving rearrangements between two or more derivative chromosomes, or where derivative chromosomes are involved in new rearrangements the detailed system (karyotype format) is preferred. It is acceptable to combine the short system (karyotype format) (see Section 5.4.2.1) and the detailed system (karyotype format) (see Section 5.4.2.2) for designating complex karyotypes.

5.5.4 Dicentric Chromosomes

a. The **dicentric** (**dic**) chromosome replaces two normal chromosomes. A dicentric chromosome is counted as one chromosome, with the chromosome count becoming 45. There is no need to indicate the missing chromosome(s) (*cf.*, whole-arm and Robertsonian translocations, Sections 5.5.18.2 and 5.5.18.3 respectively). Two breakpoints are specified, and the centromeres are presumed to be derived from the two chromosomes involved.
b. **Isodicentric** chromosomes (**idic**), involve a single breakpoint on sister chromatids and a subsequent reunion, and the chromosome count is unchanged as the **idic** chromosome replaces one of the normal homologues.
c. In rearrangements involving different chromosomes, the chromosomes are listed in chromosome order, *i.e.*, the sex chromosomes (X before Y) followed by the autosomes in numerical order.
d. For isodicentrics that derive from a single chromosome, there is no need to repeat the chromosome number in the detailed system (karyotype format) (see Sections 4.4.4 and 5.4.2.2).
e. Where a dicentric or tricentric derivative chromosome has no short arm segment, the description starts at the end of the lowest chromosome number.
f. The term **der** may be used instead of **dic**, but the combination of *der dic* should never be used.

i. 45,XX,dic(13;13)(q14;q32)
or
45,XX,dic(13;13)(13pter→13q14::13q32→13pter)Karyotype shows breakage and reunion at bands 13q14 and 13q32 on the two homologous chromosomes 13 to form a dicentric chromosome. There is no normal chromosome 13. **Note:** the **pter** to **qter** rule applies and the chromosome number is given before **pter** and the breakpoint in the ISCN description as different chromosome 13 homologues are involved.

ii. 45,XX,dic(13;15)(q22;q24)
or
45,XX,dic(13;15)(13pter→13q22::15q24→15pter)Karyotype shows a dicentric chromosome with breakage and reunion at bands 13q22 and 15q24. The missing chromosomes 13 and 15 are not indicated since they are replaced by the dicentric chromosome. The karyotype contains one normal chromosome 13, one normal chromosome 15, and the dic(13;15). The resulting net imbalance of this abnormality is loss of the segments distal to 13q22 and 15q24.

iii. 46,XX,+13,dic(13;15)(q22;q24)Karyotype shows a dicentric chromosome with breakage and reunion at bands 13q22 and 15q24 (same as above example) that replaces one chromosome 13 and one chromosome 15. There are two normal chromosomes 13, one normal chromosome 15 and the dic(13;15). The resulting net imbalance is partial trisomy for the segment 13pter to 13q22 and loss of the segment 15q24 to 15qter.

iv. 45,XY,dic(14;21)(p11.2;p11.2)
or
45,XY,dic(14;21)(14qter→14p11.2::21p11.2→21qter)Karyotype shows a dicentric chromosome with breakage and reunion at bands 14p11.2 and 21p11.2. The missing chromosomes 14 and 21 are not indicated since they are replaced by the dicentric

chromosome. The karyotype contains one normal chromosome 14, one normal chromosome 21, and the dic(14;21). The resulting net imbalance of this abnormality is loss of the segments distal to 14p11.2 and 21p11.2. For description of Robertsonian translocations, see Section 5.5.18.3.

v. 47,XY,+dic(17;?)(q22;?)
or
47,XY,+dic(17;?)(17pter→17q22::?)Karyotype shows a supernumerary dicentric chromosome composed of one chromosome 17 with a break at band 17q22 and an unknown chromosome with an intact centromere.

vi. 46,X,idic(Y)(q12)
or
46,X,idic(Y)(pter→q12::q12→pter)Karyotype shows breakage and reunion at band Yq12 on sister chromatids to form an isodicentric Y chromosome. The resulting net imbalance is loss of the segment Yq12 to Yqter and gain of Ypter to Yq12.

vii. 46,XX,idic(21)(q22.3)
or
46,XX,idic(21)(pter→q22.3::q22.3→pter)Karyotype shows breakage and reunion at band 21q22.3 on sister chromatids to form an isodicentric chromosome 21, and one normal chromosome 21, indicated by the 46 count. Even though there are effectively three copies of the chromosome 21 long arm, the normal chromosome 21 is not designated with a **plus** (+) sign.

viii. 47,XX,+idic(13)(q22)
or
47,XX,+idic(13)(pter→q22::q22→pter)Karyotype shows a supernumerary isodicentric chromosome 13. There are two chromosomes 13 plus the idic(13).

ix. 47,XY,+dic(15;15)(q12;q12)
or
47,XY,+dic(15;15)(15pter→15q12::15q12→15pter)Karyotype shows a supernumerary apparently dicentric chromosome 15. There are two chromosomes 15 and a dicentric chromosome 15. This rearrangement has historically been referred to as inv dup(15)(q12) and usually results from recombination between homologues, hence dic(15;15)(q12;q12)(or **psu dic**, see below) is a more appropriate designation. Where a mechanism based on the fusion between two sister chromatids is proven, the abbreviation **idic** may be used: 47,XY,+idic(15)(q12) or 47,XY,+idic(15)(pter→q12::q12→pter). **Note:** the chromosome number is given before **pter** and the breakpoint in the ISCN description as different chromosome 15 homologues are involved.

g. Complex dicentric chromosomes must be described as derivative chromosomes, see Section 5.5.3.

h. A **pseudodicentric chromosome** is a dicentric structure in which only one centromere is active. Such chromosomes use the abbreviation **psu dic** (similarly, **pseudotricentric**, **psu trc**, *etc*.), and the segment with the presumptively active centromere, based on the morphology in the majority of metaphases, is always written first. If the active centromere cannot be determined, the lowest chromosome number is written first.

i. 45,XX,psu dic(15;13)(q12;q12)
or
45,XX,psu dic(15;13)(15pter→15q12::13q12→13pter)Karyotype shows one chromosome 13 and one chromosome 15 are replaced with a pseudodicentric chromosome. The karyotype contains one normal chromosome 13, one normal chromosome 15, and the psu dic(15;13). The centromere of the chromosome stated first, *i.e.*, chromosome 15, is the active one. **Note**: if the active centromere is not known the ISCN description would be 45,XX,psu dic(13;15)(q12;q12)

ii. 46,XX,psu idic(20)(q11.2)
or
46,XX,psu idic(20)(pter→q11.2::q11.2→pter)Karyotype shows one chromosome 20 is replaced with a pseudoisodicentric chromosome, resulting in three copies of 20pter to 20q11.2. The psu idic(20) has one active centromere.

5.5.5 Duplications

a. **Duplications** (**dup**) are a gain of a chromosome segment at the original chromosome location, *i.e.*, in tandem. When a gain of a chromosome segment is found elsewhere in the genome, **der** or **ins** is used depending on the type of rearrangement. The orientation of the duplicated segment is indicated by the order of the bands from **pter** to **qter**. **Note**: no arrow is used in the short system (karyotype format) to indicate the orientation.

i. 46,XX,dup(1)(p34p31)
or
46,XX,dup(1)(pter→p31::p34→qter)Karyotype shows duplication of the segment between bands 1p34 and 1p31 with no change in orientation.

ii. 46,XX,dup(1)(p31p34)
or
46,XX,dup(1)(pter→p31::p31→p34::p31→qter) or
dup(1)(pter→p34::p31→p34::p34→qter)Karyotype shows duplication of the segment between bands 1p34 and 1p31 with reverse orientation of the duplicated segment. **Note**: only the detailed (karyotype format) will clarify the location of the duplicated segment.

iii. 46,XX,dup(1)(q22q25)
or
46,XX,dup(1)(pter→q25::q22→qter)Karyotype shows duplication of the segment between bands 1q22 and 1q25 with no change in orientation.

iv. 46,XY,dup(1)(q25q22)
or
46,XY,dup(1)(pter→q25::q25→q22::q25→qter) or
dup(1)(pter→q22::q25→q22::q22→qter)Karyotype shows duplication of the segment between bands 1q22 and 1q25 with reverse orientation of the duplicated segment. **Note**: only the detailed system (karyotype format) will clarify the location of the duplicated segment.

5.5.6 Fission

a. The abbreviation **fis** is used to denote **centric fission**.

i. 47,XY,–10,+fis(10)(p10),+fis(10)(q10)
or
47,XY,–10,+fis(10)(pter→p10:),+fis(10)(:q10→qter)Karyotype shows a break in the centromere of chromosome 10 resulting in two derivative chromosomes composed of the short and long arms, respectively. The **breakpoints** (**:**) are assigned to 10p10 and 10q10 according to the morphology of the derivative chromosomes.

5.5.7 Fragile Sites

a. **Fragile sites** (**fra)** may occur as normal variants (see Section 2.6.2), however for those associated with specific diseases and/or phenotypic abnormalities, the following nomenclature is used.

i. 46,X,fra(X)(q27.3)Karyotype shows a fragile site in subband Xq27.3 on one X chromosome in a female.

ii. 46,Y,fra(X)(q27.3)Karyotype shows a fragile site in subband Xq27.3 on the X chromosome in a male.

iii. 45,fra(X)(q27.3)Karyotype shows a fragile site in subband Xq27.3 on the X chromosome in an individual with Turner syndrome.

iv. 47,XY,fra(X)(q27.3)Karyotype shows a fragile site in subband Xq27.3 on one X chromosome in an individual with Klinefelter syndrome.

v. 46,XX,fra(11)(q23)Karyotype shows a fragile site in band 11q23 on one chromosome 11.

5.5.8 Homogeneously Staining Regions

a. The abbreviation **hsr** is used to describe the presence, but not the size, of a **homogeneously staining region** in a chromosome arm, segment, or band.

b. **hsr** are frequently associated with gene amplification in a variety of neoplasms and therefore the numbers of metaphases are given in the ISCN description.

i. 46,XX,hsr(1)(p22)[10]
or
46,XX,hsr(1)(pter→p22::hsr::p22→qter)[10]Karyotype shows a homogeneously staining region in band 1p22 in a neoplastic sample.

ii. 46,XY,hsr(21)(q22)[10]
or
46,XY,hsr(21)(pter→q22::hsr::q22→qter)[10]Karyotype shows a homogeneously staining region in band 21q22 in a neoplastic sample.

c. When a chromosome contains multiple **hsr**(s) or one **hsr** and another structural change, it is by definition a derivative chromosome and should be designated accordingly (see Section 5.5.3).

i. 46,XX,der(1)hsr(1)(p22)hsr(1)(q31)[10]
or
46,XX,der(1)(pter→p22::hsr::p22→q31::hsr::q31→qter)[10]Karyotype shows two homogeneously staining regions in chromosome 1: one in band 1p22 in the short arm and the other in band 1q31 in the long arm in a neoplastic sample.

d. When an **hsr** is associated with a deletion, the breakpoint is assigned to the band closest to the telomere of the short arm.

i. 46,XY,der(1)del(1)(p33p21)hsr(1)(p33)[10]
or
46,XY,der(1)(pter→p33::hsr::p21→qter)[10]Karyotype of a neoplastic sample where the segment between bands 1p33 and 1p21 is replaced by a homogeneously staining region that may be smaller or larger than the deleted segment.

ii. 46,XX,der(2)del(2)(q21q31)hsr(2)(q21)[10]
or
46,XX,der(2)(pter→q21::hsr::q31→qter)[10]Karyotype of a neoplastic sample where the segment between bands 2q21 and 2q31 is replaced by a homogeneously staining region.

e. When a homogeneously staining region is located at the interface between segments of different chromosomes involved in a rearrangement, the **hsr** is assigned to the breakpoints in both chromosomes according to the ISCN description for structural chromosome aberrations, *i.e.*, the two chromosomes involved are presented in the first parentheses and the breakpoints in the second.

i. 46,XX,der(1)ins(1;7)(q21;p21p11.2)hsr(1;7)(q21;p11.2)[10]
or
46,XX,der(1)(1pter→1q21::7p21→7p11.2::hsr::1q21→1qter)[10]Karyotype of a neoplastic sample shows an insertion of the segment 7p21 to 7p11.2 in original orientation into the long arm of chromosome 1 at band 1q21. The derivative chromosome also contains an **hsr** at the interface between the recipient and donor chromosomes. The **hsr** is located distal to the segment inserted from chromosome 7.

ii. 46,XX,der(1)ins(1;7)(q21;p11.2p21)hsr(1;7)(q21;p11.2)[10]
or
46,XX,der(1)(1pter→1q21::hsr::7p11.2→7p21::1q21→1qter)[10]Karyotype of a neoplastic sample shows an insertion of the segment 7p21p11.2 in reverse orientation into the long arm of chromosome 1 with breakage and reunion at band 1q21. The derivative chromosome also contains an **hsr** at the interface between the recipient and donor chromosomes. The **hsr** is located proximal to the segment inserted from chromosome 7.

5.5.9 Insertions

a. Insertions are three-break rearrangements in which part of one chromosome is inserted at a point of breakage in the same, or another chromosome.

b. An **insertion** (**ins**) is described with the recipient chromosome given first, followed by the inserted segment. The orientation of the inserted segment is indicated by the order of the bands of the inserted segment from **pter** to **qter** of the recipient chromosome. For clarity, the use of the detailed system (karyotype format) may be used.

5.5.9.1 Insertions within a Chromosome

a. When an **insertion** (**ins**) within a single chromosome occurs, the breakpoint at which the chromosome segment is inserted is specified first. The remaining breakpoints are specified in the same way as in a two-break rearrangement, *i.e.*, the breakpoint of the inserted segment that is closest to **pter** is listed first.

i. 46,XX,ins(2)(p13q31q21)
or
46,XX,ins(2)(pter→p13::q31→q21::p13→q21::q31→qter)Karyotype shows the long arm segment between bands 2q21 and 2q31.is inserted into the short arm at band 2p13. The original orientation of the inserted segment relative to **pter** and **qter** is reversed in its new position, *i.e.*, band 2q31 is now closer to 2pter than band 2q21

ii. 46,XY,ins(2)(p13q21q31)
or
46,XY,ins(2)(pter→p13::q21→q31::p13→q21::q31→qter)The insertion is the same as in the previous example except that the orientation of the bands within the segment is maintained relative to **pter** and **qter**, *i.e.*, band 2q21 of the inserted segment remains closer to 2pter than band 2q31

5.5.9.2 Insertions between Two Chromosomes

a. Interchromosomal **insertions** (**ins**) are three-break rearrangements in which part of one chromosome is inserted at a point of breakage in the same or another chromosome. The **recipient** chromosome is specified **first**, regardless of whether it is a sex chromosome or an autosome with a number higher or lower than that of the donor chromosome. The **donor** chromosome is listed **last**, even if it is a sex chromosome.

b. The remaining breakpoints are specified in the same way as in a two-break rearrangement, *i.e.*, the breakpoint of the inserted segment that is closest to the **pter** of the recipient chromosome is listed first.

i. 46,X,ins(5;X)(p14;q21q25)
or
46,X,ins(5;X)(5pter→5p14::Xq21→Xq25::5p14→5qter;Xpter→Xq21::Xq25→Xqter)
Karyotype shows an insertion of the segment Xq21 to Xq25 into the short arm of chromosome 5 at 5p14. It is apparent from the order of the breakpoints that the segment is inserted in the original orientation, **pter** to **qter** (see Section 5.5.9). The recipient chromosome is listed first.

ii. 46,XX,ins(5;2)(p14;q32q22)
or
46,XX,ins(5;2)(5pter→5p14::2q32→2q22::5p14→5qter;2pter→2q22::2q32→2qter)K
aryotype shows an insertion of the segment 2q22 to 2q32 into the short arm of chromosome 5 at 5p14. The original orientation of the inserted segment relative to **pter** and **qter** is reversed in its new position, *i.e.*, 2q32 is now closer to **pter** of the recipient chromosome than 2q22. **Note**: the recipient chromosome is specified first.

iii. 46,XY,ins(5;2)(p14;q22q32)
or
46,XY,ins(5;2)(5pter→5p14::2q22→2q32::5p14→5qter;2pter→2q22::2q32→2qter)K

aryotype shows breakage and reunion at the same bands as in the previous example except that band 2q22 remains closer than band 2q32 to the **pter** of the recipient chromosome.

iv. 46,XX,ins(5;2)(q31;p13p23)
or
46,XX,ins(5;2)(5pter→5q31::2p13→2p23::5q31→5qter;2pter→2p23::2p13→2qter)Karyotype shows an insertion of bands 2p23 to 2p13 from chromosome 2 into band 5q31 with reversal of orientation relative to the terminal short arm of the recipient chromosome 5.

v. 46,XX,ins(5;2)(q31;p23p13)
or
46,XX,ins(5;2)(5pter→5q31::2p23→2p13::5q31→5qter;2pter→2p23::2p13→2qter)Karyotype shows an insertion of bands 2p23 to 2p13 from chromosome 2 into band 5q31 in a conserved orientation relative to **pter** of the recipient chromosome 5.

vi. 46,XY,der(5)ins(5;2)(q31;p23p13)dmatKaryotype shows a derivative chromosome 5 resulting from malsegregation of a balanced maternal insertion. There is one derivative chromosome 5 containing the insertion of material from chromosome 2, one normal chromosome 5, and two normal chromosomes 2. **Note:** although inherited from the mother who has a balanced interchromosomal insertion, the rearranged chromosome is not the result of a meiotic crossing-over but from malsegregation of the maternal insertion, and the abbreviation **der** is used instead of **rec** (see Section 5.5.3).

vii. 46,X,der(X)ins(X;7)(p21;q22q21)Karyotype shows a derivative X chromosome resulting from an insertion of the segment from 7q21 to 7q22 into band Xp21, with band 7q22 closer to Xpter than band 7q21. There are two normal chromosomes 7.

5.5.9.3 Complex Insertions

a. Where more than two chromosomes are involved in a complex reciprocal insertional event, the chromosome listed **first** is the chromosome that is the sex chromosome or the autosome with the **lowest** number, the chromosome that is listed next **receives** a segment from the first chromosome, and the chromosome specified last **donates** a segment to the first listed chromosome.

i. 46,XY,ins(5;6)(q13q23;q15q23)
or
46,XY,ins(5;6)(5pter→5q13::6q15→6q23::5q23→5qter;6pter→6q15::5q13→5q23::6q23→ 6qter)Karyotype shows a balanced four-break reciprocal insertion involving two chromosomes. The segment between bands 5q13 and 5q23 in chromosome 5 is inserted into chromosome 6 between 6q15 and 6q23, and the chromosome 6 segment between bands 6q15 and 6q23 is inserted into chromosome 5 between 5q13 and 5q23.

ii. 46,XX,ins(5;14;9)(q13q23;q24q21;p12p23)
or
46,XX,ins(5;14;9)(5pter→5q13::9p12→9p23::5q23→5qter;14pter→14q21::5q13→5q23::14q24→14qter;9pter→9p23::14q24→14q21::9p12→9qter)Karyotype shows a balanced six-break rearrangement with insertion of three interstitial segments. The segment between bands 5q13 and 5q23 on chromosome 5 replaces the segment between bands 14q21 and 14q24 on chromosome 14, the segment 14q21 to 14q24 replaces the

segment between bands 9p12 and 9p23 on chromosome 9, and the segment 9p12 to 9p23 replaces the segment 5q13 to 5q23. The orientations of the segments in relation to the centromere are apparent from the order of the bands. The segment 14q21 to 14q24 is inverted.

5.5.10 Inversions

a. The abbreviation **inv** is used. Whether it is a **paracentric** or **pericentric inversion** is apparent from the band designations. In all cases, the breakpoint closer to **pter** of the inverted chromosome is specified first.
b. There is no semicolon between the band designations within the same chromosome.

i. 46,XX,inv(2)(p23p13)
or
46,XX,inv(2)(pter→p23::p13→p23::p13→qter)Karyotype shows a **paracentric** inversion involving the short arm of chromosome 2 in which breakage and reunion have occurred at bands 2p23 and 2p13.

ii. 46,XX,inv(3)(q21q26.2)
or
46,XX,inv(3)(pter→q21::q26.2→q21::q26.2→qter)Karyotype shows a **paracentric** inversion involving the long arm of chromosome 3 in which breakage and reunion have occurred at bands 3q21 and 3q26.2.

iii. 46,XY,inv(3)(p13q21)
or
46,XY,inv(3)(pter→p13::q21→p13::q21→qter)Karyotype shows a **pericentric** inversion in which breakage and reunion have occurred at bands 3p13 and 3q21. The breakpoint in the short arm is specified first.

iv. 46,Y,inv(X)(p21q24)
or
46,Y,inv(X)(pter→p21::q24→p21::q24→qter)Karyotype shows a **pericentric** inversion in which breakage and reunion have occurred at bands Xp21 and Xq24. The normal sex chromosome is listed before the inversion of the X chromosome. The breakpoint in the short arm is specified first.

5.5.11 Isochromosomes

a. The abbreviation **i** (not iso) is used for **isochromosomes** and **idic** for **isodicentric chromosomes**.
b. Isochromosomes are usually formed through a centric mis-division and result in chromosome arms that are a mirror image of each other and genetically homozygous. See also Section 5.5.4.
c. The breakpoints in isochromosomes are assigned to the centromeric bands p10 and q10. The isochromosome designation is inferred from the banded chromosome morphology.

d. When it is not proven that both arms are homozygous the abbreviation **der** is used instead. However, for classical isochromosomes that are proven to be true isochromosomes in most cases (*e.g.*, i(9)(p10), i(12)(p10), i(18)(p10), i(X)(q10)), the abbreviation **i** may be used.

e. Complex isochromosomes, including isoderivative chromosomes, are described as derivative chromosomes, see Section 5.5.3.

i. 46,XX,i(17)(q10)
or
46,XX,i(17)(qter→q10::q10→qter)Karyotype shows an isochromosome for the entire long arm of one chromosome 17 and consequently the breakpoint is assigned to 17q10. There is one normal chromosome 17. The shorter designation i(17q) may be used in text but not in the ISCN description to describe this isochromosome.

ii. 46,X,i(X)(q10)
or
46,X,i(X)(qter→q10::q10→qter)Karyotype shows one normal X chromosome and an isochromosome for the long arm of one X chromosome. This is unbalanced as there is a single copy of the short arm of the X chromosome and three copies of the long arm of the X chromosome.

iii. 47,XY,i(X)(q10)A male karyotype showing an isochromosome of the long arm of the X chromosome in addition to normal X and Y chromosomes.

iv. 46,XX,idic(17)(p11.2)
or
46,XX,idic(17)(qter→p11.2::p11.2→qter)Karyotype shows an isodicentric chromosome composed of the long arms of chromosome 17 and the short arm material between the centromeres and the breakpoints in 17p11.2.

v. 46,XX,i(21)(q10)Karyotype shows an isochromosome of the long arm of chromosome 21 has replaced one chromosome 21. There are two copies of the long arm of chromosome 21 in the isochromosome and one normal copy of chromosome 21. Even though there are effectively three copies of the long arm of chromosome 21, the normal chromosome 21 is not designated with a **plus** (+) sign. **Note**: if homozygosity for the long arm of chromosome 21 is not proven, an alternative description using der(21)(q10;q10) should be used (see Section 5.5.18.3).

vi. 45,XX,–21,i(21)(q10)Karyotype shows an isochromosome of the long arm of chromosome 21 has replaced one chromosome 21. The other chromosome 21 is lost. There are two copies of the long arm of chromosome 21 in the isochromosome and no normal copies of chromosome 21.

vii. 47,XX,+i(8)(q10)[10]
or
47,XX,+8,i(8)(q10)[10]Alternative descriptions of the same chromosome complement with an isochromosome of the long arm of chromosome 8 in addition to two normal chromosomes 8 in a neoplastic sample.

5.5.12 Marker Chromosomes

a. A **marker chromosome** (**mar**) is a structurally abnormal chromosome that cannot be unambiguously identified or characterized by conventional banding cytogenetics.

Numerous terms are used in the literature to describe markers, including "supernumerary marker chromosomes (SMC)", "extra structurally abnormal chromosomes (ESAC)", "supernumerary ring chromosomes (SRC)", and "accessory chromosomes (AC)"; see Liehr et al. (2004) for a review of these abnormalities.

b. The **mar** is placed in the karyotype after all identified chromosomes, unknown derivative chromosomes, **rings** (**r**) and before **double minutes** (**dmin**), see Section 4.3.

c. In the description of a karyotype, the presence of a **mar** must be preceded by a **plus** (+) sign. No attempt should be made to describe the morphology or size of markers in karyotypes, *i.e.*, min mar, A-size mar, acro mar, *etc*., should not be used. If such information is relevant, it is described in words in the text of the report.

d. When several different marker chromosomes are clonally present, they may be indicated by an *Arabic* number after the abbreviation **mar**, *e.g.*, mar1, mar2, etc. It must be stressed that mar1, mar2 etc., does not indicate a derivation of the marker from chromosome 1, chromosome 2, and so on. Order of numbering for marker chromosomes (*i.e.*, that is mar1, mar2, mar3) is a laboratory choice, usually either based on frequency or on size.

e. Multiple copies of the same marker are indicated by a **multiplication** (×) sign after the **mar** designation, *e.g.*, mar1×2 indicates two identical copies of marker 1; mar1×3 indicates three copies of marker 1.

f. Multiple different marker chromosomes are indicated by the appropriate number *before* the **mar** abbreviation, *e.g.*, 5mar.

i. 47,XX,+marKaryotype shows one supernumerary marker chromosome.

ii. 47,XX,t(12;16)(q13;p11.2),+mar[10]Karyotype of a neoplastic sample shows a translocation between chromosomes 12 and 16 involving 12q13 and 16p11.2, and one supernumerary marker chromosome in ten metaphases.

iii. 48,X,t(X;18)(p11.2;q11.2),+2mar[10]Karyotype of a neoplastic sample shows a translocation between the X chromosome and chromosome 18 involving Xp11.2 and 18q11.2, and two different marker chromosomes in ten metaphases.

iv. 47,X,t(X;18)(p11.2;q11.2),+mar1[5]/48,X,t(X;18)(p11.2;q11.2),+mar1,+mar2[12]Same example as above but one marker (mar2) is not present in all the metaphases in this neoplastic sample. **Note:** the least complex clone is given first (see Section 6.3.3.1).

v. 47~51,XY,t(11;22)(q24;q12),+1~5mar[cp10]Karyotype of a neoplastic sample shows a translocation involving chromosomes 11 and 22 and five additional marker chromosomes, but not all metaphases contain all the markers.

vi. 48,XX,i(17)(q10),+mar1,+mar2[17]/51,XX,i(17)(q10),+mar1×3,+mar2,+mar3[13]Karyotype of a neoplastic sample shows two different marker chromosomes (mar1 and mar2) in the clone with 48 chromosomes. The clone with 51 chromosomes has three copies of mar1, one copy of mar2, and a third marker chromosome, mar3.

g. When any part of an abnormal chromosome can be recognized, even if the origin of the centromere is unknown, this abnormal chromosome is referred to as a **der** and not as a **mar** (see Section 5.5.3).

i. 47,XX,+der(?)t(?;15)(?;q22)The centromere of this abnormal chromosome is unknown and hence it is designated der(?), but part of the chromosome is composed of the chromosome 15 segment distal to band 15q22.

h. **Double minutes** (**dmin**) represent a special kind of acentric structure that is recorded in the karyotype when present in more than one metaphase cell. **Note**: the **dmin** must

not be included in the chromosome count, and the abbreviation is not preceded by a **plus** (**+**) sign. In the ISCN description the abbreviation **dmin** follows any centric marker. The number of **dmin** per cell is presented before the abbreviation either in absolute numbers or as a mean or a range.

i. Where there are too many copies of **double minutes** (**dmin**) to enumerate, the **greater than** (>) sign may be used to show the minimum number of copies present.

i. 49,XX,+3mar,3dmin[10]Karyotype of a neoplastic sample shows three marker chromosomes and three **dmin** per cell.

ii. 49,XY,+3mar,~14dmin[15]Karyotype of a neoplastic sample shows three marker chromosomes and approximately 14 **dmin** per cell.

iii. 49,XX,+3mar,>50dmin[8]Karyotype of a neoplastic sample shows three marker chromosomes and more than 50 **dmin** per cell.

iv. 49,XX,+3mar,9~>50dmin[8]Karyotype of a neoplastic sample shows three marker chromosomes and 9 to more than 50 **dmin** per cell.

j. **Acentric fragments** (**ace**) other than **dmin**, even if present in more than one cell, must not be presented in the karyotype, and must be recorded in chromosome breakage studies (see Chapter 12).

5.5.13 Neocentromeres

a. A **neocentromere** is a functional centromere that has arisen or is active within a region not known to have a centromere. A chromosome with a neocentromere may be described with the abbreviation **neo** or as a derivative chromosome (**der**) with the assumption that a new centromere has arisen (or is activated) within the region(s) from which the chromosome segment is derived.

b. A supernumerary marker chromosome containing a neocentromere may require the use of the detailed (karyotype format) depending on the circumstance.

i. 47,XX,+der(3)(:q28→qter)
or
47,XX,+neo(3)(:q28→qter)Karyotype shows a supernumerary derivative chromosome comprising the segment 3q28 to 3qter. This segment does not usually include a centromere and has a neocentromere. In this example, either **neo** or **der** could be used. The location of the neocentromere could be indicated by the abbreviation **neo**: 47,XX,+der(3)(:q28→neo→q28→qter). **Note:** the detailed system (karyotype format) may provide more clarity in describing this chromosome.

ii. 47,XX,der(3)(:p11→q11:),+neo(3)(pter→p11::q11→q26→neo→q26→qter)Karyotype shows that chromosome 3 is replaced by a derivative small chromosome containing the chromosome 3 centromere and by a large chromosome composed of the remaining part of chromosome 3 where a neocentromere is activated at 3q26.

iii. 47,XX,+neo(10)(qter→q25::q25→qter)
or
47,XX,+neo(10)(qter→q25::q25→q26→neo→q26→qter)
or
47,XX,+der(10)(qter→q25::q25→q26→neo→q26→qter)Karyotype shows a supernumerary chromosome that is a duplication of the segments between bands 10q25

and 10qter. This segment does not usually include a centromere and has a neocentromere. The location of the neocentromere could be indicated as shown.

5.5.14 Quadruplications

a. The abbreviation **qdp** is used. It is not possible to indicate the orientation(s) of the segment with the short system (karyotype format).

i. 46,XX,qdp(1)(q23q32)
or
46,XX,qdp(1)(pter→q32::q23→q32::q23→q32::q23→qter)Karyotype shows quadruplication of the segment between bands 1q23 and 1q32.

5.5.15 Recombinant Chromosomes

a. A **recombinant** chromosome (**rec**) is a structurally rearranged chromosome with a new segmental composition resulting from *meiotic* crossing-over between a displaced segment and its normally located counterpart in certain types of structural heterozygotes, *i.e.*, these recombinant chromosomes arise during gametogenesis as predictable consequences of crossing over in inversion or insertion heterozygotes (see Section 5.4.3.2).
b. The abbreviation **rec** should *not* be used in the description of acquired chromosome abnormalities, nor those resulting from malsegregation.
c. If parental karyotypes are unknown or a parental rearrangement has not been identified, the abnormal chromosome should be designated as a **der**, not **rec**.
d. The recombinant chromosome is specified in parentheses immediately following the abbreviation **rec**. The chromosome designation used indicates the origin of the centromere of the specific recombinant chromosome.

i. 46,XX,rec(6)dup(6p)inv(6)(p22.2q25.2)dmat
or
46,XX,rec(6)(pter→q25.2::p22.2→pter)dmatKaryotype shows a recombinant chromosome 6 with a duplication of the segment 6p22.2 to 6pter and a deletion of 6q25.2 to 6qter due to meiotic crossing-over of a maternal inversion of chromosome 6 involving the segment 6p22.2 to 6q25.2.

ii. 46,XX,rec(21)del(21)ins(21)(p13q22.2q22.3)dpat
or
46,XX,rec(21)(pter→q22.2::p22.3→qter)dpatKaryotype shows a recombinant chromosome 21 with a deletion of segment 21q22.2 to 21q22.3 due to a meiotic crossing-over of a paternal intrachromosomal insertion of chromosome 21 involving the insertion of bands 21q22.2 to 21q22.3 into 21p13.

iii. 46,XY,rec(1)dup(5q)ins(1;5)(q32;q11.2q22)dinh,der(5)ins(1;5)dinh
46,XY,rec(1)(1pter→1q32::5q11.2→5q22::5q22→5qter)dinh,der(5)(5pter→5q11.2::5q22→qter)dinhKaryotype shows recombinant chromosomes 1 and 5 resulting in a duplication of segment 5q22 to 5qter and deletion of the segment from 1q32 to 1qter due to a meiotic crossing-over in a parent who carries an interchromosomal insertion of the segment from 5q11.2 to 5q22 into band 1q32.

5.5.16 Ring Chromosomes

a. A **ring** chromosome (**r**), may be composed of one or several chromosomes.

- Where the origin of the centromere is known it is given in parentheses immediately after the abbreviation **r** and followed by the breakpoints, *e.g.*, 47,XX,+r(3)(p25q29)
- Where the centromere is known and the breakpoints cannot be identified but additional studies confirm chromosome origin the identity of the ring chromosome can be given in parentheses immediately after the abbreviation **r**, *e.g.*, 47,XX,+r(3)
- If no part of the ring chromosome including the centromere is identified then it is given without chromosome designation or breakpoints, *e.g.*, 47,XY,+r

5.5.16.1 Ring Chromosomes Derived from One Chromosome

a. As in other rearrangements affecting a single chromosome, there is no semicolon between the band designations.

i. 46,XX,r(7)(p15q31)
or
46,XX,r(7)(::p15→q31::)Karyotype shows a ring chromosome in which breakage and reunion have occurred at bands 7p15 and 7q31. The segments distal to these breakpoints are deleted.

ii. 46,XX,r(20)(p13q13.3)
or
46,XX,r(20)(::p13→q13.3::)Karyotype shows a ring chromosome in which breakage and reunion have occurred at bands 20p13 and 20q13.3 is identified at 550 band resolution with no discernable deletion of material at either breakpoint.

5.5.16.2 Ring Chromosomes Derived from More than One Chromosome

a. Ring chromosomes derived from more than one chromosome may contain one or several centromeres.

b. **Monocentric ring chromosomes** are described as **derivative** (**der**) chromosomes (see Section 5.5.3). The chromosome that provides the centromere is listed first. The order and orientation of the remaining segment is apparent from the order of the breakpoints.

i. 46,XX,der(1)r(1;3)(p36.1q23;q21q27)
or
46,XX,der(1)(::1p36.1→1q23::3q21→3q27::)Karyotype shows a ring chromosome composed of chromosome 1 with breakpoints in 1p36.1 and 1q23, and the acentric segment between bands 3q21 and 3q27 of chromosome 3.

ii. 46,XX,der(1)r(1;3)(p36.1q23;q27q21)
or
46,XX,der(1)(::1p36.1→1q23::3q27→3q21::)Karyotype shows a ring chromosome with the same breakpoints as in the previous example, but the orientation of the acentric segment of chromosome 3 is reversed.

iii. 46,XY,der(8)r(8;2)(p21.3q24.1;q23q33)
or

46,XY,der(8)(::8p21.3→8q24.1::2q23→2q33::)Karyotype shows a ring chromosome composed of part of chromosome 8 from 8p21.3 to 8q24.1 and an acentric fragment of chromosome 2 long arm from bands 2q23 to 2q33. As the chromosome 8 segment contains the centromere, it is listed before the acentric fragment from chromosome 2.

iv. 46,XX,der(1)r(1;?)(p36.1q23;?)
or
46,XX,der(1)(::1p36.1→1q23::?::)Karyotype shows a ring chromosome composed of chromosome 1 with breakpoints in 1p36.1 and 1q23, and an unknown acentric segment.

c. If the centromere of the ring chromosome is not known, but segments from other chromosomes contained in the ring are recognized, the ring is designated **der(?)**.

i. 47,XX,+der(?)r(?;3;5)(?;q21q26.2;q13q33)
or
47,XX,+der(?)(::?→cen?→?::3q21→3q26.2::5q13→5q33::)Karyotype shows a ring chromosome with two acentric segments, 3q21 to 3q26.2 and 5q13 to 5q33, and the origin of the centromere is unknown.

d. **Dicentric** or **tricentric ring chromosomes** are designated by the abbreviation **r** preceded by the triplet **dic** or **trc.**

e. In **dicentric ring chromosomes** (**dic r**), the sex chromosomes or the autosome with the lowest number is specified first.

i. 47,XX,+dic r(1;3)(p36.1q32;p24q26.2)
or
47,XX,+dic r(1;3)(::1p36.1→1q32::3p24→3q26.2::)Karyotype shows a dicentric ring chromosome composed of chromosomes 1 and 3 in which 1q32 is joined with 3p24 and 3q26.2 is joined with 1p36.1.

f. In **tricentric ring chromosomes** (**trc r**), the sex chromosomes or the autosome with the lowest number is specified first. The orientation of the chromosomes will be apparent from the order of the breakpoints.

i. 47,XX,+trc r(1;3;12)(p36.1q32;q26.3p24;p12q23)
or
47,XX,+trc r(1;3;12)(::1p36.1→1q32::3q26.3→3p24::12p12→12q23::)Karyotype shows a tricentric ring chromosome in which 1q32 is joined to 3q26.3, 3p24 is joined to 12p12, and 12q23 is joined to 1p36.1.

g. When the origin of the ring chromosome is known, the description of the ring is placed in the appropriate chromosome number order, *e.g.*, 49,XX,+1,+3,r(7),+8

h. When the origin of the ring chromosome is not known, the presence of the ring (**r**) abbreviation, preceded by a **plus** (**+**) sign, is indicated at the end of the karyotype, but before any other marker chromosome (see Section 4.3), *e.g.*, 50,XX,+1,+3,+8,+r and 50,XX,+1,+3,+8,+r+mar

i. Different ring chromosomes may be indicated by an *Arabic* number after the abbreviation **r**, *e.g.*, r1, r2, *etc.*, whereas several copies of unidentified ring chromosomes are indicated by the appropriate number before the ring chromosome abbreviation, *e.g.*, 5r. The order for numbering the different ring chromosomes is at the discretion of the laboratory.

i. 48,XX,+r1,+r2[10]Karyotype of a neoplastic sample with two distinctly different clonally occurring ring chromosomes. **Note:** the designations r1 and r2 do not indicate

that the derivation is from chromosomes 1 and 2. When the origin of a ring chromosome is known, the appropriate chromosome is placed in parentheses, *e.g.*, r(1), r(2), *etc.*

ii. 51,XY,+5r[10]Karyotype shows a neoplastic sample with a total of five ring chromosomes but it is not known if any of the rings are identical.

5.5.17 Telomeric Associations

a. The abbreviation **tas** is used to describe a **telomeric association**, which is typically a single cell abnormality. However, it is only reported in the ISCN description if it is a clonal abnormality.
b. In telomeric associations between two chromosomes, the sex chromosome or the autosome with the lowest number is specified first.
c. When more than two chromosomes are involved, the end chromosome that is a sex chromosome or has the lowest autosomal number, is specified first, followed by the other chromosomes in the order they are associated with the chromosome listed first.
d. In the short system (karyotype format), the terminal bands of the chromosomes involved in telomeric association(s) are given in the second parentheses; the orientation of the chromosomes will be apparent from the order in which the breakpoints are listed.
e. Chromosomes involved in telomeric associations are counted as separate chromosomes, as it is not proven that there is true chromosome fusion with terminal breakpoints.

i. 46,XX,tas(12;13)(q24.3;q34)
or
46,XX,tas(12;13)(12pter→12qter→13qter→13pter)Karyotype shows an association between the telomeric regions of the long arms of chromosomes 12 and 13.

ii. 46,Y,tas(X;12;3)(q28;p13q24.3;q29)
or
46,Y,tas(X;12;3)(Xpter→Xqter→12pter→12qter→3qter→3pter)Karyotype shows an association between the telomeric regions of the long arm of the X chromosome and the short arm of chromosome 12, and between the telomeric regions of the long arm of chromosome 12 and the long arm of chromosome 3.

iii. 46,X,tas(1;X;12;7)(p36.3;q28p22.3;p13q24.3;p22)
or
46,X,tas(1;X;12;7)(1qter→1pter→Xqter→Xpter→12pter→12qter→7pter→7qter)Karyotype shows an association between the telomeric regions of the short arm of chromosome 1 and the long arm of the X chromosome, between the telomeric regions of the short arm of the X chromosome and the short arm of chromosome 12, and between the telomeric regions of the long arm of chromosome 12 and the short arm of chromosome 7.

5.5.18 Translocations

5.5.18.1. Reciprocal Translocations

a. **Translocation** (**t**) refers to the exchange of terminal segments of chromosomes. When a translocation is balanced, there is no discernable gain or loss of chromosomal material.
b. The sex chromosome or the autosome with the lowest number is always specified first. If both sex chromosomes are involved, the X chromosome is listed before the Y chromosome.
c. To distinguish homologous chromosomes, one of the numerals may be **underlined** (_) (see Sections 4.4.2 and 5.5.18.1.2).

5.5.18.1.1 Two-Break Rearrangements

i. i.46,XY,t(2;5)(q21;q31)
or
46,XY,t(2;5)(2pter→2q21::5q31→5qter;5pter→5q31::2q21→2qter)Karyotype shows a translocation between chromosomes 2 and 5 where the segment distal to 5q31 is translocated to chromosome 2 at 2q21 and the segment of chromosome 2 distal to 2q21 is translocated to chromosome 5 at 5q31.

ii. 46,XY,t(2;5)(p12;q31)
or
46,XY,t(2;5)(5qter→5q31::2p12→2qter;5pter→5q31::2p12→2pter)Karyotype shows breakage and reunion have occurred at bands 2p12 and 5q31. The segments distal to these bands are exchanged.

iii. 46,X,t(X;13)(q27;q12)
or
46,X,t(X;13)(Xpter→Xq27::13q12→13qter;13pter→13q12::Xq27→Xqter)Karyotype shows breakage and reunion at bands Xq27 and 13q12. The segments distal to these bands are exchanged. Since one of the chromosomes involved in the translocation is a sex chromosome, it is designated first. **Note**: the correct designation is 46,X,t(X;13) and not 46,XX,t(X;13). Similarly, an identical translocation in a male is designated 46,Y,t(X;13) and not 46,XY,t(X;13).

iv. 46,t(X;Y)(q22;q11.23)
or
46,t(X;Y)(Xpter→Xq22::Yq11.23→Yqter;Ypter→Yq11.23::Xq22→Xqter)Karyotype shows a reciprocal translocation between an X chromosome and a Y chromosome with breakpoints at bands Xq22 and Yq11.23.

v. 46,t(X;18)(p11.2;q11.2),t(Y;1)(q11.23;p31)
or
46,t(X;18)(18qter→18q11.2::Xp11.2→Xqter;18pter→18q11.2::Xp11.2→Xpter),t(Y;1)(Ypter→Yq11.23::1p31→1pter;Yqter→Yq11.23::1p31→1qter)Karyotype shows two reciprocal translocations, each involving one sex chromosome. Breakage and reunion have occurred at bands Xp11.2 and 18q11.2 as well as at bands Yq11.23 and 1p31. **Note:** abnormalities of the X chromosome are listed before those of the Y chromosome.

5.5.18.1.2 Three-Break Rearrangements

a. For balanced translocations involving three separate chromosomes, with one breakpoint in each chromosome, the sex chromosome or autosome with the lowest number is specified first. The chromosome listed next receives a segment from the first chromosome, and the chromosome specified last donates a segment to the first listed chromosome.

i. 46,XX,t(2;7;5)(p21;q22;q23)
or
46,XX,t(2;7;5)(5qter→5q23::2p21→2qter;7pter→7q22::2p21→2pter;5pter→5q23::7q22→7qter)Karyotype shows a translocation of the segment of chromosome 2 from 2p21 to 2pter onto chromosome 7 at band 7q22, the segment on chromosome 7 from 7q22 to 7qter is translocated onto chromosome 5 at 5q23, and the segment of chromosome 5 from 5q23 to 5qter is translocated onto chromosome 2 at 2p21.

ii. 46,X,t(X;22;1)(q24;q11.2;p33)
or
46,X,t(X;22;1)(Xpter→Xq24::1p33→1pter;22pter→22q11.2::Xq24→Xqter;22qter→22q11.2::1p33→1qter)Karyotype shows that the segment on one X chromosome distal to Xq24 is translocated onto chromosome 22 at band 22q11.2, the segment distal to 22q11.2 is translocated onto chromosome 1 at band 1p33, and the segment distal to 1p33 is translocated onto the X chromosome at band Xq24.

iii. 46,XX,t(2;7;7)(q21;q22;p13)
or
46,XX,t(2;7;7)(2pter→2q21::7p13→7pter;7pter→7q22::2q21→2qter;7qter→7q22::7p13→7qter)Karyotype shows that the segment on chromosome 2 distal to 2q21 is translocated onto chromosome 7 at band 7q22, the segment on chromosome 7 distal to 7q22 is translocated onto the homologous chromosome 7 at band 7p13, and the segment distal to 7p13 on the latter chromosome is translocated onto chromosome 2 at 2q21. **Note**: underlining is used only to emphasize that the chromosomes are homologous.

iv. 46,XX,t(9;22;17)(q34;q11.2;q22)[10]
or
46,XX,t(9;22;17)(9pter→9q34::17q22→17qter;22pter→22q11.2::9q34→9qter;17pter→17q22::22q11.2→22qter)[10]Karyotype of a neoplastic sample shows that the segment of chromosome 9 distal to 9q34 is translocated onto chromosome 22 at band 22q11.2, the segment of chromosome 22 distal to 22q11.2 is translocated onto chromosome 17 at 17q22, and the segment of chromosome 17 distal to 17q22 is translocated onto chromosome 9 at 9q34.

v. 46,Y,t(X;15;18)(p11.1;p11.1;q11.1)
or
46,Y,t(X;15;18)(18qter→18q11.1::Xp11.1→Xqter;Xpter→Xp11.1::15p11.1→15qter;18pter→18q11.1::15p11.1→15pter)Karyotype shows that the segment of the X chromosome distal to Xp11.1 is translocated onto chromosome 15 at band 15p11.1, the segment of chromosome 15 distal to 15p11.1 is translocated onto chromosome 18 at 18q11.1, and the segment of chromosome 18 distal to 18q11.1 is translocated to Xp11.1. The normal Y chromosome is listed before the abnormal X chromosome.

5.5.18.1.3 Four-Break and More Complex Rearrangements

a. The same rule as for three-break rearrangements is followed in four-break and more complex balanced translocations for order and chromosome listing.

i. 46,XX,t(3;9;22;21)(p13;q34;q11.2;q21)[10]
or
46,XX,t(3;9;22;21)(21qter→21q21::3p13→3qter;9pter→9q34::3p13→3pter;22pter →22q11.2::9q34→9qter;21pter→21q21::22q11.2→22qter)[10]Karyotype of a neoplastic sample shows a four-break rearrangement where the segment of chromosome 3 distal to 3p13 is translocated onto chromosome 9 at 9q34, the segment of chromosome 9 distal to 9q34 is translocated onto chromosome 22 at 22q11.2, the segment of chromosome 22 distal to 22q11.2 is translocated onto chromosome 21 at 21q21, and the segment of chromosome 21 distal to 21q21 is translocated onto chromosome 3 at 3p13.

ii. 46,XX,t(3;9;9;22)(p13;q22;q34;q11.2)[10]
or
46,XX,t(3;9;9;22)(22qter→22q11.2::3p13→3qter;9pter→9q22::3p13→3pter;9pter→ 9q34::9q22→9qter;22pter→22q11.2::9q34→9qter)[10]Karyotype of a neoplastic sample shows a four-break rearrangement involving the two homologous chromosomes 9. The segment on chromosome 3 distal to 3p13 is translocated onto chromosome 9 at band 9q22, the segment on chromosome 9 distal to 9q22 is translocated onto the homologous chromosome 9 at 9q34, the segment on the latter chromosome 9 distal to 9q34 is translocated onto chromosome 22 at 22q11.2, and the segment on chromosome 22 distal to 22q11.2 is translocated onto chromosome 3 at 3p13.

b. The **derivative chromosomes** produced by *malsegregation* of reciprocal translocations and insertions are described using the conventions outlined in Section 5.5.3.

5.5.18.2. Whole-Arm Translocations

a. Whole-arm translocations are described by assigning the breakpoints to the centromeric bands p10 for short arm and q10 for long arm according to the morphology of the abnormal chromosomes. The breakpoints are assigned to (p10;p10) when both short arms are joined together, and (p10;q10) when a short arm of one chromosome and the long arm of the second chromosome are joined together.

b. In **balanced whole-arm translocations**, the breakpoint in the chromosome that is a sex chromosome or the autosome with the lowest number is assigned to p10.

i. 46,XY,t(1;3)(p10;q10)
or
46,XY,t(1;3)(1pter→1p10::3q10→3qter;3pter→3p10::1q10→1qter)Karyotype shows a reciprocal whole-arm translocation in which the short arm of chromosome 1 is joined at the centromere with the long arm of chromosome 3 and the long arm of chromosome 1 is joined to the short arm of chromosome 3.

ii. 46,XY,t(1;3)(p10;p10)
or

46,XY,t(1;3)(1pter→1p10::3p10→3pter;1qter→1q10::3q10→3qter)Karyotype shows a reciprocal whole-arm translocation in which the short arms of chromosomes 1 and 3 and the long arms of these chromosomes, respectively, are joined at the centromeres.

c. In the description of karyotypes containing derivative chromosomes resulting from **unbalanced whole-arm translocations** (see Section 5.5.3), the derivative chromosome (**der**) replaces the two normal chromosomes involved in the translocation. The two missing normal chromosomes are not specified. The imbalance(s) can be inferred from the karyotype designation.

i. 45,XX,der(1;3)(p10;q10)
or
45,XX,der(1;3)(1pter→1p10::3q10→3qter)Karyotype shows a derivative chromosome consisting of the short arm of chromosome 1 and the long arm of chromosome 3. The missing chromosomes 1 and 3 are not indicated since they are replaced by the derivative chromosome. The karyotype contains one normal chromosome 1, one normal chromosome 3, and the der(1;3). The resulting net imbalance of this abnormality is monosomy for the long arm of chromosome 1 and monosomy for the short arm of chromosome 3.

ii. 46,XX,+1,der(1;3)(p10;q10)Karyotype shows a derivative chromosome consisting of the short arm of chromosome 1 and the long arm of chromosome 3 (same as above) replaces one chromosome 1 and one chromosome 3. There are, however, two normal chromosomes 1, *i.e.*, an additional chromosome 1 in relation to the expected loss due to the der(1;3). Consequently, this gain is indicated as +1. The karyotype contains two normal chromosomes 1, one normal chromosome 3, and the der(1;3). The resulting net imbalance is trisomy for 1p and monosomy for 3p.

iii. 46,XX,der(1;3)(p10;q10),+3Karyotype shows a derivative chromosome consisting of the short arm of chromosome 1 and the long arm of chromosome 3 (same as above) has replaced one chromosome 1 and one chromosome 3. There are, however, two normal chromosomes 3, *i.e.*, an additional chromosome 3 in relation to the expected loss due to the der(1;3). Consequently, this gain is indicated as +3. The karyotype contains one normal chromosome 1, two normal chromosomes 3, and the der(1;3). The resulting net imbalance is monosomy for 1q and trisomy for 3q.

iv. 47,XX,+der(1;3)(p10;q10)Karyotype shows an extra derivative chromosome consisting of the short arm of chromosome 1 and the long arm of chromosome 3 (same as above). There are two normal chromosomes 1, two normal chromosomes 3, and the der(1;3). The resulting net imbalance is trisomy for 1p and trisomy for 3q.

v. 44,XY,–1,der(1;3)(p10;q10)Karyotype shows a derivative chromosome consisting of the short arm of chromosome 1 and the long arm of chromosome 3 (same as above) has replaced one chromosome 1 and one chromosome 3. There is, however, no normal chromosome 1, indicated as –1 in relation to the expected presence of one chromosome 1 due to the der(1;3). The karyotype contains no chromosome 1, one normal chromosome 3, and the der(1;3). The resulting net imbalance is nullisomy for 1q, monosomy for 1p, and monosomy for 3p.

5.5.18.3. Robertsonian Translocations

a. **Robertsonian** translocations (**rob**) are constitutional whole-arm translocations of the acrocentric chromosomes 13, 14 ,15, 21 and 22. The breakpoints mostly occur in the short arms, resulting in dicentric chromosomes. Breaks may also occur in one short arm and one long arm of the participating chromosomes, resulting in monocentric rearrangements. Usually there is simultaneous loss of the remaining short arms.

b. Although either **rob** or **der** can adequately describe these whole-arm translocations, **der** is the preferred designation. The abbreviation **rob** should not be used in the description of acquired abnormalities.

i. 45,XX,der(13;21)(q10;q10)Karyotype shows that breakage and reunion have occurred at band 13q10 and band 21q10 in the centromeres of chromosomes 13 and 21. The derivative chromosome has replaced one chromosome 13 and one chromosome 21 and there is no need to indicate the missing chromosomes. The karyotype contains one normal chromosome 13, one normal chromosome 21, and the der(13;21). The resulting net imbalance is loss of the short arms of chromosomes 13 and 21.

ii. 46,XX,der(13;21)(q10;q10),+21Karyotype shows a derivative chromosome consisting of the long arm of chromosome 13 and the long arm of chromosome 21 (same as above) has replaced one chromosome 13 and one chromosome 21. There are, however, two normal chromosomes 21, *i.e.*, an additional chromosome 21 in relation to the expected loss due to the der(13;21). Consequently, this gain is indicated as +21. The karyotype contains one normal chromosome 13, two normal chromosomes 21, and the der(13;21). The resulting net imbalance is loss of the short arm of chromosome 13 and trisomy for the long arm of chromosome 21.

iii. 46,XX,+13,der(13;21)(q10;q10)Karyotype shows a derivative chromosome consisting of the long arm of chromosome 13 and the long arm of chromosome 21 (same as above) has replaced one chromosome 13 and one chromosome 21. The karyotype contains two normal chromosomes 13, one normal chromosome 21, and the der(13;21). Consequently, this gain is indicated as +13. The resulting net imbalance is loss of the short arm of chromosome 21 and trisomy for the long arm of chromosome 13.

c. If only a single chromosome is involved in the rearrangement, the extra chromosome is indicated by the 46 chromosome count in the presence of a whole-arm rearrangement and the addition of a normal chromosome.

i. 46,XX,+21,der(21;21)(q10;q10)Karyotype shows a derivative chromosome composed of the long arms of chromosome 21. There are two copies of the long arm of chromosome 21 in the derivative chromosome and one normal chromosome 21, indicated by the 46 chromosomes count. The normal chromosome 21 is designated with a **plus** (**+**) sign. **Note**: for an alternative description of this same rearrangement as an isochromosome if homozygosity for the long arm of the rearranged chromosome is proven, see Section 5.5.11.

d. If it is proven that the derivative chromosome resulting from a whole-arm translocation is **dicentric**, *i.e.*, the breakpoints are assigned to p11.2 or q11.2, the abbreviation **dic** is used and the dicentric chromosome is described accordingly (see Section 5.5.4).

5.5.18.4. Jumping Translocations

a. Jumping translocations are described with the ISCN description for translocations. The cell lines/ clones are presented with the largest cell line/clone listed first. Cell lines/clones of equal size are given according to Sections 4.5.3, 5.1 and 6.3.3.2.

i. 46,XX,t(4;7)(q35;q11.2)[6]/46,XX,t(1;7)(p36.3;q11.2)[4]/46,XX,t(7;9)(q11.2;p24)[3] Karyotype shows three clonal translocations involving band 7q11.2. The segment 7q11.2 to 7qter is translocated to bands 1p36.3, 4q35, and 9p24.

ii. 46,XX,+13,der(13;13)(q10;q10)[5]/45,XX,der(13;15)(q10;q10)[5]Karyotype shows a clonal translocation where the chromosome 13 long arm is translocated either to a chromosome 13 leading to trisomy 13 as there is one apparently normal chromosome 13 and one derivative chromosome 13 (with two copies of the long arm of chromosome 13), or on one chromosome 15 in a balanced state. **Note:** there is a reduction in the chromosome number when the derivative chromosome replaces one chromosome 13 and one chromosome 15.

5.5.19 Tricentric Chromosomes

a. A **tricentric** (**trc**) chromosome has three centromeres.

b. In the description of a tricentric chromosome, if the sex chromosome centromere is involved, it is given first followed by the autosomes in numerical order. For tricentric chromosomes involving only autosomes, numerical order is followed (lowest to highest).

c. The other chromosome segments are listed in the order they are attached to the chromosome listed first. The orientation of the chromosomes will be apparent from the order of the breakpoints specified in the second parentheses.

d. A tricentric chromosome is counted as one chromosome, with the normal chromosome count then becoming 44. There is no need to indicate the missing normal chromosomes.

i. 44,XX,trc(4;12;9)(q31.2;q22p13;q34)
or
44,XX,trc(4;12;9)(4pter→4q31.2::12q22→12p13::9q34→9pter)Karyotype shows a tricentric chromosome in which band 4q31.2 is joined to12q22 and 12p13 is joined to 9q34.

5.5.20 Triplications

a. The abbreviation **trp** is used. It is not possible to indicate the orientation(s) of the segment in the short system (karyotype format), but this can be done with the detailed system (karyotype format).

i. 46,XX,trp(1)(q21q32)
or
46,XX,trp(1)(pter→q32::q21→q32::q21→qter)Karyotype shows triplication of the segment between bands 1q21 and 1q32, one of several possible orientations of the triplications of this segment. **Note: trp** indicates that the three copies are tandem.

ii. 46,XX,trp(1)(q32q21)
or

46,XX,trp(1)(pter→q32::q32→q21::q21→qter)Karyotype shows triplication of the segment between bands 1q21 and 1q32 with one segment in an opposite orientation to the above example.

5.6 Multiple Copies of Rearranged Chromosomes

a. The **multiplication** (×) sign can be used to describe multiple copies of a rearranged chromosome but it is not used to denote multiple copies of normal chromosomes.
b. The number of copies (×2, ×3, *etc*.) is placed after the abnormality.
c. Extra copies of a rearranged chromosome**,** when present, do not require the breakpoints to be repeated, *i.e*., they are specified the first time they appear in the karyotype (see also Section 4.2.1).

i. 46,XX,del(6)(q13q23)×2[10]Karyotype of a neoplastic sample shows two chromosomes 6 with an interstitial deletion of the long arm between 6q13 and 6q23, and no normal chromosome 6. Since the two abnormal chromosomes replace the two normal chromosomes, there is no need to indicate the missing normal chromosomes.
ii. 48,XY,+del(6)(q13q23)×2[10]
or
48,XY,+6,+6,del(6)(q13q23)×2[10]Karyotype of a neoplastic sample shows two apparently normal chromosomes 6 plus two additional chromosomes 6 with an interstitial deletion of the long arm between 6q13 and 6q23.
iii. 47,XX,del(6)(q13q23)×2,+del(6)[15]Karyotype of a neoplastic sample shows three copies of chromosome 6 with an interstitial deletion of the long arm between 6q13 and 6q23, and no normal chromosomes 6, *i.e.,* two of the deleted chromosomes replace the two normal chromosomes 6. **Note**: in the ISCN description the supernumerary chromosome 6 with an interstitial deletion is preceded by a **plus** (+) sign.
iv. 48,XX,del(6)(q13q23)×2,+7,+7[10]Karyotype of a neoplastic sample shows two chromosomes 6 with an interstitial deletion of the long arm between 6q13 and 6q23. There are no normal chromosomes 6; there is gain of two chromosomes 7.
v. 48,XX,t(8;14)(q24.1;q32),+der(14)t(8;14)×2[10]Karyotype of a neoplastic sample shows a balanced translocation, t(8;14) plus two additional copies of the derivative chromosome 14. There is one apparently normal chromosome 8, one apparently normal chromosome 14 and there are three derivative chromosomes 14 from the t(8;14).
vi. 92,XXXX,t(8;14)(q24.1;q32)×2[10]Karyotype of a neoplastic sample shows a tetraploid clone with two balanced translocations, t(8;14). The two derivative chromosomes 8 and 14 replace two normal chromosomes 8 and 14. There are two normal chromosomes 8 and 14.
vii. 94,XXYY,t(8;14)(q24.1;q32)×2,+der(14)t(8;14)×2[15]
or
94,XXYY,t(8;14)(q24.1;q32)×2,+14,+14,der(14)t(8;14)×2[15]Karyotype of a neoplastic sample shows a hypertetraploid clone with two balanced translocations, t(8;14) plus two additional copies of the derivative chromosome 14. There are two normal chromosomes 8 and 14.
viii. 93,XXXX,t(8;14)(q24.1;q32)×2,der(14)t(8;14)×2,+der(14)t(8;14)[15]Karyotype of a neoplastic sample shows a hypertetraploid clone with two balanced translocations,

t(8;14) and three extra copies of the derivative chromosome 14, *i.e.*, there are five derivative chromosomes 14, and there is no normal chromosome 14.

ix. 94,XXYY,t(8;14)(q24.1;q32)×2,+14,der(14)t(8;14)×2,+der(14)t(8;14)[10]Karyotype of a neoplastic sample shows a hypertetraploid clone with two balanced translocations, t(8;14). There are six copies of chromosome 14: one chromosome 14 is apparently normal and five are derivative chromosomes 14 from the t(8;14).

x. 47,XX,+8,i(8)(q10)×2[10]
or
47,XX,i(8)(q10),+i(8)[10]Karyotype of a neoplastic sample with an alternative description of the same chromosome complement to describe two copies of an isochromosome for the long arm of chromosome 8 and one normal chromosome 8.

xi. 49,XX,+1,+der(1)t(1;16)(p13;q13)×2,t(1;16)[10]A karyotype of a neoplastic sample with two additional copies of a derivative chromosome 1, from a translocation involving chromosomes 1 and 16. In this case, the numerical gain of chromosome 1 is listed first. The derivative chromosome 1 with the breakpoint band designation is listed before the translocation that is given without the band designation. **Note:** the alphabetical order rule applies for the **der** and **t** abnormalities.

5.7 Ploidy Anomalies

a. All chromosome changes, whether constitutional or acquired, are expressed in relation to the appropriate ploidy level (see Section 6.3.7), *i.e.*,

- In near-haploid cells (23 chromosomes) in relation to one chromosome of each type (chromosome numbers up to 34).
- In near-diploid cells (46 chromosomes) in relation to two chromosomes of each type (chromosome numbers 35–57).
- In near-triploid cells (69 chromosomes) in relation to three chromosomes of each type (chromosome numbers 58–80).
- In near-tetraploid cells (92 chromosomes) in relation to four chromosomes of each type (chromosome numbers 81–103), and so on.

v. 26,X,+4,+6,+21[12]The near-haploid karyotype shows two copies of chromosomes 4, 6, and 21, and a single copy of all other chromosomes in a neoplastic sample.

vi. 69,XXX,del(7)(p11.2)The triploid karyotype shows two normal chromosomes 7 and a chromosome 7 with a terminal deletion of the short arm at 7p11.2.

vii. 70,XXX,+del(7)(p11.2)The near-triploid karyotype shows three normal chromosomes 7 and an additional, structurally abnormal chromosome 7 with a terminal deletion of the short arm at 7p11.2.

viii. 71,XXX,+8,+10The near-triploid karyotype shows four copies of chromosomes 8 and 10, and three copies of all other chromosomes. **Note:** the number of metaphases is added for a neoplastic sample.

ix. 69,XXY,del(7)(q22),inv(7)(p13q22),t(7;14)(p15;q11.1)The triploid karyotype shows no normal chromosome 7. One chromosome 7 has a long arm deletion, one chromosome 7 has an inversion, and one chromosome 7 is involved in a balanced translocation with chromosome 14. **Note:** there is **comma** (**,**) separating the chromosome 7 abnormalities to indicate that the abnormalities are on different chromosome 7 homologues.

x. 69,XXX,der(7)inv(7)(p13q22)del(7)(q22),t(7;14)(p15;q11.1)The triploid karyotype shows one derivative chromosome 7 with an inversion involving the segment 7p13 to 7q22, and a terminal deletion at 7q22. Another chromosome 7 is involved in a reciprocal translocation with chromosome 14, and there is one normal chromosome 7.

xi. 92,XXYY,del(7)(p11.2),t(7;14)(p15;q11.1)The tetraploid karyotype shows two normal and two abnormal chromosomes 7: one chromosome 7 with a terminal deletion of the short arm, and one chromosome 7 is involved in a balanced translocation with chromosome 14. **Note**: underlining of one homologue is optional (see Section 4.4.2).

xii. 92,XXYY,del(7)(p11.2),del(7)(q22),del(7)(q34)The tetraploid karyotype shows one normal chromosome 7 and three chromosomes 7 with different terminal deletions.

xiii. 89,XXYY,–1,–3,–5,+8,–21[5]The near-tetraploid male karyotype shows three copies of chromosomes 1, 3, 5, and 21, five copies of chromosome 8, and four copies of all other autosomes in a neoplastic sample.

b. In neoplasms, an appropriate and biologically meaningful ploidy level should be selected for the description of the karyotype. The ploidy level (n, 2n, 3n, etc.) may be given in **angle brackets** (< >) after the chromosome number (see Section 6.3.7).

. 76~102<4n>,XXXX,…[15]The chromosome numbers vary between hypertriploidy and hypertetraploidy. The symbol <4n> indicates that all neoplastic abnormalities are expressed in relation to the tetraploid level.

i. 58<2n>,XY,+X,+4,+6,+8,+10,+11,+14,+14,+17,+18,+21,+21[10]Karyotype of a neoplastic sample with near-triploidy, and the abnormalities are described in relation to the diploid chromosome number. The chromosomes with three copies are listed as additional.

c. **Endoreduplication** (**end**) is the replication of the chromosomes without chromatid separation or cytokinesis (Fig. 7). Technologies such as SNP microarray may be helpful in differentiating between endoreduplication and other mechanisms (*e.g.*, aborted mitosis and cell fusion) that may produce a similar copy number change.

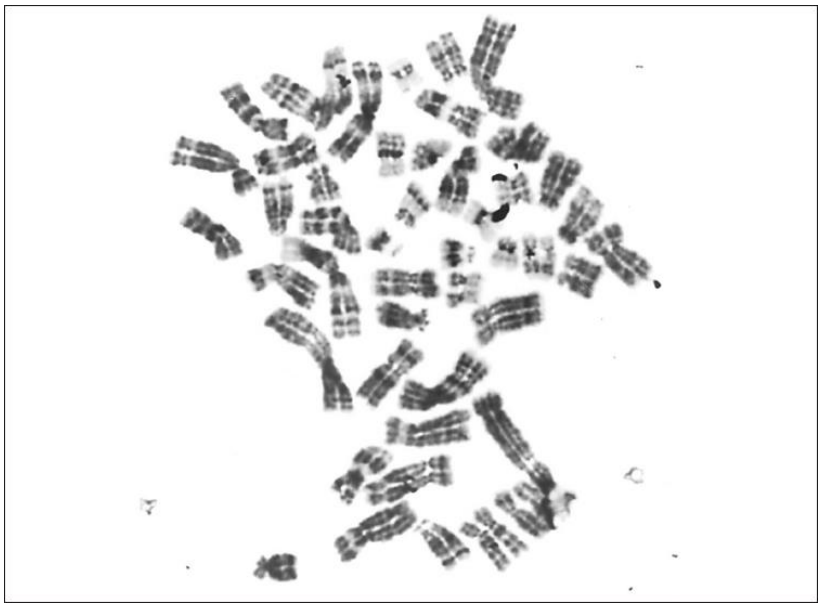


Figure 7. *Metaphase chromosomes in a cell which has undergone endoreduplication (courtesy of Dr. N. Mandahl*

6 Neoplasia

6.1 Introduction

This section defines terms and provides nomenclature for the description of chromosome abnormalities in neoplasia. Unless otherwise indicated the examples in this chapter are given at 400 **bands per haploid set** (**bphs**). See Section 10.3 for nomenclature to describe targeted karyotype analysis and Chapters 7, 8, 9, 10 and 11 for molecular cytogenomic and sequencing assays.

6.2 General Principles

a. See Chapter 4 for general nomenclature rules applicable to neoplasia.
b. In the description of a karyotype the total number of chromosomes is given first in the ISCN description, followed by a **comma** (**,**) followed by the sex chromosome constitution. Autosomes are specified only if they are abnormal and are listed in increasing number order.
c. The number of cells is given in **square brackets** (**[ ]**) for each abnormal clone and the normal cell line, if present (see Section 5.1).
d. Only chromosome abnormalities with demonstrated clonality are reported in the ISCN description (see Section 4.5).

- The location of a breakpoint is specified by the band in which the break has occurred according to the banding resolution of the assay.
- When the same abnormality has been seen at a higher resolution in a previous sample, then the higher resolution breakpoints may be reported in subsequent samples.
- Depending on the banding resolution, a breakpoint may appear to be in a band other than that known to contain the gene involved in the rearrangement. Nevertheless, the breakpoint listed in ISCN corresponds to the band/subband visualised by the banding technique.

e. The normal cell line when present, is listed last in the nomenclature description.
f. Non-clonal abnormalities are not included in the ISCN description; however, they may be discussed in the interpretative text.
g. The karyotype designation of each different clone and subclone is separated by a **slant line** (/).
h. In chimerism **secondary to stem cell transplant**, the recipient cell line(s) are given first, followed by the donor cell line(s). The recipient and donor cell line(s) are separated by a **double slant line** (//) (see Section 4.5.3).
i. The **stemline** (**sl**) is the most basic clone of a neoplastic population, and deviating subclones arising by clonal evolution are termed **sidelines** (**sdl**).

j. **idem** (Latin = the same) can be used to describe sidelines and subclones in relation to the first clone in the ISCN description. This term makes no assumption regarding the stemline.
k. Where individual clones are not discernible because of the genomic heterogeneity of the tumor, a **composite** karyotype (**cp**) is required.
l. Where chromosome quality is poor and/or there are insufficient metaphases to allow the complete karyotype to be determined, an **incomplete** (**inc**) karyotype may be given.

6.3 Clones and Subclones

A clone is defined as a cell population derived from a single progenitor (see Section 4.5). It is not necessarily completely homogeneous because subclones may have evolved during development and progression of the neoplasm.

a. Clonal chromosome abnormalities, including the number of metaphases analyzed, are reported in the ISCN description. For nomenclature for the targeted scoring of additional metaphases to establish clonality or assess clone size, see Section 10.3.

i. 46,XY,t(7;11)(p15;p15)[12]/46,XY[8]Chromosome analysis shows a clone with a translocation between chromosomes 7 and 11 in twelve metaphases at 400 bphs. This 7;11 translocation in hematological neoplasms forms the *NUP98*::*HOXA9* fusion gene. The *NUP98* and *HOXA9* genes are located on 11p15.4 and 7p15.2, respectively, although these subband are not apparent at 400 bphs.

b. When a cytogenetic abnormality has been reported in a previous study and then is found in a single metaphase at follow-up, it should be reported in the ISCN.

i. 46,XX,t(9;22)(q34;q11.2)[1]/46,XX[19]Karyotype shows a single metaphase with an isolated translocation between chromosomes 9 and 22 in a follow-up cytogenetic analysis of a case with the same abnormal clone at initial presentation.

c. When a single abnormal metaphase is confirmed by a different method (*e.g.*, FISH, microarray, genome mapping), and thus shown to be clonal, it should be reported in the karyotype (see Section 4.5.3).

i. 46,XX,del(20)(q11.2q13.3)[1]/46,XX[19].nuc ish (D20S108×1,RH74808×2)[40/200]An interstitial deletion in the long arm of chromosome 20 is present in a single metaphase from a neoplastic sample. FISH with a 20q12 probe, D20S108, and a control probe for 20q13.3, RH74808, confirmed the deletion of 20q and the clonality of this abnormality.

6.3.1 Clone Size

i. 46,XX[20]An apparently normal female karyotype is identified in 20 metaphases in a neoplastic sample. **Note:** the number of metaphases is given in **square brackets** (**[ ]**).
ii. 46,XX,t(8;21)(q22;q22)[23]A clone with a translocation between chromosomes 8 and 21 is identified in all 23 metaphases by cytogenetic analysis at 400bphs.
iii. 46,XX,t(9;22)(q34;q11.2)[18]/45,XX,der(7;9)(q10;q10)t(9;22),der(22)t(9;22)[2]
or
46,XX,t(9;22)(q34;q11.2)[18]/45,XX,der(7;9)(7qter→7q10::9q10→9q34::22q11.2→22qter),der(22)(22pter→22q11.2::9q34→9qter)[2]

or
46,XX,t(9;22)(q34;q11.2)[18]/45,XX,der(7;9)(7qter→7q10::9q10→9q34::22q11.2→22qter),der(22)t(9;22)[2]A neoplastic sample shows eighteen metaphases with 46 chromosomes and a translocation between chromosomes 9 and 22 as the sole cytogenetic abnormality. A subclone of two metaphases has 45 chromosomes and the derivative chromosome 9 from the t(9;22) is further involved in a whole-arm translocation with chromosome 7. The missing chromosomes 7 and 9 are not indicated since they are replaced by the derivative chromosome, der(7;9). There is loss of the short arms of chromosomes 7 and 9. **Note:** the breakpoints need not be repeated when the same abnormality is described in additional clones/subclones.

b. The **mainline** is the most frequent chromosome constitution of a neoplastic cell population. **Mainline** is a purely quantitative term to describe the largest clone and does not necessarily indicate the most basic clone in terms of progression.

i. 46,XX,t(9;22)(q34;q11.2)[3]/47,XX,+8,t(9;22)[17]The clone with 47 chromosomes and trisomy 8 represents the mainline in this karyotype, although it has most probably evolved from the clone with 46 chromosomes. **Note:** the order of the cytogenetically related clones is determined by their complexity (see Section 6.3.3.1).

ii. 46,XX,der(2)t(2;5)(p23;q35)[10]/47,XX,+2,der(2)t(2;5)[16].nuc ish (3′ALK×2,5′ALK×3)(3′ALK con 5′ALK)×2[135/200]/(3′ALK×1,5′ALK×2)(3′ALK con 5′ALK)×1[65/200]The clone with 47 chromosomes represents the mainline in this karyotype, although it has most probably evolved from the clone with 46 chromosomes. Rearrangement involving the *ALK* gene is confirmed by interphase FISH analysis with a breakapart probe.

c. When the largest clones (two or more) are of equal size, a neoplasm will have more than one mainline.

i. 45,XX,−7[10]/47,XX,+8[10]Karyotype shows two clones of equal size, each representing the mainline. Monosomy 7 clone is listed before trisomy 8 clone following the chromosome order rule. For rules concerning clone order when the clones are unrelated see Section 6.3.3.2

6.3.2 Order of Chromosome Abnormalities

a. Clonal chromosome abnormalities are listed with sex chromosome abnormalities first, and X before Y, followed by autosomes in order of lowest to highest number. The normal sex chromosome is listed first in the ISCN description when the other sex chromosome is abnormal (see Section 4.3).

i. 45,X,−Y,t(8;21)(q22;q22)[20]A translocation between chromosomes 8 and 21 is identified in twenty metaphases by cytogenetic analysis at 400bphs. The 8;21 translocation in hematological neoplasms forms the *RUNX1*::*RUNX1T1* fusion gene. The *RUNX1T1* gene is known to be located at 8q21.3. At 400bphs the breakpoint is at the interface of 8q21.3 and 8q22. The breakpoint is designated as 8q22 as it is more distal to the centromere (see Section 5.4.1).

ii. 46,XX,t(10;11)(p12;q14–22),del(13)(q12q22),i(17)(q10)[10]/46,XX[5]Karyotype shows a translocation involving chromosomes 10 and 11, an interstitial deletion of

chromosome 13 and an isochromosome of the long arm of chromosome 17 in ten metaphases. At 300bphs 11q14 to 11q22 appear as the single band, 11q14–22. No abnormality is detected in five metaphases. The normal cell line is listed last in the ISCN description.

iii. 46,Y,i(X)(q10)[20]/46,XY[10]Karyotype of a neoplastic sample shows an isochromosome of the long arm of the X chromosome in twenty metaphases and an apparently normal male karyotype in ten metaphases. The normal Y chromosome is given before the abnormal X chromosome in the ISCN description.

6.3.3 Order of Clones

6.3.3.1 Cytogenetically Related Clones

The order of cytogenetically related clones in the ISCN description is determined by the sequential application of the following rules:

a. Cytogenetically related clones and subclones are written in order of increasing **complexity**, irrespective of their size (see Section 4.5.3). Only the **number** of aberrations and not the **size** of the altered genomic segment is considered in the application of this rule (see Table 7).

i. 46,XY,inv(16)(p13.1q22)[10]/46,XY,del(7)(q21),inv(16)[5]Karyotype shows a pericentromeric inversion of chromosome 16 as the sole abnormality in ten metaphases. A subclone comprising of five metaphases shows the inv(16) and a terminal deletion of 7q. **Note:** the stemline, if present, is the **least complex** clone and is therefore listed first in the ISCN description.

b. Where abnormalities in different clones with equal complexity involve chromosomes of a different number, the **chromosome order** rule applies, X before Y, followed by autosomes in increasing number.

i. 46,XY,t(1;19)(q23;p13.3),del(9)(p21)[10]/47,XY,t(1;19),+21[10]Two subclones identified by karyotype contain a translocation between chromosomes 1 and 19. The subclone with a terminal deletion of chromosome 9 is given before the subclone with gain of chromosome 21 in the ISCN description. **Note:** the cytogenetically related clones are of equal karyotypic complexity, therefore the **chromosome order** rule applies.

c. Where abnormalities in different clones with equal complexity involve the same number chromosome, the **gain before loss, before structural change** rule applies.

i. 47,XX,t(6;9)(p22;q34),+9[10]/45,XX,t(6;9),−9[10]Two subclones identified by karyotype contain a translocation between chromosomes 6 and 9. The subclone with gain of chromosome 9 is given before the subclone with loss of chromosome 9 in the ISCN description. **Note:** the cytogenetically related clones are of equal karyotypic complexity, and the abnormalities involve the same number chromosome, therefore the **gain before loss, before structural change** rule applies.

d. Where structural abnormalities of the same number chromosome are present in different clones with equal complexity, they are reported **alphabetically**. If structural abnormalities involving the same chromosome are of the same type, then the **pter** to **qter** rule applies.

i. 45,XX,−5,add(7)(q34)[15]/45,XX,−5,t(7;8)(q22;q22)[15]Karyotype shows two subclones with monosomy 5. One clone shows additional material of unknown origin replacing the distal long arm of chromosome 7 from 7q34 and the other shows a translocation involving chromosome 7 at 7q22 and chromosome 8 at 8q22. Since chromosome 7 is involved in both clones then the alphabetical rule of abbreviations applies. In this example **add** is listed before **t**.

ii. 47,XY,+8,del(17)(p13)[15]/47,XY,+8,del(17)(q21)[15]Karyotype shows two subclones with trisomy 8. The subclone with a terminal deletion at 17p13 is given before the subclone with a terminal deletion at 17q21 in the ISCN description. **Note:** the clones are of equal karyotypic complexity, and the abnormalities are of the same type on the same number chromosome, therefore the **pter** to **qter** rule applies.

iii. 48,XY,+8,+17[15]/47,XY,+8,del(17)(p13)[15]/47,XY,+8,del(17)(q21)[15]Karyotype shows three subclones with trisomy 8 and abnormalities of chromosome 17. The subclone with trisomy 17 is given first (gains before losses before structural change); the subclone with a terminal deletion at 17p13 is given before the subclone with a terminal deletion at 17q21 in the ISCN description (**pter** to **qter** rule applies).

6.3.3.2 Cytogenetically Unrelated Clones

The order of cytogenetically unrelated clones in the ISCN description is determined by the sequential application of the following rules:

a. Cytogenetically unrelated abnormal clones are written in order of the **size of the clone** with the largest clone first, followed by the next largest and so on (see Section 4.5).

i. 46,XX,t(3;9)(p13;p13)[14]/48,XX,+3,+9[11]/46,XX,t(1;6)(p11;p12)[9]/47,XX,t(6;10)(q12;p15),+7[6]/45,X,−X[3]/46,XX,inv(6)(p22q23)[3]/46,XX[7]Karyotype shows six apparently unrelated abnormal clones. They are given in the order of **decreasing size**, irrespective of the type of abnormality or chromosome number involved. Only clones of the same size are listed according to the chromosome order rule therefore the clone with loss of the X chromosome is given before the clone with an inversion of chromosome 6. The normal cell line is listed last.

b. Where abnormalities in different clones of equal size involve chromosomes of a different number, the **chromosome order** rule applies; X before Y, followed by autosomes in increasing number.

i. 47,XX,+8[10]/47,XX,+21[10]Karyotype shows two apparently unrelated clones of equal size and complexity. The clone with trisomy 8 is given in the ISCN description before that of the clone with trisomy 21 following the **chromosome order** rule.

c. Where abnormalities in different clones of equal size involve the same chromosome, the **gain before loss, before structural change** rule applies.

i. 47,XY,+Y[20]/45,X,−Y[20]Karyotype shows two clones of equal size; one clone has Y chromosome gain and the other has Y chromosome loss. The karyotypically unrelated clones are of equal complexity and the abnormalities involve the same chromosome therefore the **gain before loss, before structural change** rule applies.

ii. 47,XX,+8[10]/46,XX,t(8;21)(q22;q22)[10]Karyotype shows two apparently unrelated clones of equal size. The clone with trisomy 8 is given in the ISCN description before

the clone with a translocation between chromosomes 8 and 21 following the **gain before loss before structural change** rule.

d. Where structural abnormalities of the same number chromosome are present in different clones with equal complexity, they are reported **alphabetically**. If structural abnormalities involving the same chromosome are of the same type, then the **pter** to **qter** rule applies.

i. 46,XX,del(9)(q13q22)[10]/46,XX,t(9;22)(q34;q11.2)[10]Karyotype shows two apparently unrelated clones of equal size. Each clone shows a structural change of chromosome 9 so the alphabetical rule determines the order of the clones in the ISCN description, **del** before **t**.

ii. 46,XY,del(9)(p13)[15]/46,XY,del(9)(q22)[15]Karyotype shows two apparently unrelated clones of equal size. One clone shows a terminal deletion of the short arm of chromosome 9, and the other shows a terminal deletion from the long arm of chromosome 9. Therefore, the **pter** to **qter** rule determines the order of the clones in the ISCN description.

iii. 46,XX,add(7)(q22)[15]/46,XX,t(7;9)(q22;p21)[15]Karyotype shows two apparently unrelated clones of equal size. One clone shows additional material of unknown origin replacing the distal long arm of chromosome 7 from 7q22 and the other shows a translocation between chromosome 7 at 7q22 and chromosome 9 at 9p21. Since there is a chromosome 7 abnormality in both clones then the alphabetical rule of abbreviations applies. In this example **add** is listed before **t**.

6.3.3.3 Mixed Cytogenetically Related and Unrelated Clones

a. If a neoplasm contains both related and unrelated clones, the cytogenetically related clones are presented according to the rules in Section 6.3.3.1, followed by the unrelated clones according to the rules in Section 6.3.3.2.

i. 45,XY,−5[3]/44,XY,−5,−7[15]/45,XY,−10[15]/46,XY,del(11)(q23)[15]Karyotype shows two cytogenetically related clones and two cytogenetically unrelated clones. The cytogenetically related clones are given first in order of increasing complexity, followed by the unrelated clones. Since the unrelated clones are the same size they are given in chromosome order.

ii. 50,XX,t(2;6)(p22;q16),+5,+5,+8,+11[19]/51,sl,+8[7]/52,sdl1,+9[12]/46,XX,del(3)(q13)[11]/47,XX,+7[6]/46,XX,t(1;3)(p22;p14)[4]
or
50,XX,t(2;6)(p22;q16),+5,+5,+8,+11[19]/51,idem,+8[7]/52,idem,+8,+9[12]/46,XX,del(3)(q13)[11]/47,XX,+7[6]/46,XX,t(1;3)(p22;p14)[4]Karyotype shows three cytogenetically related clones and three additional cytogenetically unrelated clones. The cytogenetically related clones are given first in order of increasing complexity followed by the three unrelated clones in order of decreasing frequency.

b. If a previously identified abnormality is found among other unrelated clones, it should be given first, regardless of the number of metaphases in which it is identified.

i. 46,XY,t(9;22)(q34;q11.2)[6]/46,XY,t(1;3)(p22;p14)[14]The t(9;22)(q34;q11.2) is identified at initial presentation. At follow-up the t(9;22) is persisting and an unrelated clone involving t(1;3)(p22;p14) has emerged. Although the number of metaphases in

the unrelated clone is larger, it is written after the previously identified clone in the ISCN description.

6.3.4 Clonal Evolution

Where possible the nomenclature in this section should be used to describe subclones so that clonal evolution is evident. In some neoplastic studies clonal evolution is not linear and this may result in a mix of abnormal metaphases with clonal and nonclonal changes. For these cases a composite karyotype can be used to describe the clonal abnormalities (see Section 6.3.5).

a. The **stemline** (**sl**) is the most basic clone of a neoplastic cell population and is listed first in the ISCN description. All additional deviating subclones are termed **sidelines** (**sdl**). To describe the stemlines and sidelines, these abbreviations, or the term **idem** (Latin = same), can be used**. Note:** it may be unclear whether the least complex clone in a karyotype is the stemline or is, itself, an evolved subclone. In this case, **idem** is preferred.

- If **sl** is used in the ISCN description, it indicates that the sideline contains the sex chromosome complement and the karyotypic abnormalities of the stemline.
- **sdl** indicates that the subclone contains the sex chromosome complement and the karyotypic abnormalities of the sideline.
- **idem** refers only to the karyotype of the clone listed first and replaces the sex chromosome complement and the abnormalities of the first clone.

b. In neoplastic karyotypes where **idem** is used, the chromosome number of each subclone is given and followed by the additional changes in the subclone in relation to the most basic clone, that is given first.

c. The terms **idem** and **sl** must not be intermixed in the ISCN description.

d. If more than one **stemline** (**sl**) is present, as may occur in concomitant neoplasms, these may be referred to as **sl1**, **sl2**, *etc*.

e. If more than one **sideline** (**sdl**) is present, these may be referred to as **sdl1**, **sdl2**, *etc*. For each of these, several sub-sidelines may also exist. The use of **sdl** in this instance reduces clarity and so **idem** is preferred.

f. The term **sl** or **sdl** multiplied by a number (×2, ×3, *etc*.) may be used to describe aberrant polyploid clones. Alternatively, the term **idem** multiplied by a number (×2, ×3, *etc*.,) may be used. Additional abnormalities in the polyploid clone may then be indicated using conventional terminology.

i. 46,XY,t(8;21)(q22;q22)[26]/47,XY,t(8;21),+21[7]
or
46,XY,t(8;21)(q22;q22)[26]/47,idem,+21[7]
or
46,XY,t(8;21)(q22;q22)[26]/47,sl,+21[7]Karyotype shows a clone of twenty-six metaphases with 46 chromosomes and a translocation between chromosomes 8 and 21 as the sole abnormality. A subclone of seven metaphases with 47 chromosomes and the t(8;21), shows trisomy 21. Alternatively, **idem** or **sl** may be used to replace the sex chromosome complement and abnormalities seen in the initial clone.

ii. 46,XX,t(9;22)(q34;q11.2)[3]/47,sl,+8[17]/48,sdl1,+9[3]/49,sdl2,+11[12]
or
46,XX,t(9;22)(q34;q11.2)[3]/47,idem,+8[17]/48,idem,+8,+9[3]/49,idem,+8,+9,+11[12]Karyotype shows a clone with 46 chromosomes representing the **stemline** (**sl**); the three subclones with 47, 48 and 49 chromosomes are sidelines. In the subclone with 47 chromosomes and trisomy 8, **sl** indicates the sex chromosome complement and the presence of the abnormal chromosomes seen in the **stemline**, *i.e.*, XX and t(9;22)(q34;q11.2). This subclone is **sideline 1** (**sdl1**). In the subclone, **sdl2**, with 48 chromosomes and trisomy 9, **sdl1** indicates the sex chromosome complement and the presence of the abnormalities seen in the first **sideline**, *i.e.*, XX,t(9;22)(q34;q11.2) and trisomy 8, and so on. As an alternative, in each subclone the sex chromosome complement and the translocation 9;22 are replaced by **idem**. The terms **idem** and **sl** must not be intermixed in the ISCN description.

iii. 46,XX,t(8;21)(q22;q22)[12]/45,sl,−X[19]/46,sdl1,+8[5]/47,sdl2,+9[8]
or
46,XX,t(8;21)(q22;q22)[12]/45,idem,−X[19]/46,idem,−X,+8[5]/47,idem,−X,+8,+9[8]
The clone with t(8;21) as the sole abnormality is the most basic and hence represents the stemline; the other subclones are listed in order of increasing karyotypic complexity of the aberrations acquired during clonal evolution.

iv. 48,XX,t(12;16)(q13;p11.1),+17,+20[23]/49,sl,+6[8]/50,sdl,+7,−8,+9[4]
or
48,XX,t(12;16)(q13;p11.1),+17,+20[23]/49,idem,+6[8]/50,idem,+6,+7,−8,+9[4]Karyotype shows a subclone with 49 chromosomes that has the abnormalities seen in the stemline plus an extra chromosome 6. There is a subclone with 50 chromosomes that has the abnormalities of the sideline and has also acquired trisomy 7, monosomy 8, and trisomy 9.

v. 26,X,+4,+6,+21[3]/52,sl×2[13]
or
26,X,+4,+6,+21[3]/52,idem×2[13]Karyotype shows a near-haploid stemline with two copies of chromosomes 4, 6, and 21, and a single copy of all other chromosomes. In the subclone, doubling of the near-haploid clone (likely due to endoreduplication), is also identified.

vi. 52,XX,+4,+4,+6,+6,+21,+21[9]/51,idem,−10[3]/46,XX[18]A subsequent sample of the diagnostic example (v) (see above) shows cytogenetic relapse: nine metaphases have 52 chromosomes with the same chromosome complement as reported in the diagnostic sample. A subclone showing clonal evolution comprises three metaphases with 51 chromosomes and loss of one chromosome 10. Eighteen metaphases show an apparently normal female karyotype. The stemline (26,X,+4,+6,+21) seen in the diagnostic sample is not detected**. Note:** only the term **idem** can be used in this ISCN description (and not **sl**) since the diagnostic stemline is not present.

vii. 46,XY,t(9;22)(q34;q11.2)[3]/92,sl×2[5]/93,sdl,+8[2]
or
46,XY,t(9;22)(q34;q11.2)[3]/92,idem×2[5]/93,idem×2,+8[2]Karyotype shows a stemline with a translocation between chromosomes 9 and 22 as the sole cytogenetic abnormality. Two additional abnormal subclones are identified. One is tetraploid due to doubling of the stemline. The other is near-tetraploid because of gain of chromosome 8

in the tetraploid sideline. As an alternative, **idem** may be used, but all subclones refer back to the stemline.

viii. 46,XY,t(9;22)(q34;q11.2)[3]/47,idem,+8[10]/47,idem,+19[3]/48,idem,+8,+der(22)t(9;22)[4]Karyotype shows a stemline with a translocation between chromosomes 9 and 22 as the sole cytogenetic abnormality. Three abnormal subclones show clonal evolution. The first subclone has trisomy 8 and the t(9;22) from the stemline, the second subclone has trisomy 19 and the t(9;22) from the stemline, and the third subclone has an additional derivative chromosome 22 and is probably derived from the 47,idem,+8[10] subclone. The order of the first and second subclones in the ISCN description is determined by the complexity and chromosome order rules. The third subclone is listed last as it is more complex than the previous subclones. **Note:** the use of **idem** is preferred as **sl** and **sdl** would reduce clarity.

ix. 45,XY,−7[5]/46,sl1,+8[6]/46,XY,t(9;22)(q34;q11.2)[3]/92,sl2×2[5]/93,sl2×2,+8[2]
or
45,XY,−7[5]/46,idem,+8[6]/46,XY,t(9;22)(q34;q11.2)[3]/92,XXYY,t(9;22)×2[5]/93,XXYY,+8,t(9;22)×2[2]In a neoplasm with unrelated clones, there may be clonal evolution arising from each unrelated stemline. In the above example, the first stemline, **sl1**, shows monosomy 7 and the subclone derived from it showing trisomy 8. The second stemline, **sl2**, shows t(9;22) and clonal evolution gives rise to the subclone showing tetraploidy. Further clonal evolution is found in a sideline showing gain of chromosome 8, but to avoid confusion between sidelines of **sl1** and **sl2**, the term **sdl** is not used when referring to subclones of a second stemline. The alternative use of **idem** is shown for comparison. **Note: idem** refers only to **sl1**.

x. 48,XX,t(12;16)(q13;p11.1),+17,+20[7]/96,sl×2,inv(3)(q21q26.2),t(3;6)(p25;q21)[19]
or
48,XX,t(12;16)(q13;p11.1),+17,+20[7]/96,idem×2,inv(3)(q21q26.2),t(3;6)(p25;q21)[19]Karyotype shows a mainline with 96 chromosomes representing doubling of the hyperdiploid stemline, inversion of one chromosome 3 and an apparently balanced reciprocal translocation between one other chromosome 3 homologue and chromosome 6 *i.e.*, there are two normal chromosomes 3 and three normal chromosomes 6 in this near-tetraploid subclone. **Note:** inv(3) is given before t(3;6) following the alphabetical order rule.

xi. 53,XY,+1,+12,+14,t(14;18)(q32;q21),+15,+16,+18,+20[21]/53,sl,del(7)(q21)[9]
or
53,XY,+1,+12,+14,t(14;18)(q32;q21),+15,+16,+18,+20[21]/53,idem,del(7)(q21)[9]Karyotype shows a stemline with a reciprocal translocation of chromosomes 14 and 18, and trisomy of chromosomes 1, 12, 14, 15, 16, 18 and 20. A sideline shows the same sex chromosome complement and chromosome abnormalities as the stemline, with an additional (apparently terminal) deletion of the long arm of chromosome 7.

xii. 45,XY,t(1;6)(p34.1;q22),−3[13]/49,sl,+3,+del(7)(q11.2),+8,+9[22]
or
45,XY,t(1;6)(p34.1;q22),−3[13]/49,idem,+3,+del(7)(q11.2),+8,+9[22]Karyotype shows four additional changes in the subclone with 49 chromosomes in relation to the apparent stemline. It is possible that the two clones in this example arose through divergent clonal evolution from an undetected stemline with 46,XY,t(1;6). In this case **idem** may be more appropriate than **sl**. **Note:** the stemline has monosomy 3

whereas the sideline has two normal chromosomes 3, *i.e.*, the +3 in this situation does not indicate that the clone has trisomy 3. Alternatively, the karyotype may be written in full for clarity.

xiii. 45,XX,dic(9;20)(p13;q11.2)[11]/46,sl,+21[19]
or
45,XX,dic(9;20)(p13;q11.2)[11]/46,idem,+21[19]Karyotype shows a stemline with a dicentric chromosome involving chromosome 9 with a breakpoint at band 9p13 and chromosome 20 with a breakpoint at 20q11.2. The segments from 9pter to 9p13 and from 20q11.2 to 20qter are not present. There is a subclone with gain of chromosome 21.

xiv. 47,XX,inv(6)(p21q25),+12,del(13)(q12q14)[17]/47,sl,−inv(6),+mar[11]
or
47,XX,inv(6)(p21q25),+12,del(13)(q12q14)[17]/47,idem,−inv(6),+mar[11]Chromoso me analysis shows a stemline with an inversion of chromosome 6, trisomy 12 and an interstitial deletion of the long arm of chromosome 13. The inversion of chromosome 6 is absent from the sideline and the breakpoints do not need to be repeated. It is possible that these two clones arose through divergent clonal evolution from an undetected stemline with trisomy 12 and interstitial deletion of the long arm of chromosome 13, in which case the use of **idem** may be preferred. **Note:** there is monosomy 6 in the sideline. **Note:** the karyotype may be written in full for clarity. 47,XX,inv(6)(p21q25),+12,del(13)(q12q14)[17]/47,XX,−6,+12,del(13)(q12q14),+mar [11]

xv. 47,XX,inv(6)(p21q25),+12,del(13)(q12q14)[17]/48,sl,+6,−inv(6),+mar[11]
or
47,XX,inv(6)(p21q25),+12,del(13)(q12q14)[17]/48,idem,+6,−inv(6),+mar[11]Chromo some analysis shows a stemline with an inversion of chromosome 6, trisomy 12 and an interstitial deletion of the long arm of chromosome 13. There are two normal chromosomes 6 in the sideline and the inversion of chromosome 6 is absent. **Note:** the karyotype may be written in full for clarity 47,XX,inv(6)(p21q25),+12,del(13)(q12q14)[17]/48,XX,+12,del(13)(q12q14),+mar[11].

xvi. 46,XY,−2,−9,add(10)(q26),del(20)(q11.2q13.3),+mar1,+mar2[15]/44,sl,add(3)(p12),− 5,+8,−add(10),−mar2[5]
or
46,XY,−2,−9,add(10)(q26),del(20)(q11.2q13.3),+mar1,+mar2[15]/44,idem,add(3)(p12),−5,+8,−add(10),−mar2[5]Karyotype shows a subclone with 44 chromosomes that has lost the abnormal chromosome 10 (with additional material at band 10q26) and one of the marker chromosomes seen in the stemline. **Note:** there is monosomy 10 in the subclone. There are three additional changes in the subclone; additional material of unknown origin attached to 3p12, monosomy 5, and trisomy 8. Alternatively, the ISCN could be written in full for clarity:46,XY,−2,−9,add(10)(q26),del(20)(q11.2q13.3),+mar1,+mar2[15]/44,XY,−2,a dd(3)(p12),−5,+8,−9,−10,–del(20),+mar1[5].

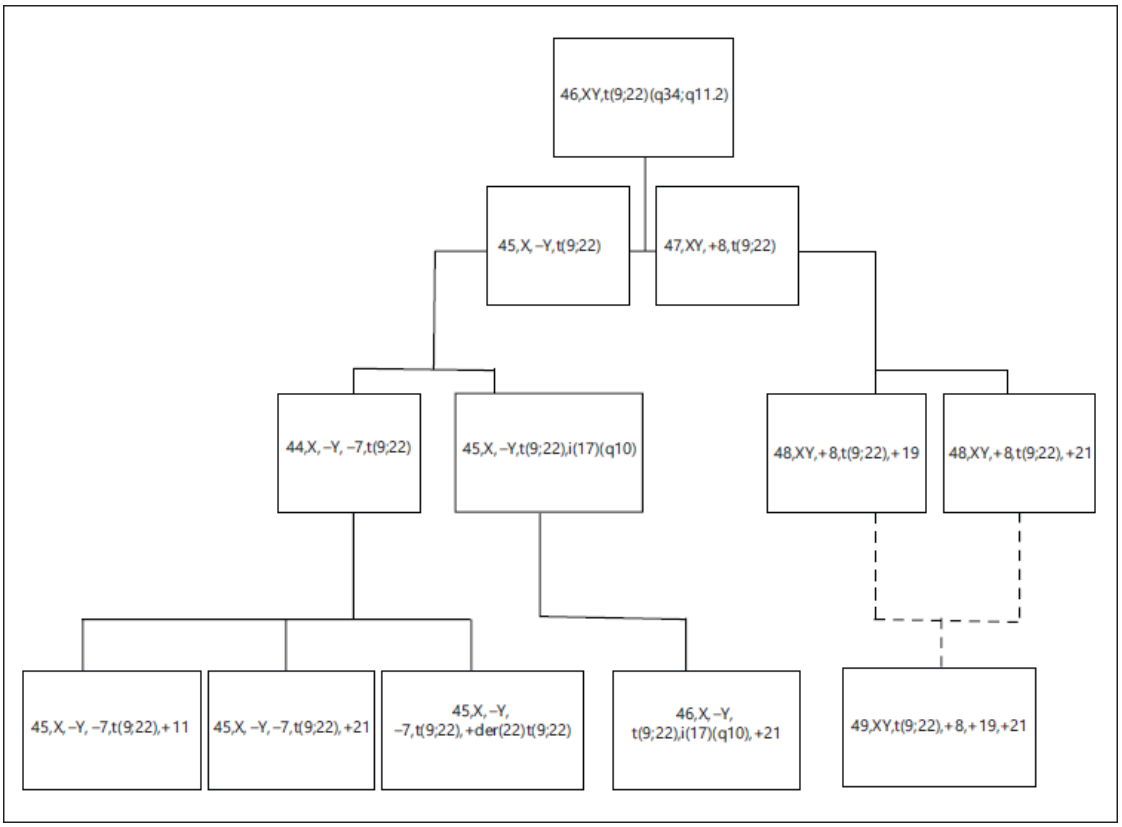


Fig. 8. *Divergent clonal evolution.*

xvii. 46,XY,t(9;22)(q34;q11.2)[10]/45,idem,−Y[4]/47,idem,+8[4]/44,idem,−Y,−7[4]/45,idem,−Y,i(17)(q10)[3]/48,idem,+8,+19[3]/48,idem,+8,+21[3]/45,idem,−Y,−7,+11[3]/45,idem,−Y,−7,+21[3]/45,idem,−Y,−7,+der(22)t(9;22)[3]/46,idem,−Y,i(17),+21[7]/49,idem,+8,+19,+21[3]The karyotype of this example is represented diagrammatically in Figure 8 and described above. The karyotype shows a stemline with 46 chromosomes and a t(9;22)(q34;q11.2). Clonal evolution has resulted in two unrelated sidelines:

- a sideline with Y chromosome loss *i.e.*, 45,X,−Y,t(9;22)
- a second sideline with trisomy 8 *i.e.*, 47,XY,+8,t(9;22)

The −Y sideline then shows further clonal evolution that branches:

- one subclone shows monosomy 7 *i.e.*, 44,X,−Y,−7,t(9;22)
- another subclone shows an isochromosome of the long arm of chromosome 17 *i.e.*, 45,X,−Y,t(9;22),i(17)(q10)

The monosomy 7 subclone (with t(9;22) and −Y) has three subclones:

- 45,X,−Y,−7,t(9;22),+11
- 45,X,−Y,−7,t(9;22),+21
- 45,X,−Y,−7,t(9;22),+der(22)t(9;22)

The i(17q) subclone has a sub-subclone with trisomy 21:

- 46,X,−Y,t(9;22),i(17),+21

The sideline with +8 shows a divergent branch of clonal evolution. It has two subclones:

- one subclone with gain of chromosome 19 *i.e.*, 48,XY,+8,t(9;22),+19
- another subclone with gain of chromosome 21 *i.e.*, 48,XY,+8,t(9;22),+21

One of these subclones shows further clonal evolution. It is possible that either the subclone with +19 gained a chromosome 21 or the +21 clone gained a chromosome 19. This is represented by the dotted lines in Figure 8. The nomenclature description does not make any assumption concerning the subclone/sub-subclone relationship but rather describes each clone and subclone firstly following the chromosome order rule (−Y before +8) and then by increasing order of complexity. **Note:** the description of cell lines with divergent clonal evolution is not possible using **sl** and **sdl**. The karyotype is described following the ISCN rules (see Section 6.3.3.1).

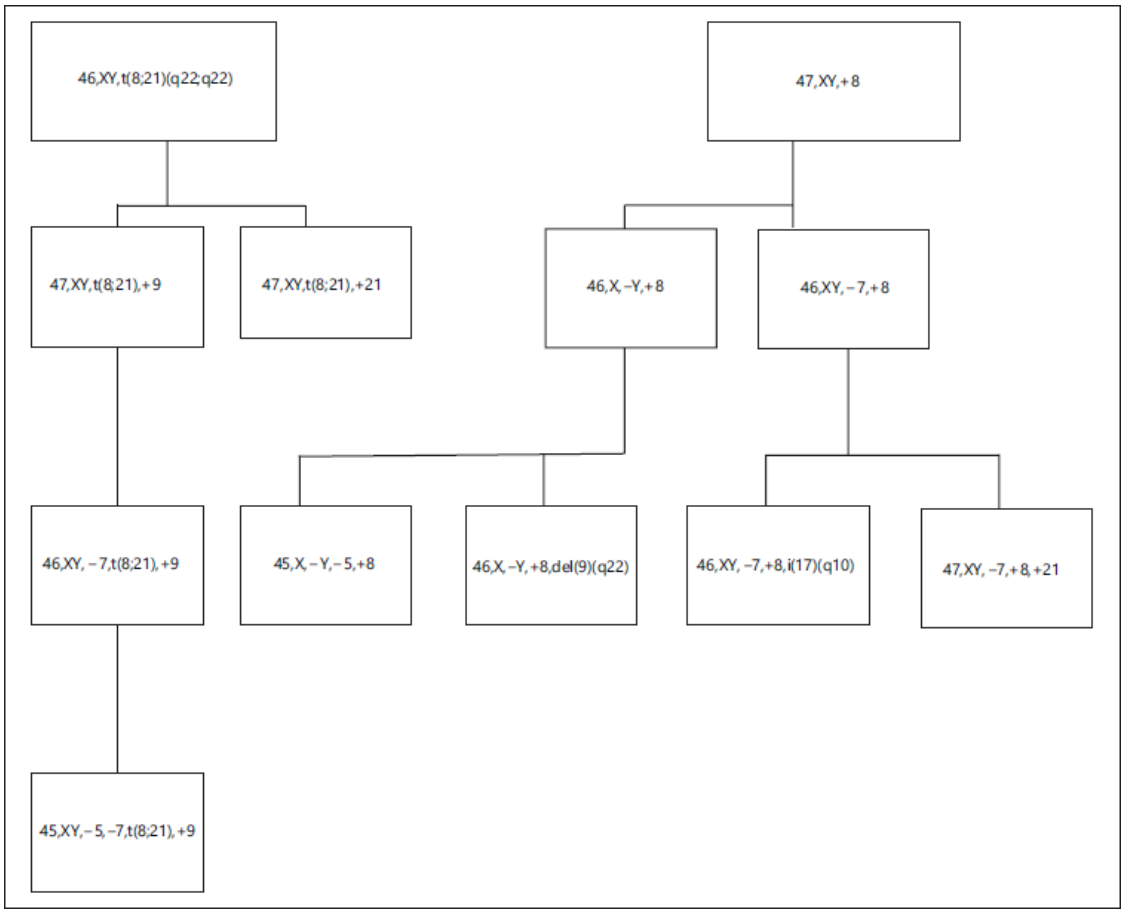


Fig. 9. *Clonal evolution in cytogenetically unrelated stem lines.*

xviii. 46,XY,t(8;21)(q22;q22)[29]/47,idem,+9[3]/47,idem,+21[3]/46,idem,−7,+9[6]/45,idem,−5,−7,+9[3]/47,XY,+8[15]/46,X,−Y,+8[3]/46,XY,−7,+8[9]/45,X,−Y,−5,+8[6]/46,X,−Y,+8,del(9)(q22)[2]/46,XY,−7,+8,i(17)(q10)[3]/47,XY,−7,+8,+21[5]
or
46,XY,t(8;21)(q22;q22)[29]/47,sl1,+9[3]/47,sl1,+21[3]/46,sl1,−7,+9[6]/45,sl1,−5,−7,+9[3]/47,XY,+8[15]/46,sl2,−Y[3]/46,sl2,−7[9]/45,sl2,−Y,−5[6]/46,sl2,−Y,del(9)(q22)[2]/46,sl2,−7,i(17)(q10)[3]/47,sl2−7,+21[5]The karyotype of this example is represented diagrammatically in Figure 9 and described above. The karyotype shows two unrelated stemlines that each show clonal evolution.The larger stemline is listed first followed by the related sidelines applying the rules:

- sex chromosomes (X before Y) before autosomes,
- autosomes in order of increasing number,
- increasing order of complexity.

The smaller unrelated stemline (47,XY,+8) is given next followed by its related sidelines, applying the same rules. **Note: idem** does not distinguish between the two stem lines and so for clarity **sl1** and **sl2** may be used.

6.3.5 Composite Karyotype

a. In many instances, especially in solid tumors, there is karyotypic heterogeneity within the neoplasm, but different metaphases nevertheless share some cytogenetic characteristics.
b. Every effort should be made to describe the subclones so that clonal evolution is evident. However, in some instances, a **composite karyotype** (**cp**) will have to be created. The composite karyotype contains only clonally occurring abnormalities and gives the range of chromosome numbers in the metaphases containing the clonal abnormalities. A karyotype may show a mix of fully characterised clones and subclones, in addition to subclone(s) being given as composite(s) (see Section 6.3.5).
c. The total number of metaphases in which the clonal changes are observed is given in **[ ]** after the karyotype, preceded by **cp**. The abbreviation **cp** is not used to describe obvious random loss in an otherwise **normal** result *i.e.*, random losses or gains should be interpreted as consistent with technical artifact and should not be included in nomenclature. This is distinct from the **composite karyotype** (**cp**) where clonal changes are identified in the context of non-clonal abnormalities.
d. It is not always apparent from a **composite karyotype** (**cp**) how many metaphases have each abnormality. This information may be expressed by providing the number of metaphases in **square brackets** (**[ ]**) after each abnormality.

i. 45~48,XX,del(3)(p12)[2],−5[4],+8[2],+11[3][cp7]A composite karyotype is constructed from analysis of seven metaphases, each with at least one of the abnormalities listed. Two metaphases show a terminal deletion of the short arm of chromosome 3 with a breakpoint in 3p12, four metaphases show monosomy 5, two metaphases show trisomy 8, and three metaphases show trisomy 11. Some metaphases show more than one of these abnormalities. **Note:** the sum of the clonal abnormalities

indicates a chromosome count of 47 but metaphases with 45 and up to 48 chromosomes are identified.

ii. 47~55,XX,del(3)(p12),+i(6)(p10),del(7)(q11.2),+8,dup(11)(q13q25),+16,+17,der(18)t(18;20)(q23;q11.1),+21,+21,+22[cp24]All of the abnormalities may not be present in a single metaphase but each of the abnormalities in this cytogenetic analysis is present in at least two metaphases. **Note:** some metaphases with 55 chromosomes show additional non-clonal chromosome gains and losses.

iii. 63~74(35,X,+X,+1,+6,+8,+10,+11,+14,+15,+18,+19,+21,+22)×2,−2,−5,−16[cp12]In this composite karyotype of twelve metaphases, where the chromosome number ranges between 63 and 74, each metaphase shows at least one of the listed abnormalities. There is an apparent doubling of hypodiploid cells with further loss of chromosomes 2, 5 and 16 (see Section 6.3.7). **Note:** while the count falls within the near-triploid range, it is reported relative to haploid in conjunction with supporting evidence from the result of a previous diagnostic sample or from alternative methods *e.g.*, SNP microarray.

iv. 69~73,XXY,+Y,+1,−4,−13,del(17)(p11.2),+21,+21,+22[cp10]/46,XY[10]A composite karyotype in a male shows near-triploidy with gain of a Y chromosome, aneuploidy of several autosomes (chromosomes 1, 4, 13, 21 and 22), and an apparently terminal deletion of 17p. **Note:** in males all sex chromosome deviation is expressed in relation to XXY in triploid neoplasms (see Section 6.3.7).

e. In a **composite karyotype** the sum of the aberrations listed may indicate a higher or lower chromosomes number than that actually seen.

i. 48,XX,+7,+9
48,XX,+7,+11
48,XX,+9,+11
48,XX,+9,+13
48,XX,+13,+21

The composite karyotype of these five metaphases is:
48,XX,+7,+9,+11,+13[cp5]
or
48,XX,+7[2],+9[3],+11[2],+13[2][cp5]The chromosome number of the five metaphases containing a clonal abnormality is 48, which is given as the chromosome number of the composite karyotype, although the sum total of all the clonal changes indicates a chromosomes number of 50. **Note:** a metaphase with 50 chromosomes is not present.

ii. 42,XX,−2,−16,−21,−22
45,XX,−7,+9,−20
46,XX,−7,+8,−12,+13
43,XX,−7,−18,−20
46,XX,−7,+8
The composite karyotype of these five metaphases is:

43~46,XX,−7,+8[cp4]
or
43~46,XX,−7[4],+8[2][cp4]**Note:** the metaphase with 42 chromosomes is not included because the abnormalities are due to random loss and are not part of the clone.

iii. 51,XY,+1,−7,+8,t(9;22)(q34;q11.2),+11,+13,+19,+der(22)t(9;22)
51,XY,+1,+5,−7,+8,t(9;22)(q34;q11.2),+11,+19,+der(22)t(9;22)
51,XY,+1,+5,−7,+8,t(9;22)(q34;q11.2),+13,+19,+der(22)t(9;22)
52,XY,+1,+5,−7,+8,t(9;22)(q34;q11.2),+11,+13,+19,+der(22)t(9;22)
46,XY,t(9;22)(q34;q11.2)[5]

The composite karyotype of these metaphases is: 46,XY,t(9;22)(q34;q11.2)[5]/51~52,sl,+1,+5,−7,+8,+11,+13,+19,+der(22)t(9;22)[cp4]
or
46,XY,t(9;22)(q34;q11.2)[5]/51~52,idem,+1,+5,−7,+8,+11,+13,+19,+der(22)t(9;22)[cp4]
or
46,XY,t(9;22)(q34;q11.2)[5]/51~52,idem,+1,+5[3],−7,+8,+11[3],+13[3],+19,+der(22)t(9;22) [cp4]Karyotype shows a stemline with a 9;22 translocation. Multiple metaphases are found with gain and loss of chromosomes, likely due to clonal evolution. As not all aberrations are present in all metaphases, these metaphases are combined into a composite karyotype. **Note:** the stemline shows the t(9;22) and the subclone is shown using a composite karyotype.

iv. 25,XY,−1,−1,−2,−2,inv(3)(q21q26.2),−7,+8,−9,−9,−10,−11,−11,−12,−12,−13,−14,−15,−16,−17,−18,−20,−20,−22,−22
45,XY,inv(3)(q21q26.2),−7,+8,−19
46,XY,inv(3)(q21q26.2),−7,+8
45,XY,inv(3)(q21q26.2),−7
46,XY,inv(3)(q21q26.2),−7,+21
44,XY,−3,inv(3)(q21q26.2),−7
46,XY,inv(3)(q21q26.2),−7,+14
47,XY,inv(3)(q21q26.2),+8
47,XY,inv(3)(q21q26.2),+8,+14,−21
47,XY,inv(3)(q21q26.2),+14
46,XY,inv(3)(q21q26.2)

The composite karyotype of the ten near-diploid metaphases is: 44~47,XY,inv(3)(q21q26.2),−7,+8,+14[cp10]All metaphases analyzed show an inversion of chromosome 3. Nine metaphases also show gain or loss of various chromosomes, likely due to clonal evolution. Not all aberrations are present in all metaphases, therefore, ten metaphases are combined into a composite karyotype. **Note:** the metaphase with 25 chromosomes, shows random loss of several chromosomes and is excluded from the composite karyotype since it does not contribute to establishing the clonality of the abnormalities and its chromosome number would alter the ploidy level erroneously.

v. 48,X,i(X)(q10),+8,+9
47,XX,+9,del(17)(p13)
47,X,i(X)(q10),+11
47,X,i(X)(q10),+9,del(17)(p13)
47,X,i(X)(q10),+8
48,XX,+8,+9

The composite karyotype of these six metaphases is: 47~48,XX,i(X)(q10),+8,+9,del(17)(p13)[cp6]
or
47~48,XX,i(X)(q10)[4],+8[3],+9[4],del(17)(p13)[2][cp6]Two metaphases show two normal sex chromosomes (XX) that are given in the composite karyotype and the abnormality affecting an X chromosome is also given since it is seen in four metaphases. **Note:** there is no metaphase with three X chromosomes.

vi. 45,X,−X
45,X,−X,del(16)(q24)
46,X,−X,del(16)(q24),+21
46,X,−X,+21
44,X,−X,−7
46,XX

The composite karyotype of these six metaphases is: 44~46,X,−X,del(16)(q24),+21[cp5]/46,XX[1]The abnormality of the sex chromosome complement in the neoplastic sample is indicated in the composite karyotype. Loss of chromosome 7 in the metaphase with 44,X,−X,−7, is not clonal and therefore is not included in the composite karyotype. **Note:** additional chromosome analysis (if possible) is appropriate to exclude monosomy 7.

f. A composite karyotype may contain such seemingly paradoxical abnormalities as loss and gain of the same chromosome. For example, if the following six metaphases are karyotyped:

i. 45,XX,−15,del(17)(p11.2)
46,XX,+7,−15,del(17)(p11.2)
46,XX,+12,−15
47,XX,+7
47,XX,+15,del(17)(p11.2)
48,XX,+12,+15

The composite karyotype of these six metaphases is: 45~48,XX,+7,+12,+15,−15,del(17)(p11.2)[cp6]
or
45~48,XX,+7[2],+12[2],+15[2],−15[3],del(17)(p11.2)[3][cp6]Trisomy 15 and monosomy 15 are both clonal changes, present in two and three metaphases, respectively. If there are both gains and losses of the same chromosome, gains are listed before the losses in the ISCN (see Section 4.5.3).

Notified in the ISCN 2024. Full details can be found in the published Erratum and the ISCN online has been corrected.

6.3.6 Incomplete Karyotype

a. When chromosome quality is poor and/or metaphases are scarce, it may be necessary to create an **incomplete** (**inc**) karyotype (see Section 5.1).
b. The use of this term is limited to rare instances when one or more abnormalities can be identified, but it is uncertain whether the remaining chromosomes are morphologically normal. The karyotype may contain unidentified structural or numerical changes in addition to the abnormalities listed.
c. The abbreviation **inc** is placed at the end of the nomenclature description, after the description of identifiable abnormalities, and is preceded by a **comma** (**,**).

i. 46,XX,del(1)(q21),inc[4]A neoplastic sample where it has only been possible to identify a clonally occurring deletion of the long arm of chromosome 1, but analysis is incomplete. Without the abbreviation **inc**, the del(1)(q21) would be the sole anomaly present in this neoplasm.
ii. 46,XX,der(19)t(1;19)(q23;p13),inc[4]The chromosomes in this example could be counted however, the banding and morphology are too poor to allow complete analysis. A derivative chromosome 19 from a translocation between chromosomes 1 and 19 is identified. Use of **inc** indicates that this may not be the sole clonal abnormality in this neoplastic sample.
iii. 53~57,XY,+1,+3,+6,t(9;22)(q34;q11.2),+21,+3mar,inc[cp10]This abnormal neoplastic sample has, in addition to the abnormalities presented that include three marker chromosomes, other changes that could not be identified. The abbreviation **cp** indicates a **composite** karyotype from 10 cells (see Section 6.3.5).
iv. 45~47,XY,–5,inc[cp2]/46,XY[19].nuc ish (D5S721/D5S23,CSF1R)×1[25/200]A single metaphase with 45,XY,−5 and a single metaphase with the karyotype 47,XY,−5,+17,+18 are identified, although the presence of additional clonal changes could not be excluded. FISH confirmed the monosomy 5 cell line but interphase FISH for chromosomes 17 and 18 failed to achieve a result. The trisomies of chromosomes 17 and 18 have not been confirmed and therefore cannot be reported. Whether this sample is reported or additional testing is undertaken to confirm the finding is at the discretion of the laboratory.
v. 31<2n>,XY,−1,−2,inv(3)(q21q26.2),−7,+8,−9,−9,−10,−12,−13,−14,−15,−16,−17,−18,−21,−21,−22
45,XY,inv(3)(q21q26.2),−7,+8,−9
Taken together these two metaphases can be reported as: 31~45,XY,inv(3)(q21q26.2),−7,+8,–9,inc[cp2]Only two metaphases are found on karyotype; both show an inversion of chromosome 3, monosomy 7, trisomy 8 and monosomy 9. There are fourteen other chromosome losses in one of the metaphases. Not all aberrations are present in both metaphases, therefore these metaphases are combined into an incomplete karyotype. **Note:** it is necessary to include the metaphase with 31 chromosomes in the karyotype, even though it shows probable random loss of several chromosomes, because it establishes clonality of the abnormalities in the other metaphase. The interpretative comment should include a statement concerning the lack of accuracy of the chromosome number. The monosomies of chromosome 7 and 9 are included according to the rule that two metaphases with identical losses of one or more chromosomes and the same structural abnormality may be considered clonal

(see Section 4.5.1). They may be discussed in the interpretive text at the discretion of the laboratory. Confirmatory investigations could also be considered before reporting this case.

6.3.7 Modal Number and Ploidy Levels

a. The modal number is the most common chromosome number in a neoplastic cell population.
b. The modal number may be expressed as a range between two chromosome numbers.
c. Modal numbers are given in either the haploid (n), diploid (2n), triploid (3n) or tetraploid (4n) range. When the chromosome number is not equal to a multiple of the haploid number, it may be expressed as near-haploid (n±), hypohaploid (n−), hyperhaploid (n+), near-diploid (2n±), hypodiploid (2n−), hyperdiploid (2n+), near-triploid (3n±), hypotriploid (3n−), hypertriploid (3n+), near-tetraploid (4n±), hypotetraploid (4n−), hypertetraploid (4n+), and so on (see Table 6).

Table 6. Ploidy levels, including ranges of chromosome numbers constituting each level.

Near-haploidy (23±)	**≤34**	**Near-pentaploidy (115±)**	**104–126**
Hypohaploidy	<23	Hypopentaploidy	104–114
Hyperhaploidy	24–34	Hyperpentaploidy	116–126
Near-diploidy (46±)	**35–57**	**Near-hexaploidy (138±)**	**127–149**
Hypodiploidy	35–45	Hypohexaploidy	127–137
Hyperdiploidy	47–57	Hyperhexaploidy	139–149
Near-triploidy (69±)	**58–80**	**Near-heptaploidy (161±)**	**150–172**
Hypotriploidy	58–68	Hypoheptaploidy	150–160
Hypertriploidy	70–80	Hyperheptaploidy	162–172
Near-tetraploidy (92±)	**81–103**	**Near-octaploidy (184±)**	**173–195**
Hypotetraploidy	81–91	Hypooctaploidy	173–195
Hypertetraploidy	93–103	Hyperoctaploidy	185–195

d. Each range is determined as n±n/2, with n/2 defined operationally as 11 chromosomes.
e. The ploidy level is expressed within **angle brackets** (< >) *e.g.*, 58<2n>,XX,+X,+8,+11,+14,+17,+18,+18,+19,+20,+21,+21,+22[10]
f. Ploidy levels are recommended but exceptions may be made if biologically significant or clinically relevant in the specific disease.

i. 81<3n>,XXX,+X,+X,+X,+X,+X,+1,+1,+3,+3,+14,+14,+14,−15,+21[10]A neoplasm in a female shows 81 chromosomes but is reported relative to triploid since most chromosomes are trisomic and this is biologically significant for the disease in question, even though the count is in the near-tetraploid range.
ii. 58<2n>,XY,+X,+4,+6,+8,+9,+10,+14,+14,+17,+18,+21,+21[20]A neoplastic sample in the hypotriploid range is reported relative to a diploid chromosome number, which is biologically significant in this particular disease.

g. Pseudodiploid, pseudotriploid, *etc*., are used to describe a karyotype that has the number of chromosomes equal to a multiple of the haploid number (euploid) but is abnormal because of the presence of acquired numerical and/or structural aberrations.

i. 46,XX,−5,+8[10]A neoplastic sample with a pseudodiploid karyotype of 46 chromosomes with monosomy 5 and trisomy 8.
ii. 69<3n>,XXY,−5,−7,+10,+17[8]A neoplastic sample with a pseudotriploid karyotype of 69 chromosomes with loss of chromosomes 5 and 7 and tetrasomy of chromosomes 10 and 17.

d. Doubling of a clone may occur *e.g.*, by endoreduplication. Doubled hyperhaploid clones leading to **masked hypodiploidy** may be the largest clones at diagnosis. Classification of masked hypodiploidy is clinically challenging and can impact patient management. Additional chromosome abnormalities can arise after chromosome doubling. To clarify the true ploidy of masked hypodiploid karyotypes, the stemline can be noted in the ISCN description immediately following the chromosomes number of the masked hypodiploid clone. Additional testing must be performed to provide supporting evidence of the stemline.

e. The description of sex chromosome abnormalities poses a special problem in male neoplasms with uneven ploidy levels (haploid, triploid, pentaploid, *etc*.) because the expected sex chromosome constitution cannot be deduced. For example, the sex chromosome constitution of a triploid neoplasm might theoretically be XXY or XYY. By convention, in males all sex chromosome deviation should be expressed in relation to X in haploid neoplasms, to XXY in triploid neoplasms, to XXXYY in pentaploid neoplasms, and so on.

i. 25,X,+Y,+21[1]/50,XY,+X,+Y,+21,+21[19]
or
25,X,+Y,+21[1]/50(25,X,+Y,+21)×2[19]Karyotype shows one metaphase with a hyperhaploid karyotype and nineteen metaphases with an apparently hyperdiploid karyotype resulting from a doubling of the hyperhaploid clone. **Note:** the single near-haploid metaphase is included in the report since its clonality is demonstrated by the presence of doubled near-haploid metaphases (see Section 6.3).
ii. 50(25,X,+X,+21)×2[9]/46,XX[11]An apparently hyperdiploid clone comprised of nine metaphases arose from the doubling of a hyperhaploid clone. Eleven metaphases show an apparently normal female karyotype. **Note:** doubling of the hyperhaploid clone is only reported as 50(25,X,+X,+21)×2 with supporting evidence from an alternative method *e.g.,* FISH shows the near-haploid stemline, SNP microarray shows homozygosity of disomic chromosomes, or a hyperhaploid clone in a previous analysis.
iii. 55,XX,+X,+X,+6,+10,+10,+18,+18,der(18)t(18;19)(q21;p11∼12)x2,+21,+21[7]/46,XY[13]
or
55(27,X,+X,+10,+der(18)t(18;19)(q21;p11∼12),+21)×2,+6[7]/46,XY[13]An apparently hyperdiploid clone arises from the doubling of a hyperhaploid clone, and there is gain of an additional chromosome 6 after the doubling. The sex chromosome constitution of neoplastic cells may not reflect the sex chromosome complement of the individual's normal cells. In this example the hyperhaploid clone contains the X chromosome (the Y chromosome is lost in the formation of the hyperhaploid clone) and has gained another copy of the X chromosome. The apparently normal male karyotype is present in thirteen metaphases. **Note:** notation for the doubling of a hyperhaploid

clone can only be used when it is supported by the results obtained from alternative methods, or from a previous analysis.

iv. 68,XY,−X[10]Karyotype of a neoplasm in a male shows triploidy with loss of a sex chromosome in all ten metaphases obtained for analysis.

v. 26,X,+Y,t(6;14)(q13;q32),+14,+21[6]/27,idem,+18[2]/52,idem×2[9]/46,XY[4]
or
26,X,+Y,t(6;14)(q13;q32),+14,+21[6]/27,idem,+18[2]/52(26,X,+Y,t(6;14),+14,+21)×2[9]/46,XY[4]
or
26,X,+Y,t(6;14)(q13;q32),+14,+21[6]/27,sl,+18[2]/52,sl×2[9]/46,XY[4]The stemline is represented by six hyperhaploid metaphases. A subclone of two metaphases exhibits an additional chromosome 18. Nine metaphases show an apparently hyperdiploid clone arising from the doubling of the hyper-haploid stemline. No abnormality is detected in four metaphases.

vi. 32,−X,+Y,+3,+5,+7,+9,+11,+15,+18,+19,+21[16]/46,XY[14]Karyotype of a neoplastic sample shows hyperhaploidy with additional copies of chromosomes 3, 5, 7, 9, 11, 15, 18, 19 and 21 relative to the haploid set in 16 metaphases. Fourteen metaphases show an apparently normal male karyotype. **Note:** the sex chromosome complement is described as −X and +Y following the convention that sex chromosomes are expressed in relation to X in haploid neoplasms.

6.4 Constitutional Karyotype

a. The same clonality criteria (see Section 6.3) apply to metaphases containing the constitutional karyotype as to metaphases containing acquired chromosome abnormalities.
b. A normal diploid clone, when present, is listed last.
c. A constitutional abnormality may be indicated by the letter **c** after the abnormality designation. **Note:** when the inheritance is known the **c** is replaced by the relevant abbreviation **mat**, **pat, dmat,** or **dpat**.
d. In the description of the karyotype, the constitutional and acquired anomalies are listed in chromosomes number order (see Section 4.3).
e. A clone with only a constitutional abnormality is listed last (as it is the normal clone for that individual).
f. If the karyotype includes a constitutional and an acquired gain of the same chromosome, the constitutional gain is listed first.

i. 47,XXYc[5]/46,XY[15] or 47,XY,+X[5]/46,XY[15]Karyotype of a neoplastic sample in a male with either constitutional mosaicism for an extra X chromosome or acquired gain of one X chromosome. In this example **or** is used to describe the alternative options when further studies are not possible, or have not yet been undertaken.

ii. 48,XX,+8,+21c[20]Karyotype of a neoplastic sample with a constitutional trisomy 21 and an acquired trisomy 8.

iii. 47,X,t(X;18)(p11.1;q11.1),+21c[20]Karyotype of a neoplastic sample with a constitutional trisomy 21 and an acquired t(X;18).

iv. 47,XXYc,t(9;22)(q34;q11.2)[20]Karyotype of a neoplastic sample with a constitutional XXY sex chromosome complement and an acquired t(9;22).

v. 48,XY,+8,inv(10)(p12q22)mat,+21[20]Karyotype of a neoplastic sample with a constitutional, maternally inherited inversion of chromosome 10 and acquired trisomies 8 and 21. **Note:** when the inheritance is known, **mat** or **pat** takes the place of the **c**.

vi. 47,XX,del(5)(q15),+mar c[20]Karyotype of a neoplastic sample with a constitutional marker chromosome of unknown origin and an acquired deletion of the long arm of one chromosome 5. For constitutional markers, there is a space between **mar** and **c** (see Section 4.4.1).

vii. 48,XY,+8,+21c[3]/49,idem,+9[5]/47,XY,+21c[12]Karyotype of a neoplastic sample with a constitutional trisomy 21 and acquired trisomies 8 and 9. The clone with only the constitutional trisomy 21 is listed last irrespective of the size of this clone.

viii. 47,XX,t(2;13)(q37;q14),der(14;21)(q10;q10)c,+18,+mar[3]/45,XX,der(14;21)c[17]An individual with a constitutional Robertsonian translocation between chromosomes 14 and 21 shows two cell lines by cytogenetic analysis. The neoplastic clone shows an acquired t(2;13), trisomy 18 and an unidentified marker chromosome in addition to the constitutional der(14;21). The constitutional cell line with the der(14;21) is listed last.

g. To describe acquired abnormalities affecting one of the chromosomes of a pair that is involved in a constitutional abnormality, the constitutional aberration must always be given, even if none of the neoplastic metaphases have this particular aberration. Thus, an acquired abnormality is always presented in relation to the constitutional karyotype.

i. 46,XXYc,−X[20]Neoplastic sample from a patient with Klinefelter syndrome with an acquired loss of one X chromosome.

ii. 46,XX,+21c,−21[20]Karyotype of a patient with a constitutional trisomy 21 and the acquired abnormality in the neoplastic metaphases is a loss of one chromosome 21.

iii. 45,Xc,t(X;18)(p11.1;q11.1)[20]Neoplastic sample from a patient with Turner syndrome (45,X) shows an acquired t(X;18), *i.e.*, the only X chromosomes is involved in the translocation and consequently there is no normal X chromosome in the neoplastic metaphases. **Note:** in a female with a normal sex chromosome constitution and acquired t(X;18), the karyotype would be: 46,X,t(X;18)(p11.1;q11.1)[20].

iv. 46,XX,der(9)t(9;11)(p22;q23)t(11;12)(p13;q22)c,der(11)t(9;11)t(11;12)c,der(12)t(11;12)c[20]A female patient with a known constitutional t(11;12)(p13;q22) shows an acquired t(9;11) that is a recurrent rearrangement in Acute Myeloid Leukemia. The derivative chromosome 11 involved in the t(11;12)c is also involved in the t(9;11) abnormality. The resulting karyotype, with both constitutional and acquired aberrations, should list each aberrant chromosome as a derivative. The abbreviation, **c**, is used to show that each derivative chromosome has a component of the constitutional translocation.

v. 44,X,−Y,der(13;14)(q10;q10)c[5]/45,XY,der(11)t(11;14)(q13;q32),der(13;14)(q10;q10)c t(11;14)[5]/45,XY,der(13;14)(q10;q10)c[5]Male patient with a constitutional Robertsonian der(13;14)(q10;q10) shows loss of the Y chromosome in five metaphases. There is also a t(11;14) in a neoplastic clone. The derivative chromosome 14 involved in the der(13;14)c is described as der(13;14)(q10;q10)c t(11;14). **Note:** there is a space between **c** and t(11;14).

vi. 46,XY,t(2;15)(q21;q26.1)mat,der(6)t(6;17)(q23;q21),der(7;12)(p10;q10),+mar[cp3]/46,XY,t(2;15)mat[7]//46,XX,t(2;15)c[10]A male recipient of an allogeneic stem cell transplant from his mother has a known constitutional t(2;15)(q21;q26.1) and shows a composite karyotype composed of three metaphases, with a der(6)t(6;17), der(7;12) and

a marker chromosome. Seven metaphases contain only the constitutional t(2;15) without acquired clonal abnormalities. **Note:** the ten metaphases from the female donor also exhibit a constitutional t(2;5).

6.5 Counting Chromosome Abnormalities

The recommended method for counting chromosome abnormalities is outlined below and in Tables 7 and 8.

a. Only acquired clonal abnormalities are counted. Constitutional abnormalities are not counted.
b. Where multiple clones are present, each independent abnormality is counted only once.
c. Disease-specific definitions, as described in Chun et al. (2010), Grimwade et al. (2010), Baliakas et al. (2019) and Haase et al. (2019), are used for cytogenomic prognostic risk assessment. **To determine cytogenetic complexity in a specific disease, it is mandatory to count chromosome abnormalities in the same manner as described in the corresponding study on which the prognostic system was based**.
d. Two approaches have been employed to deal with more than one clone: counting the total number of distinct chromosomal abnormalities in the entire sample or counting clonal chromosomal abnormalities in metaphases with the highest number of abnormalities. They have been adopted in different studies for risk stratification. The former method has the advantage of accounting for heterogeneity of the tumor genome and is applicable in cases of composite karyotype. Consequently, this approach has been applied in Table 7.

Table 7. Counting chromosome abnormalities.

Abnormality Type	Examples	Abnormality count
Numerical gain	Trisomy Duplication of a derivative chromosome	1
Numerical loss	Monosomy, includes –Y	1
Balanced structural abnormality (no gain, no loss of chromosomal material)	Simple balanced translocation Complex balanced translocation (involving three or more chromosomes) Inversion Balanced insertion	1
Unbalanced aberrations involved one chromosome (leading to gain or loss of chromosomal material)	Isochromosome Deletion[a] Duplication[a] Additional material of unknown origin [add] Simple ring chromosome Isodicentric chromosome Homogeneously staining region[b] Double minutes Unidentified marker chromosome	1
	Tetrasomy of same chromosome Triplication or quadruplication Isoderivative chromosome	2
Unbalanced aberrations involved two or more chromosome	Unbalanced translocation Unbalanced insertion Derivative chromosome[c] Complex ring chromosome Isoderivative chromosome	2
Ploidy abnormalities	Multiplication of complete chromosome set (normal or aberrant)	1
Multiple clones (subclones or independent clones)	Count chromosome abnormalities in each clone and each new abnormality in the subclone(s) separately Number of chromosome abnormalities is determined by the total count of abnormalities in the entire sample	
Constitutional abnormalities	Not included in the count; if aetiology unknown then include as above	0

[a]Includes multiples of one chromosome.
[b]An hsr is considered to be one event for the purpose of counting abnormalities.
[c]Abnormalities related to a derivative chromosome are not counted as additional. See example 38 in Table 8.

Table 8. *Example karyotypes with abnormality count.*

	Karyotype	Abnormality	Abnormality count
1	47,XX,+8[20]	Trisomy	1
2	45,XX,−7[10]/46,XX[10]	Monosomy	1
3	46,XY,t(8;21)(q22;q22)[18]/46,XY[2]	Balanced translocation	1
4	46,XY,t(9;22;17)(q34;q11.2;p11.2)[20]	Complex balanced translocation	1
5	46,XY,inv(16)(p13.1q22)[20]	Inversion	1
6	46,XX,ins(5;2)(p14;q22q32)[7]/46,XX[13]	Balanced insertion	1
7	46,XY,i(17)(q10)[8]/46,XY[12]	Isochromosome	1
8	46,XY,del(7)(q22q32)[20]	Deletion	1
9	46,XY,der(7)del(7)(p15)del(7)(q32)[20]	Multiple deletions in one chromosome[a]	1
10	46,XY,dup(1)(q21q32)[20]	Duplication	1
11	46,XY,r(7)(p22q21)[5]/46,XY[15]	Simple ring chromosome	1
12	46,XX,add(11)(p15)[20]	Additional material of unknown origin[b]	1
13	46,XX,idic(7)(q11.2)[9]/46,XX[24]	Isodicentric chromosome	1
14	46,XX,hsr(4)(q25)[15]/46,XX[5]	Homogeneously staining region	1
15	46,XY,5~20dmin[13]/46,XY[7]	Double minutes	1
16	47,XY,+mar[4]/46,XY[16]	Unidentified marker chromosome	1
17	48,XX,+8,+8[20]	Tetrasomy of same chromosome	2
18	46,XX,trp(1)(q21q32)[20]	Triplication or quadruplication	2
19	46,XY,ider(20)(q10)del(20)(q11.2q13.1)[17]/46,XY[3]	Isoderivative chromosome	2
20	46,XX,der(19)t(1;19)(q23;p13.3)[11]/46,XX[9]	Unbalanced translocation	2
21	46,XY,der(22)ins(22;9)(q11.2;q34q34)del(22)(q13)[20]	Unbalanced insertion and deletion	2
22	46,XX,der(5)t(5;7)(q14;q11.2)t(7;18)(q22;q21.1)t(18;21)(q23;q11.2)[20]	Derivative chromosome	2
23	45,XX,der(1)r(1;3)(p34q23;q21q27),−7,del(12)(p13p11.2)[12]/46,XX[8]	Complex ring chromosome involving two chromosomes Monosomy Deletion	4
24	46,XX,ider(9)(q10)t(9;22)(q34;q11.2)[16]/46,XX[11]	Isoderivative chromosome involving two chromosomes	2
25	92,XXYY[19]/46,XY[1]	Tetraploidy	1
26	46,XX,+1,der(1;7)(q10;p10)[20]	Unbalanced translocation	2
27	46,XY,+1,der(1;7)(q10;p10)[11]/46,idem,add(3)(q12)[6]/46,XY[3]	Unbalanced translocation Additional material of unknown origin	3
28	49,XY,+Y,+1,der(1;7)(q10;q10),+8,+14,del(20)(q11.2q13.3)[15]/46,XY[5]	Unbalanced translocation Three trisomies Deletion	6
29	46,XX,der(5)t(5;7)(q14;q11.2)t(7;18)(q22;q21.1)t(18;21)(q23;q11.2),hsr(11)(q23),5~25dmin[20]	Unbalanced translocation Homogeneous staining region Double minutes	4
30	47,XX,del(3)(q21),del(5)(q13q34),del(7)(q22),+8,+8,der(10;15)(q10;q10),t(12;21)(q24.1;q22)[19]/46,XX[1]	Three deletions[c] Tetrasomy of same chromosome Unbalanced translocation Balanced translocation	8
31	47,XY,del(5)(q14q34),del(7)(q21q36),+8[3]/47,idem,del(20)(q11.2q13.1)[15]/46,XY[2]	Three deletions Trisomy	4
32	48,XY,+8,+19[5]/46,XY,i(17)(q10),del(20)(q11q13)[3]/46,XY[12]	Two trisomies (1st clone) Isochromosome (2nd clone) Deletion (2nd clone)	4
33	46,XX,del(7)(q22q36)[8]/47,XX,del(5)(q14q34),+8,del(17)(p13p11.2)[4]/46,XX[8]	Deletion (1st clone) Two deletions (2nd clone) Trisomy (2nd clone)	4
34	47~49,XX,+7,+9,+11,+13[cp5]	Four trisomies	4
35	54,XX,+X,+6,+10,+14,+17,+18,+21,+21[20]	Eight trisomies	8
36	55,XX,+X,dup(1)(q42.1q21.3),+4,+6,+10,+14,+17,+18,+21,+21[17]/46,XX[3]	Seven trisomies Tetrasomy Duplication	10
37	60<2n>,XY,+X,+Y,+4,+5,+6,+8,+8,der(9)t(9;11)(q34;q13),+del(10)(q24),+11,+12,+14,+18,+21,+21[18]/46,XY[2]	Ten trisomies Two tetrasomies One derivative chromosome One deletion	17
38	46,XX,der(2)add(2)(p23)t(2;11)(q31;p15),t(4;11)(q21;q23),der(11)t(2;11)[18]/46,XX[2]	Two balanced translocations Additional material of unknown origin on one translocation derivative[d]	3
39	47,XX,+21c[20]	Constitutional abnormality	0

[a]Multiple deletions of a single chromosome count as 1. They may occur in a single event.
[b]Additional material of unknown origin (add) scores 1 since the origin of the extra genomic segment is unknown *e.g.*, an add could be a single copy gain.
[c]Deletions of different chromosomes score 1 for each chromosome.
[d]der(11)t(2;11) is not counted as a separate additional abnormality as it is related to the der(2).

7 In situ Hybridization

7.1 Introduction

Fluorescence *in situ* hybridization (FISH) is a targeted method to investigate whole chromosomes, chromosome regions, and/or gene regions for the presence or absence of numerical and/or structural abnormality. The history of developments in FISH technology is well documented (Cremer et al., 1986; Landegent et al., 1987; Lichter et al., 1988; Lichter et al., 1990; Pinkel et al., 1988; Trask, 1991; Wiegant et al., 1993; Guan et al., 1994; Liehr et al., 2006). The application of FISH probes to free, linearly extended chromatin fibers (fiber FISH) increased the resolution of FISH interphase mapping to ≤1 kb (Wiegant et al., 1992; Parra and Windle, 1993). Fiber FISH is not commonly used in the diagnostic setting and the nomenclature is not included in ISCN 2024; however, the nomenclature remains available in ISCN 2020.

7.1.1 General Principles and Rules

These rules apply to metaphase and interphase *in situ* hybridization (ISH).

a. *In situ* hybridization is performed on preparations of **metaphase chromosomes** (**ish**) or **interphase nuclei** (**nuc ish**):
- The abbreviation **ish** is followed by a space, the chromosome and/or abbreviation for the type of abnormality or band location and then the metaphase *in situ* hybridization results (see Section 7.2.1).
- The abbreviation **nuc ish** is followed by a space, and then the interphase *in situ* hybridization results (see Section 7.3.1).
- If the conventional karyotype or another technique precedes the *in situ* hybridization result in the ISCN description, then the result of this technique is followed by a **period** (**.**) before **ish** or **nuc ish**.

b. *In situ* hybridization probes are given in the ISCN description in capital letters and are described in the nomenclature using one of the following identifiers (listed below in order of preference):
- STS marker name, *i.e.*, D-number, or BAC clone name.
- Gene symbol, designated according to either the UCSC or Ensembl Genome Browsers (www.genome.ucsc.edu/ and www.ensembl.org/) or HUGO-approved nomenclature (http://www.hugo-international.org/).
- Probe manufacturer's name for the region or loci/locus. Examples of each of these are provided within this chapter.

c. Gene names for probes are not italicized in the ISCN description but the corresponding gene loci are italicized in the report text.

d. Probes are listed in the ISCN description in chromosome order, *i.e.*,

- Probes on sex chromosomes are given before those on autosomes (and X before Y).
- Probes on lower number autosomes are given before those on higher number autosomes. Where there are two or more derivative chromosomes on metaphase *in situ* hybridization the derivative with the lowest number is listed first and the probes are given **pter** to **qter**.
- Probes on the same chromosome are written in the order from **pter** to **qter** as they appear on the chromosome being described.

e. When contig probes are used each locus may be separated by a **single slant line** (/) in the ISCN description. Alternatively, a single probe within the contig may be given in the nomenclature with the complete contig composition described in the report text.

f. Fusion genes are not described using a **double colon** (**::**) in the *in situ* hybridization ISCN description. However, they are described in the interpretive comment using a **double colon** (**::**) (*e.g.*, *BCR*::*ABL1*) (Bruford et al., 2021) while probe cocktails are described using a **slant line** (*e.g.,* ABL1/BCR).

g. Cell numbers are given in **square brackets** (**[ ]**) for all neoplastic samples and to describe constitutional mosaicism/chimerism.

h. Inclusion of the control probe, when present, is optional in the ISCN description if it has a normal signal pattern but inclusion is mandatory if the control probe has an abnormal signal pattern. Its inclusion is preferred where it provides additional information, *e.g.*, for sex determination.

i. **Amplification** (**amp**) can be used when there are too many signals to allow enumeration or where the number of signals or the ratio compared to the control meets the clinical criterion for gene amplification in the disease under investigation.

7.2 Prophase/Metaphase *in situ* Hybridization (ish)

7.2.1 Principles and Rules

a. Observations on normal **metaphase** chromosomes are expressed by the abbreviation **ish** followed by a space, then the chromosome number, chromosome arm, region, band, or subband location of the locus or loci tested. This is followed in parentheses by the designation of the probe(s) and their signal patterns as described in the examples below. The chromosome band description in this chapter is based on the GRCh38 for in-house probes and as stated by the manufacturer for commercial probes.

b. Clones/cell lines in metaphase *in situ* hybridization are given largest to smallest and the normal cell line is listed last *e.g.*, 47,XX,+12[20].ish del(17)(p13p13)(TP53)[17]/del(17)(p13p13)(TP53–),del(17)(p13p13)(TP53–)[12]/17p13(TP53)×2[13] (see Section 4.5.3).

a. In sex determination and whole chromosome enumeration the abbreviated system (karyotype format) is used in which only the chromosome number is given in the ISCN description, *e.g.*, ish X(DXZ1)×1[20]/X(DXZ1)×2[10] and ish 8(D8Z2)×3[5]/8(D8Z2)×2[5].

b. When reporting **normal** metaphase results (see Sections 7.2.2, 7.2.6.1), including neoplasia (see Section 7.2.2), and in **whole chromosome aneusomy** (see Section 7.5).

- A **multiplication** (×) sign and the number of signals seen is given outside the parenthesis when the number of signals is the same for all probes.
- The **multiplication** (×) sign and the number of signals is given inside the parentheses when the copy number differs between probes on the same hybridization (see Section 7.2.2).

c. When reporting **abnormal** metaphase results *in situ* hybridization observations on the structurally **abnormal** metaphase chromosome(s) are expressed using the abbreviation **ish** followed by a space and then the abbreviation of the type of structural abnormality, followed in separate parentheses by the chromosome(s), the breakpoint(s), the probes used, and their signal patterns.

- The **presence** (+) or **absence** (–) of a locus is given within the same parentheses as the probe in the description of abnormal **ish** (see Section 7.2.3).
- When the number of signals on an abnormal chromosome can be counted, it may be indicated by multiple **plus** (+) signs. Tandem duplication is designated by a **double plus** (++) sign. Non-tandem duplication is shown with a **comma** (**,**) separating the probes (see Sections 7.2.3 and 7.2.4).

d. In metaphase *in situ* hybridization probes in multiple hybridizations are reported in a single set of parentheses, described in the **pter** to **qter** orientation of the centromeric segment of the chromosome being studied.

e. Breakpoints need not be given in the **ish** nomenclature unless their inclusion clarifies or refines the breakpoints given in the conventional karyotype. If *in situ* hybridization further clarifies the karyotype and, in retrospect, the abnormality can be visualized with banding, the karyotype may be rewritten to reflect this new information. If the abnormality is cryptic and cannot be visualized by banding, the abnormality should not be listed in the banded karyotype.

f. Probes on different chromosomes involved in a structural rearrangement are separated using a **semicolon** (**;**).

g. **Whole chromosome paints** (**wcp**) are listed in the **pter** to **qter** orientation of the chromosome being studied, *e.g.*, ish t(2;17)(q32;q24)(wcp2+,AC005181+,wcp17+;wcp17+,AC005181+,wcp2+)

h. If whole chromosome paints are used with telomeric and subtelomeric probes, the telomeric probe is designated as the most terminal, followed by the whole chromosome paint and then the subtelomeric probe when writing the nomenclature description from **pter** to **qter**.

7.2.2 Normal Signal Pattern

i. ish 17p11.2(RAI1)×2Metaphase *in situ* hybridization shows a normal signal number for the RAI1 locus specific probe on chromosome 17.

ii. 46,XX.ish X(DXZ1×2,SRY×0)Karyotype shows no abnormality in a female. Metaphase *in situ* hybridization confirms the sex chromosome complement. Probes for the X centromere and the *SRY* gene are used, and *SRY* is not detected. Where the clinical question is whether *SRY* is present or not, it is appropriate to indicate the status in the nomenclature. **Note:** the band location of *SRY* is not given in the ISCN description because the Y chromosome is not present.

iii. 46,XY.ish X(DXZ1)×1,Y(SRY,DYZ3)×1Karyotype shows no abnormality in a male. Metaphase *in situ* hybridization confirms the sex chromosome complement. **Note:** the band locations are not given on the X and Y chromosomes in the abbreviated system (karyotype format) when the assay is used for enumeration of the sex chromosome complement.

iv. 46,XY.ish 4p16.3(NSD2/D4S166)×2Karyotype shows no abnormality in the father of a child with der(4)t(4;11)(p16.3;p15). Metaphase *in situ* hybridization shows no abnormality with a probe for the critical region of Wolf-Hirschorn syndrome (NSD2/D4S166 probe) and a control probe, CTC-963K6. **Note:** the result for the control probe need not be given where the result is normal.

v. 46,XY.ish 22q11.2(D22S75)×2Karyotype shows no abnormality in a male. Metaphase *in situ* hybridization using a probe in the 22q11.2 deletion syndrome region (D22S75) shows a normal hybridization pattern. The control probe is not given.

vi. 46,XX.ish 17p11.2(RAI1)×2,21q22.13(D21S259/D21S341/D21S342)×2Karyotype shows no abnormality in a female. Probes for the *RAI1* gene on chromosome 17 and the Down syndrome critical region on chromosome 21 are both present in the normal copy number (two copies) by *in situ* hybridization. All loci of the contig probe are listed in this example.

vii. 46,XY.ish 13(D13Z1/D21Z1)×2,21(D13Z1/D21Z1)×2Karyotype shows no abnormality in a male. *In situ* hybridization with probes for the alpha satellites of chromosomes 13/21 shows a normal pattern. **Note:** *in situ* hybridization testing cannot differentiate the alpha satellite regions of chromosomes 13 and 21 because of sequence homology.

viii. ish 13(D13S319,LAMP1)×2[10]*In situ* hybridization shows no evidence of loss of D13S319 and LAMP1 probes on chromosome 13 in a neoplastic sample.

ix. 46,XX[20].ish 13q14(D13S319)×2[10],14q32(IGH)×2[10],16q23(MAF)×2[10]Karyotype of a neoplastic sample shows no abnormality in a female with a normal *in situ* hybridization pattern for the D13S319, IGH and MAF probes on metaphase chromosomes.

7.2.3 Abnormal Signal Pattern with a Single Probe

In the following metaphase *in situ* hybridization examples either the clinically relevant probe or the informative control probe has an abnormal signal pattern.

i. 46,XX.ish del(7)(q11.23q11.23)(ELN–,D7S486/D7S522+)Karyotype shows no abnormality in a female. An interstitial deletion in the Williams syndrome region of chromosome 7 is shown by *in situ* hybridization using a probe for the elastin gene (*ELN*). The control probe is given confirming that this is an interstitial, rather than a terminal deletion.

ii. 46,XX.ish del(22)(q11.2q11.2)(D22S75–,ARSA+)Karyotype shows no abnormality in a female. An interstitial deletion within the 22q11.2 deletion syndrome critical region on chromosome 22 is shown by *in situ* hybridization using a probe for D22S75. The control probe ARSA shows a normal signal pattern, confirming that this is an interstitial, rather than a terminal deletion.

iii. ish del(22)(q11.2q11.2)(N25–,ARSA+)Karyotype has not been performed. An interstitial deletion in the 22q11.2 deletion syndrome critical region on chromosome 22 is shown by *in situ* hybridization using a probe for N25. The control probe shows a normal signal pattern, confirming that this is an interstitial, rather than a terminal deletion.

iv. ish del(22)(q13.13q13.3 or q13.3)(D22S75+,ARSA–)*In situ* hybridization using a probe to the *ARSA* gene shows loss of distal 22q. In this situation, the D22S75 probe is the control probe and is given as it helps to define the extent of the deletion. Further testing may be required to establish whether the deletion is terminal or interstitial.

v. 46,XX,ins(2)(p13q21q31).ish ins(2)(wcp2+)Karyotype shows an intrachromosomal insertion on chromosome 2 in a female. The long arm segment of chromosome 2 from 2q21 to 2q31 is inserted into the short arm of the same chromosome at band 2p13. The chromosome 2 origin of the inserted segment is confirmed by metaphase *in situ* hybridization using chromosome 2 whole chromosome paint.

vi. 46,XX.ish der(X)t(X;Y)(p22.?3;p11.?2)(SRY+,DXZ1+)Karyotype shows no abnormality in a female. Metaphase *in situ* hybridization shows a cryptic unbalanced translocation between the short arms of the X and Y chromosomes with translocation of the SRY probe to Xp22, most likely at Xp22.3. The probable breakpoints are given in the *in situ* hybridization ISCN description since the translocation is cryptic on karyotype. **Note:** the der(X)t(X;Y)(p22.3;p11.2) is a known recurrent rearrangement.

vii. 46,XX.ish der(X)ins(X;Y)(p22.?3;p11.?2p11.?2)(SRY+,DXZ1+) or der(X)t(X;Y)(p22.?3;p11.?2)(SRY+,DXZ1+)The same example as above, however, the distinction between a translocation or insertion as a mechanism has not been made.

viii. 46,XX.ish der(7)ins(7;Y)(q22;p11.?2p11.?2)(SRY+)Karyotype shows no abnormality in a female. *In situ* hybridization shows that the SRY probe is present on one chromosome 7, in band 7q22, by DAPI banding analysis. As the rearrangement is cryptic, the subbands of the inserted Y chromosome material could not be elucidated by metaphase *in situ* hybridization alone and further testing would be required, *e.g.*, microarray.

ix. 46,XX,t(2;17)(q32;q24)[20].ish t(2;17)(q32;q24.3)(AC005181+;AC005181+)[20]Karyotype of a neoplastic sample shows a translocation involving chromosomes 2 and 17 in a female. Metaphase *in situ* hybridization shows that the translocation disrupts 17q24.3, corresponding to BAC clone AC005181, resulting in a probe signal on both derivative chromosomes. **Note:** the *in situ* hybridization further clarifies the 17q breakpoint although this is not visible on G-banding.

x. 47,XY,+mar.ish der(8)(D8Z2+)Karyotype shows a supernumerary marker chromosome in a male. Metaphase *in situ* hybridization, using an alpha satellite probe for chromosome 8, shows that the marker is derived, at least in part, from chromosome 8. Breakpoints could not be determined, and the composition of the derivative chromosome could not be elucidated fully.

xi. 46,XY.ish dup(17)(p11.2p11.2)(RAI1++)An apparently normal male karyotype. Metaphase *in situ* hybridization shows a tandem duplication of the region containing the *RAI1* gene on chromosome 17. There is one probe signal in the homologous chromosome 17, not indicated in the ISCN description.

xii. 46,XX[20].ish inv(21)(q11.2q22.1)(q11.2)(RUNX1+)(q22.1)(RUNX1–)[5]An apparently normal female karyotype in a neoplastic sample. *In situ* hybridization shows a cryptic inversion of the segment 21q11.2 to 21q22.1 using a probe for the *RUNX1* gene. **Note:** the inversion breakpoints are given in separate parentheses to clarify the inversion.

xiii. ish del(22)(q11.2q11.2)(D22S75–,ARSA+),del(22)(q11.2q11.2)(D22S75–,ARSA+)Karyotype has not been performed. Metaphase *in situ* hybridization with a probe for the D22S75 locus shows an interstitial deletion within the 22q11.2 deletion syndrome critical region in both chromosomes 22. **Note:** the presence of the control probe determines that the losses are interstitial. It is optional to use **underlining** (_) to differentiate between the two homologues.

xiv. 47,XX,+mar.ish mar(Acro-p+)Karyotype shows a supernumerary marker chromosome in a female. *In situ* hybridization using the Acro-p probe shows that the marker chromosome has a single acrocentric short arm region derived from an acrocentric chromosome of unknown origin.

xv. 47,XY,+mar.ish mar(Acro-p+,Acro-p+)Karyotype shows a male karyotype with a supernumerary marker chromosome. *In situ* hybridization using the Acro-p probe shows a probe signal on both ends of the marker chromosome. The marker chromosome is bisatellited and derived from an acrocentric chromosome(s) of unknown origin.

xvi. 46,XY,ins(5;2)(p14;q22q32).ish ins(5;2)(wcp2+;wcp2+)Karyotype shows a balanced direct insertion of a chromosome 2 segment into the short arm of chromosome 5. Metaphase *in situ* hybridization using chromosome 2 whole chromosome paint confirmed the presence of the chromosome 2 segment.

xvii. 46,XY,ins(5;2)(p14;q32q22).ish der(5)ins(5;2)(wcp2+)Karyotype shows an inverted insertion of a chromosome 2 segment into the short arm of chromosome 5. Metaphase *in situ* hybridization using chromosome 2 whole chromosome paint confirmed the presence of the chromosome 2 segment inserted into the short arm of chromosome 5.

xviii. 46,XX,add(4)(q31).ish der(4)dup(4)(q31q3?4)(wcp4+)add(4)(q3?4)(wcp4–)Karyotype shows material of unknown origin replacing distal chromosome 4 from band 4q31 to 4qter. *In situ* hybridization using a whole chromosome paint 4 shows that the proximal part of the additional material is derived from chromosome 4. Conventional karyotype review in conjunction with the *in situ* hybridization result suggests a duplication of the bands 4q31 to probably 4q34. However, there is additional material distal to the duplication which does not hybridize with whole chromosome 4 paint and is therefore of unknown origin. **Note:** the karyotype could be rewritten to reflect the *in situ* hybridization information.

7.2.4 Abnormal Signal Pattern with Multiple Probes

i. 46,X,+r.ish r(X)(wcpX+,DXZ1+)Karyotype shows a female with a single X chromosome, and a ring chromosome of unknown origin. The ring chromosome is shown to be derived from the X chromosome by *in situ* hybridization using a whole X chromosome paint and an alpha satellite probe, DXZ1. The breakpoints of the ring could not be determined.

ii. 46,XX,dup(5)(p15.3p14).ish dup(5)(wcp5+,D5S721/D5S23+,D5S721/D5S23+)Karyotype shows a duplication in the short arm of chromosome 5 from 5p15.3 to 5p14 in a female. Metaphase *in situ* hybridization shows a non-tandem duplication where one of the D5S721/D5S23+ probe signals is present near the telomere and the other is more centromeric. As the duplication is non-tandem the probes are separated by a comma in the ISCN description. There is one signal on the homologous chromosome 5, not indicated in the ISCN description.

iii. 46,XX,del(15)(q11.2q13).ish del(15)(SNRPN–,D15S10–)Karyotype shows an interstitial deletion of chromosome 15 involving the segment 15q11.2 to 15q13. *In situ* hybridization using the SNRPN and D15S10 probes confirms deletion of the Prader-Willi/Angelman region.

iv. 46,XY.ish del(15)(q11.2q11.2)(SNRPN–,D15S10–)Karyotype shows no abnormality in a male. *In situ* hybridization using SNRPN and D15S10 probes shows microdeletion within the Prader-Willi/Angelman region of chromosome 15.

v. 47,XX,+mar.ish add(16)(p?)(wcp16–,D16Z2+,wcp16+)Karyotype shows a supernumerary marker chromosome in a female. The chromosome 16 whole chromosome paint and the chromosome 16 alpha satellite probe (D16Z2) show that the marker is derived in part from chromosome 16. Additional material of unknown origin is present in the marker.

vi. 47,XY,+mar.ish der(17)(wcp17+,D17Z1+)Karyotype shows a supernumerary marker chromosome in a male. The chromosome 17 whole chromosome paint and a chromosome 17 specific alpha satellite probe (D17Z1) show that the marker is derived from chromosome 17.

vii. 46,XX[20].ish ins(15;17)(q24.1;q21q21)(PML+,RARA+;RARA+)[5]Karyotype of a neoplastic sample shows no abnormality in a female. A cryptic insertion of the segment 17q21 from the long arm of chromosome 17 into the 15q24.1 band of the long arm of chromosome 15 is shown using *in situ* hybridization with the dual-color, dual-fusion PML/RARA probe set. The breakpoint on chromosome 17 is within the RARA probe resulting in a signal on the derivative chromosome 15 and on the derivative chromosome 17.

viii. 46,XX[20].ish t(12;21)(p13.2;q22.1)(RUNX1+,ETV6+;RUNX1+,ETV6+)[5]Karyotype of a neoplastic sample shows no abnormality in a female. Metaphase *in situ* hybridization with the dual-color, dual-fusion ETV6/RUNX1 probe set shows an *ETV6*::*RUNX1* gene fusion from a cryptic reciprocal translocation between chromosomes 12 and 21.

ix. 47,XY,+der(4)t(4;11)(q21;q23),t(4;11)[20].ish der(4)(3′KMT2A+),t(4;11)(3′KMT2A+;5′KMT2A+,3′KMT2A–)[5]Karyotype of a neoplastic sample shows a male karyotype with a t(4;11) plus an extra copy of the der(4). *In situ* hybridization with a dual-color, break-apart KMT2A probe shows a 3′KMT2A probe signal on both copies of the der(4), and a 5′KMT2A probe signal on the derivative chromosome 11 of the t(4;11).

x. 46,XX,inv(16)(p13.1q22)[20].ish inv(16)(p13.1)(CBFB+,MYH11+)(q22)(CBFB+,MYH11+)[5]Karyotype of a neoplastic sample shows an inversion of chromosome 16 in a female. The pericentric

inversion between bands 16p13.1 and 16q22 is confirmed by dual-color, dual-fusion *in situ* hybridization probes for the *MYH11* and *CBFB* genes.

xi. 46,XY,t(9;22)(q34;q11.2)[20].ish t(9;22)(ABL1−;BCR+,ABL1+)[5]Karyotype of a neoplastic sample shows a translocation between chromosomes 9 and 22 in a male. A dual-color, single-fusion ABL1/BCR *in situ* hybridization probe set shows that the ABL1 probe signal is lost from the derivative chromosome 9 and is present on the derivative chromosome 22 distal to the BCR probe signal.

xii. 47,XY,t(9;22)(q34;q11.2),+der(22)t(9;22)[20].ish t(9;22)(ABL1−;BCR+,ABL1+),der(22)(BCR+,ABL1+)[5]Karyotype of a neoplastic sample shows a translocation between chromosomes 9 and 22 and an extra copy of the der(22) in a male. A dual-color, single-fusion ABL1/BCR *in situ* hybridization probe set shows that the ABL1 probe signal is missing from the derivative chromosome 9 and is present on both derivative chromosomes 22 distal to the BCR probe signal.

xiii. 46,XX,t(9;22)(q34;q11.2)[10].ish t(9;22)(ABL1+,BCR+;BCR+,ABL1+)[5]Karyotype of a neoplastic sample shows a translocation between chromosomes 9 and 22 in a female. A dual-color, dual-fusion ABL1/BCR probe set shows one signal for the ABL1 probe and one signal for the BCR probe on each derivative chromosome by *in situ* hybridization.

xiv. 46,XX,t(9;22)(q34;q11.2)[20].ish der(9)t(9;22)del(9)(q34q34)(ABL1–,BCR+),der(22)t(9;22)(BCR+,ABL1+)[5]Karyotype of a neoplastic sample shows a translocation between chromosomes 9 and 22 in a female. A dual-color, dual-fusion ABL1/BCR *in situ* hybridization probe set shows loss of the ABL1 probe signal from the derivative 9 that is not detected by chromosome analysis.

xv. 46,XX,t(9;22)(q34;q11.2)[20].ish der(9)t(9;22)del(9)(q34q34)(ASS1–,ABL1–,BCR+),der(22)t(9;22)(BCR+,ABL1+)[5]Karyotype of a neoplastic sample shows a translocation between chromosomes 9 and 22 in a female. A tricolor dual-fusion ASS1, ABL1, and BCR probe set shows loss of the ASS1 and ABL1 probe signals from the derivative 9 by *in situ* hybridization, that is not detected by chromosome analysis.

xvi. 47,XX,t(9;22;10)(q34;q11.2;q22),+der(22)t(9;22;10)[20].ish der(9)t(9;22;10)del(9)(q34q34)(ABL1–),der(10)t(9;22;10)del(22)(q11.2q11.2)(BCR–),der(22)t(9;22;10)×2(BCR+,ABL1+)[5]A female karyotype shows a three-way translocation between chromosomes 9, 22 and 10, and an additional copy of the derivative chromosome 22 in a neoplastic sample. *In situ* hybridization with a dual-color, dual-fusion ABL1/BCR probe set shows a conjoined BCR and ABL1 signal on both copies of the derivative chromosome 22, with loss of an ABL1 probe signal from the derivative chromosome 9 and a BCR probe signal from the derivative chromosome 10. The individual derivative chromosomes are listed in the ISCN description as there is a deletion on the der(9) with loss of the ABL1 probe signal. **Note:** there are two copies of the derivative chromosome 22 with identical *in situ* hybridization results.

xvii. 46,XX,t(9;22;10)(q34;q11.2;q22)[21].ish der(9)t(9;22;10)del(9)(q34q34)(wcp9+,ABL1–,wcp10+),der(10)t(9;22;10)del(22)(q11.2q11.2)(wcp10+,BCR–,wcp22+),der(22)t(9;22;10)(wcp22+,BCR+,ABL1+,wcp9+)[10]Same example as above but with whole chromosome paints included in the ISCN description.

xviii. 46,X,?i(Y)(p10).ish idic(Y)(q11.?21)(SRY+,DYZ3+,DYZ1–,DYZ3+,SRY+)A male karyotype shows a presumed isochromosome for the short arm of the Y

chromosome. *In situ* hybridization shows a probable breakpoint in Yq11.21 as there are two signals for the SRY probe, and the Y chromosome centromere (DYZ3) but no Yq12 alpha satellite (DYZ1) signal. **Note:** the rearrangement is demonstrated to be an isodicentric Y chromosome by *in situ* hybridization. The karyotype could be altered to reflect the structure as identified by *in situ* hybridization.

xix. 46,XX,t(2;17)(q32;q24)[20].ish t(2;17)(q32;q24.3)(RP11–76G4+;RP11–134J16+,RP11–76G4–)[20]Karyotype of a neoplastic sample shows a translocation between the long arms of chromosomes 2 and 17 in a female. The breakpoint is located between the BAC clones RP11–134J16 at 17q24.3 and RP11–76G4 at 17q25.1. The translocation results in RP11–76G4 moving to chromosome 2, with retention of RP11–134J16 on chromosome 17 as shown by *in situ* hybridization.

xx. 45,XY,der(14;21)(q10;q10).ish dic(14;21)(p11.2;p11.2)(D14Z1/D22Z1+;D13Z1/D21Z1+)Karyotype shows a Robertsonian translocation involving chromosomes 14 and 21 in a male. The translocation is shown to be dicentric by C-banding and *in situ* hybridization. The breakpoints are given in the ish ISCN description as they are more accurate than those obtained by banding.

xxi. 47,XY,+mar.ish der(17)add(17)(p11.2)del(17)(q1?1.2)(wcp17–,wcp17+,CMT1A+,D17Z1+)Karyotype shows a supernumerary marker chromosome in a male. The marker is identified by metaphase *in situ* hybridization to be derived from the short arm of chromosome 17 using whole chromosome paint 17 and probes for the *CMT1A* gene and D17Z1. Additional material of unknown origin has replaced the segment distal to 17p11.2 and there is a loss of the long arm segment distal to region 17q1 probably 17q11.2.

xxii. 46,XY.ish del(15)(q11.2q12)(D15S11+,SNRPN–,D15S10–,GABRB3+)Karyotype shows no abnormality in a male. *In situ* hybridization using probes for D15S11, SNRPN, D15S10 and GABRB3 shows an interstitial microdeletion of chromosome 15 defined by loss of the SNRPN and D15S10 probes, and retention of the D15S11 and GABRB3 probes.

xxiii. 46,X,r(X)(p22.3q22).ish r(X)(KAL1+,DXZ1+,XIST+,DXZ4–)Karyotype shows a ring X chromosome and metaphase *in situ* hybridization confirms that it includes the KAL1 probe (*ANOS1* gene) on the X chromosome short arm, the X alpha satellite DXZ1 probe and the XIST probe on the X chromosome long arm. It does not include DXZ4 at Xq23. The breakpoints in the ISCN description are obtained using information from *in situ* hybridization and review of the G-banded chromosome structure.

xxiv. 47,XX,+mar.ish der(18)t(18;19)(wcp18+,D18Z1+,wcp19+)Karyotype shows a supernumerary marker chromosome in a female. *In situ* hybridization using whole chromosome paints for chromosomes 18 and 19, and an 18 alpha satellite probe (D18Z1), shows that the marker is derived from chromosome 18 (including the centromere) and from chromosome 19.

xxv. 47,XY,+dic(15;15)(q11.1;q11.1).ish dic(15;15)(D15Z1+,D15Z4+,SNRPN–;SNRPN–,D15Z4+,D15Z1+)Karyotype shows a supernumerary dicentric chromosome 15 in a male. The dicentric chromosome 15 shows a signal for the probes D15Z1 and D15Z4 on each chromosome arm by metaphase *in situ* hybridization but lacks the SNRPN probe. **Note:** a short arm polymorphism of one chromosome 15 differentiates the

homologues and demonstrates the abnormality is a dicentric chromosome (formed from two chromosomes) rather than an isodicentric chromosome (formed from a sister chromatid exchange).

xxvi. 46,XX,del(13)(q12q14)[20].ish 4p16.3(FGFR3)×2[10],del(13)(D13S319–)[10],14q32(IGH)×2[10]Karyotype of a neoplastic sample shows an interstitial 13q deletion in a female. *In situ* hybridization probes for the *IGH*::*FGFR3* rearrangement show a normal signal pattern. The LAMP1 control probe in 13q34 is not reported because it adds no information additional to the karyotype and the D13S319 *in situ* hybridization results.

xxvii. 46,XX.ish t(4;11)(p16.3;p15)(dj908H22+,CTC-36P21–,WHS+,D4Z1+;CTC-36P21+,dj908H22–)Karyotype shows no abnormality in a female. A cryptic reciprocal translocation between chromosomes 4 and 11 is identified by *in situ* hybridization. The derivative chromosome 4 shows presence of the 11p subtelomere probe (dj908H22) signal, loss of the 4p subtelomere probe (CTC-36P21) signal, presence of the signal for the Wolf-Hirschhorn syndrome critical region (WHS) and the presence of the chromosome 4 alpha satellite probe signal (D4Z1). The derivative chromosome 11 shows presence of the chromosome 4p subtelomere (CTC-36P21) signal, and loss of the 11p subtelomere probe (dj908H22) signal.

xxviii. 46,XX.ish der(4)t(4;11)(p16.3;p15)(dj908H22+,CTC-36P21–,WHS+,D4Z1+)dmatKaryotype of a child who has inherited a normal chromosome 4, two normal chromosomes 11 and the derivative chromosome 4 of the maternal cryptic balanced translocation described in the example above. The *in situ* hybridization results of the der(4) are the same as der(4) of the mother. For explanation of inheritance nomenclature see Section 4.2.1.

xxix. 46,XX,add(4)(p16.3).ish dup(4)(wcp4+,RP11–1076P8+,WHS+,RP11–1076P8+,WHS+)Karyotype shows additional material of unknown origin attached at band 4p16.3 in a female. *In situ* hybridization using a whole chromosome paint 4, shows that the extra chromatin is derived from chromosome 4. The additional material is determined to be a duplication involving 4p16.3 by *in situ* hybridization. The duplicated segment is in the original orientation. The duplicated chromosome contains two copies of the region covered by the RP11–1076P8 BAC probe at 4p16.3, and a probe for the Wolf-Hirschhorn syndrome critical region in the original orientation relative to 4pter. **Note:** the order of probes is given according to their relative position **pter** to **qter** on the derivative chromosome.

xxx. 46,XX,add(4)(p16.3).ish dup(4)(wcp4+,RP11–1076P8+,WHS+,WHS+,RP11–1076P8+)Karyotype shows extra material replacing the distal short arm of one chromosome 4 from 4p16.3 in a female. *In situ* hybridization using a whole chromosome paint 4 shows that the extra chromatin is derived from chromosome 4. The additional material is determined to be an inverted duplication involving 4p16.3 by *in situ* hybridization. The duplicated chromosome contains two copies of the region covered by the RP11–1076P8 BAC probe and a probe for the Wolf-Hirschhorn syndrome critical region. The duplicated region is in the reverse orientation relative to 4pter.

xxxi. 46,XX,t(6;11)(q23;q22).ish t(6;11)(RP4–609N19+,RP11–226I21–,RP11–469N6+;RP11–652O18+,RP11–469N6–,RP11–226I21+)Karyotype shows a reciprocal translocation between chromosome 6 and chromosome 11 in a female. *In*

situ hybridization using subtelomeric probes shows a translocation of the chromosome 11 long arm subtelomeric probe, RP11–469N6, to the long arm of chromosome 6, and of the chromosome 6 long arm subtelomeric probe, RP11–226I21, to the long arm of chromosome 11. The positions of the subtelomeric probe for the chromosome 6 short arm, RP4–609N19, and the subtelomeric probe for the chromosome 11 short arm, RP11–652O18, are unchanged.

xxxii. 46,XX,t(14;18)(q32;q21)[20].ish t(14;18)(IGH+,BCL2+;BCL2+,IGH+)[20]/der(14)t(14;18)del(14)(q32)(IGH–,BCL2–),der(18)t(14;18)(BCL2+,IGH+)[10]Karyotype of a neoplastic sample with a translocation involving chromosomes 14 and 18 at bands 14q32 and 18q21. Metaphase *in situ* hybridization shows two clones. A balanced translocation between chromosomes 14 and 18 present in 20 metaphases and a second clone with deletion of the derivative chromosome 14 in a further ten metaphases.

7.2.5 Use of Diminished (dim) and Enhanced (enh) in Metaphase *in situ* Hybridization

i. 46,XX.ish 17p11.2(RAI1)enhKaryotype shows no abnormality in a female. An enhanced signal is observed at band 17p11.2 by metaphase *in situ* hybridization using the RAI1 probe. The probe signal appears larger on one chromosome 17 compared to the probe signal on the homologous chromosome 17.

ii. 46,X,del(X)(p11.4p11.2).ish del(X)(p11.4p11.22)(RP11–265P11,RP1–112K5)dimKaryotype shows deletion of the short arm of the X chromosome in a female. The *in situ* hybridization signals of BAC clones RP11–265P11 (Xp11.4) and RP1–112K5 (Xp11.22) are consistently less intense on the deleted X chromosome than on the normal homologue, indicating that part of each probe region is deleted and therefore identifying the proximal and distal breakpoints respectively. **Note:** the karyotype breakpoints have not been changed due to the lower level of resolution of the banded chromosomes.

7.2.6 Subtelomeric Metaphase *in situ* Hybridization

Subtelomeric *in situ* hybridization may be performed in panels so that the 41 unique chromosome ends are hybridized simultaneously.

7.2.6.1 Normal Signal Pattern

A normal result using a subtelomeric *in situ* hybridization panel is given using the short system (karyotype format), for example:

i. ish (subtel41)×2Metaphase *in situ* hybridization shows a normal result with probes to the 41 subtelomeric regions.

ii. ish 1p36.33(CEB108/T7)×2,4p16.3(GS10K2/T7)×2Targeted metaphase *in situ* hybridization shows two copies of the subtelomeric regions of 1p and 4p representing a normal finding in a relative of a translocation carrier.

iii.

7.2.6.2 Abnormal Signal Pattern

i. ish t(13;20)(q34;p13)(163C9–,dj1061L1+;163C9+,dj1061L1–)Metaphase *in situ* hybridization confirms a balanced translocation between the distal long arm of chromosome 13 and the distal short arm of chromosome 20 using the 13q subtelomere probe, 163C9, and the 20p subtelomere probe, dj1061L1.

i. ish der(13)t(13;20)(q34;p13)(163C9–,dj1061L1+)Metaphase *in situ* hybridization confirms an unbalanced translocation between the distal long arm of chromosome 13 and the distal short arm of chromosome 20. The subtelomeric region of 13q (163C9 probe) is deleted and replaced with the subtelomeric region of 20p (dj1061L1 probe).

ii. 46,XY,rec(4)dup(4p)inv(4)(p16.1q34)dmat.ish rec(4)dup(4p)(D4S3359+,D4S2930–,D4S3359+)Karyotype shows a recombinant chromosome 4 derived from a maternal pericentric inversion of chromosome 4. Metaphase *in situ* hybridization confirms the recombinant chromosome 4. There is a duplication of 4pter to 4p16.1 seen with the D4S3359 probe, and a deletion from 4q35 to 4qter seen with the D4S2930 probe. For explanation of the inheritance nomenclature see Section 4.2.1.

7.2.7 Multicolor Chromosome Painting

Multicolor FISH banding and 24 color karyotyping are techniques used to paint chromosomes with a distinct color or spectrum of colors. They can be used as a tool to clarify the G-banded analysis. The karyotype can be rewritten based on the knowledge gained from the results of these techniques. The use of these techniques should be stated in the report. Nomenclature for **wcp** (see Sections 7.2.1, 7.2.3 and 7.2.4) may be used.

7.2.8 Partial Chromosome Painting

Probes that are band specific or arm specific can be used as **partial chromosome paints** (**pcp**). The nomenclature is similar to that of **wcp** (see Sections 7.2.1, 7.2.3 and 7.2.4).

i. 46,XX,?dup(18)(p11.3p11.2).ish dup(18)(pcp18p+)Karyotype shows a suspected tandem duplication on 18p that is confirmed by *in situ* hybridization using a partial chromosome paint for 18p.

ii. 46,XY,inv(8)(p21q13).ish inv(8)(pcp8p+,pcp8p+)Karyotype shows an inversion of chromosome 8 that is confirmed by *in situ* hybridization using a partial chromosome paint for 8p.

iii. 46,X,r(X)(p22.1q13).ish r(X)(pcpXp+,DXZ1+,pcpXq+,XIST+)Karyotype with a ring X chromosome that is confirmed by *in situ* hybridization using partial chromosome paints for Xp and Xq to consist of short and long arm material of the X chromosome. The X chromosome pericentromeric region is identified by DXZ1 and the presence of *XIST* is confirmed by use of the gene probe.

7.3 Interphase/Nuclear *in situ* Hybridization (nuc ish)

7.3.1 Principles and Rules

a. **Interphase *in situ* hybridization** (**nuc ish**) includes the number of signals and their positions relative to each other.
b. See also Section 7.1.1 for general rules and principles that also apply for **nuc ish**.
c. In ISCN 2024 the chromosome band location is not included in the **nuc ish** ISCN description as the physical chromosome location cannot be seen in interphase nuclei as there are no chromosome bands.
d. To indicate the number of signals in interphase nuclei, the abbreviation **nuc ish** is followed by a space and then the probe designation in parentheses, a **multiplication** (×) sign, and the number of signals seen.
e. If probes for two or more loci are used in the same hybridization, they follow one another in a single set of parentheses, separated by a **comma** (**,**), and a **multiplication** (×) sign outside the parenthesis if the copy number is the same for all probes, and inside the parenthesis when the number of signals differs between probes.
f. Results from different hybridizations are presented in separate sets of parentheses even if all show a normal signal pattern.
g. The probes from the same chromosome number are listed from **pter** to **qter** according to their normal chromosome location, and are separated by a **comma** (**,**).
h. For a single locus with probes at the 5′ and 3′ end of a gene, the probes should be listed as they reside on the normal chromosome from **pter** to **qter** and separated by a **comma** (**,**). The chromosome order of 5′ and 3′ probes may need to be verified from the manufacturers' data sheet.
i. **Separation** of colocalized or adjacent probes is indicated by the abbreviation (**sep**). Probes that become **connected** (conjoined) because of genomic rearrangement are indicated using the abbreviation (**con**).
j. The **double colon** (**::**) is **not** used in the **nuc ish** ISCN description to indicate fusion gene formation.
k. The number of nuclei analyzed is given in **square brackets** (**[ ]**) after the ISCN description in all neoplastic studies and in mosaic constitutional studies and is not given where non-mosaic results are observed in constitutional studies.
l. When normal and abnormal nuclei are found, the number of abnormal nuclei is listed over the total number of nuclei analyzed (the denominator) for each abnormal probe. Normal nuclei are not listed as it is implied that they are the remainder of the total. The exception to this rule is in the determination of the sex chromosome complement of an individual where the normal cell line is listed last. In this situation the total number of nuclei reported is equal to the denominator (see Section 7.3.3.1).
m. Caveats of techniques, for example the semi-quantitative nature of interphase *in situ* hybridization in tissue sections or the design of a particular probe, are not indicated in the nomenclature and should be stated in the interpretive text of the report.

7.3.2 Normal Interphase Signal Pattern

i. nuc ish (D21S259/D21S341/D21S342)×2 Interphase *in situ* hybridization shows two signals for the D21S259/D21S341/D21S342 probe.

ii. 46,XY[20].nuc ish (TP53)×2[200]Karyotype shows no abnormality in 20 metaphases in a neoplastic sample in a male. Interphase *in situ* hybridization shows a normal hybridization pattern in 200 nuclei using a probe for the *TP53* gene.

iii. nuc ish (ANOS1,D21S65)×2Interphase *in situ* hybridization shows two signals for the *ANOS1* gene, using the ANOS1 probe and two signals for D21S65.

iv. nuc ish (ABL1,BCR)×2[200]Interphase *in situ* hybridization shows two signals for each of *ABL1* and *BCR* genes in 200 nuclei in a neoplastic sample.

v. 46,XY[20].ish 9q34(ABL1)×2,22q11.2(BCR)×2[20].nuc ish (ABL1,BCR)×2[100],(TP53)×2[200]Karyotype of a neoplastic sample shows no abnormality in 20 metaphases in a male. A normal *in situ* hybridization pattern is present in 20 metaphases and 100 nuclei using probes for the *ABL1* and *BCR* genes and in 200 interphase nuclei using a probe for the *TP53* gene.

vi. nuc ish (D17Z1,ERBB2)×2[100]Interphase *in situ* hybridization shows two signals for the centromere 17 probe, D17Z1, and two signals for *ERBB2 (HER2),* in 100 nuclei in a neoplastic sample.

vii. nuc ish (ETV6×2,RUNX1×3c)[200]Interphase *in situ* hybridization with a dual-color, dual-fusion ETV6/RUNX1 probe does not show rearrangement of *ETV6* and *RUNX1* in 200 nuclei in a neoplastic sample from an individual with constitutional trisomy 21.

viii. nuc ish (ATM,TP53)×2[200],(D12Z3,D13S319,LAMP1)×2[200]Interphase *in situ* hybridization shows normal signal patterns in hybridizations with different probe sets in a neoplastic sample. **Note:** the hybridizations are listed in separate sets of parentheses even when equal numbers of nuclei are scored, and the signal patterns are the same. Reporting of the LAMP1 control probe is optional but may be preferred in neoplastic studies to confirm chromosome copy number.

7.3.3 Abnormal Interphase Signal Pattern

i. nuc ish (D21S65)×3 Interphase *in situ* hybridization shows three signals for the 21q22.12 probe, D21S65.

ii. nuc ish (DXZ1×3,SRY×0) Interphase *in situ* hybridization shows three signals for DXZ1 in all nuclei. The SRY probe signal pattern is given as this is clinically relevant for sex determination.

iii. nuc ish (D20Z1×2,D20S108×1)[100/200]Interphase *in situ* hybridization shows one signal for D20S108, normally located at 20q12, and two signals for the pericentromeric D20Z1 probe signal in 100 nuclei of 200 scored in a neoplastic sample.

iv. nuc ish (D21S65,D21S64)×3Interphase *in situ* hybridization shows three signals for the 21q22.12 probe, D21S65, and three signals for D21S64 at 21q22.13.

v. nuc ish (D13S319×0,LAMP1×2)[50/200]Interphase *in situ* hybridization of a neoplastic sample shows homozygous deletion of the 13q14.2 probe, D13S319, in 50 of 200 nuclei. A normal signal pattern is observed in 150 interphase nuclei. The control probe at 13q34 (LAMP1) is shown to confirm chromosome 13 copy number.

vi. nuc ish (STS,KAL1,DXZ1)×1Interphase *in situ* hybridization shows one copy of each probe signal, listed as they appear on the normal X chromosome, **pter** to **qter**.

vii. nuc ish (TP73×1,ANGPTL×2)[107/200],(ZNF443×2,GLTSCR1×1)[105/200]Interphase *in situ* hybridization shows one signal with the 1p36.32 probe, TP73, and two signals with the 1q25.2 probe, ANGPTL, in 107 nuclei. A second hybridization shows two signals with the 19p13.2 probe, ZNF443, and one signal with the 19q13.33 (*BICRA* gene) probe, GLTSCR1, in 105 interphase nuclei. Thus, the neoplastic specimen shows loss of both 1p and 19q.

viii. nuc ish (ATM,TP53)×2[100],(D12Z3×3,D13S319×2,LAMP1×2)[50/100]Two separate *in situ* hybridizations are performed on a neoplastic sample. In the first, there is a normal hybridization pattern with two signals for each of the ATM and TP53 probes in all 100 nuclei. In the second hybridization, there are three signals for the D12Z3 probe and two signals each for the probes for D13S319 and LAMP1 in 50 of 100 nuclei. It is not critical to include the control probe (LAMP1) in the ISCN description, but it is included here to confirm chromosome 13 copy number.

ix. nuc ish (ATM×1,TP53×2)[100/200],(D12Z3×3,D13S319×2,LAMP1×2)[50/200]Two separate *in situ* hybridizations are performed on a neoplastic sample. In the first, loss of one ATM signal is observed in 100 nuclei. The 100 remaining nuclei show a normal signal pattern. In the second hybridization, there is gain of a signal for D12Z3 in 50 nuclei. A normal signal pattern is shown in 150 interphase nuclei. **Note:** D13S319, LAMP1 and TP53 probes each show a normal hybridization pattern in 200 nuclei. The LAMP1 control probe is included in the ISCN description as it is informative regarding chromosome 13 copy number.

x. nuc ish (DXZ1×1,DYZ3×1,D18Z1×2),(RB1×2,D21S259/D21S341/D21S342×3)[60/150]Interphase *in situ* hybridization in a male showed two copies of chromosomes 13 and 18 plus mosaicism for trisomy 21. **Note:** cells numbers are not given for the X, Y and 18 probe set as the three probes show a normal signal pattern.

7.3.3.1 Order of Cell Lines and Clones in nuc ish

a. Abnormal cell lines and clones detected by *in situ* hybridization are listed from **largest to smallest** number of nuclei. The exception is that the normal cell line is listed last when it is given to show the sex chromosome complement.

b. Where two or more abnormal cell lines/clones are present in **equal numbers** their order of listing is determined by the following rules (shown in order of application):

- Where the abnormality in different cell lines/clones involves probes on different chromosomes then the **chromosome order** rule applies (X before Y) followed by autosomes in increasing number.
- Where the abnormality in different cell lines/clones involves the same probe on the same chromosome then the **gain** before **loss** before **structural change** rule applies.
- Where the same type of abnormality in different cell lines/clones involves different probes on the same chromosome then the **pter** to **qter** rule applies.
- Where different abnormal signal patterns are present in an equal number of nuclei for the same probe set, the least complex cell line/clone is described first.

v. nuc ish (DXZ1×1,DYZ3×0)[12/50]/(DXZ1×1,DYZ3×2)[6/50]/(DXZ1,DYZ3)×1[32/50]Interphase *in situ* hybridization shows a single DXZ1 signal in 12 nuclei, and six nuclei show one DXZ1 and two DYZ3 signals. There is one signal for each of DXZ1 and DYZ3 in 32 nuclei. **Note:** for sex chromosome mosaicism, an exception is made to include the cell line with the normal complement (XY), and this cell line is listed last. The sum of the numerators is equal to the denominator in this example because the results of the normal cell line are included.

vi. nuc ish (D5S630,EGR1)×1[100/200]/(D5S630×2,EGR1×1)[50/200]Interphase *in situ* hybridization shows two clones in a neoplastic sample: a concomitant loss of the EGR1 signal and the D5S630 control probe (5p15) signal in 100 interphase nuclei, consistent with monosomy 5, and loss of only the EGR1 signal, consistent with a deletion of 5q, in 50 nuclei. A normal signal pattern for these probes is present in 50 nuclei. **Note:** the larger clone is listed first even though it likely evolved from the smaller clone.

vii. nuc ish (D5S630×2,EGR1×1)[150/250]/(D5S630,EGR1)×1[100/250]Interphase *in situ* hybridization of a neoplastic sample shows a signal pattern that is consistent with deletion of 5q in 150 interphase nuclei, and a signal pattern consistent with monosomy 5 in 100 nuclei. There are no nuclei with a normal signal pattern. **Note:** the larger clone is listed first.

viii. nuc ish (D5S630,EGR1)×1[50/200]/(D5S630×2,EGR1×1)[50/200]Interphase *in situ* hybridization of a neoplastic sample shows **equal numbers** of interphase nuclei with signal patterns indicating loss of D5S630 at 5p15.31 and loss of *EGR1* at 5q31.2 in one clone and loss of *EGR1* only in the second clone. There is insufficient information regarding chromosome structure to indicate whether the first clone represents a deletion in both chromosome arms, or whether it represents monosomy 5. A normal signal pattern is present in the remaining 100 nuclei. **Note:** since the number of cells are equal, the clone with the altered probe pattern closest to **pter** is listed first.

ix. nuc ish (D5S630×2,EGR1×3)[50/200]/(D5S630,EGR1)×1[50/200]/(D5S630×2,EGR1×1)[50/200]Interphase *in situ* hybridization of a neoplastic sample shows three clones of **equal size**: 50 nuclei with gain of *EGR1* at 5q31.2, and 50 nuclei with loss of D5S630 (5p15.31) and loss of *EGR1*. Fifty nuclei with loss of *EGR1*, and 50 nuclei show a normal signal pattern. There is insufficient structural information to determine whether the chromosome losses shown by *in situ* hybridization are simple deletions or more complex chromosome rearrangements. **Note:** the clone with *EGR1* gain is given before the clones with *EGR1* loss. Following the **pter** to **qter** rule, the clone with loss of D5S630 and *EGR1* is given next, followed by the clone with loss of only *EGR1*.

x. nuc ish (ATM×1,TP53×2)[100/200]/(ATM×2,TP53×1)[100/200]Interphase *in situ* hybridization of a neoplastic sample shows two clones of **equal size**. Each has a single abnormal probe pattern. In this case the clone with loss of *ATM* is listed before that with loss of *TP53* because they are listed in **chromosome order** for the abnormal probes.

xi. nuc ish (D13S319×1,LAMP1×2)[55/200]/(D13S319×2,LAMP1×1)[55/200]Interphase *in situ* hybridization in this neoplastic sample shows two clones of **equal size.** The signal

pattern in one clone is consistent with an interstitial loss within 13q14.3 (D13S319×1,LAMP1×2) and in the other clone, the signal pattern is consistent with an apparently terminal deletion involving 13q34 (D13S319×2,LAMP1×1). A normal signal pattern is present in 90 nuclei. **Note:** where two clones of **equal size** have the same number of abnormal patterns affecting the same chromosome then the clone with the abnormality closest to **pter** is listed before the clone with abnormality of a more distal probe.

xii. nuc ish (D13S319×0,LAMP1×2)[100/200]/(D13S319×1,LAMP1×2)[50/200]Homozygous deletion of D13S319 at 13q14.3 is detected in 100 of 200 nuclei by interphase *in situ* hybridization of a neoplastic sample. A heterozygous deletion is seen in 50 nuclei and the remaining 50 nuclei show a normal signal pattern. **Note:** the larger clone is given first, even though the smaller clone in this example is likely to represent the stem line. The result of the control probe, LAMP1, is given to demonstrate that the first clone represents homozygous interstitial deletion rather than nullisomy for chromosome 13.

xiii. nuc ish (D13S319×1,LAMP1×2)[100/200]/(D13S319×0,LAMP1×2)[100/200]*In situ* hybridization shows two clones of **equal size** in a neoplastic sample. Heterozygous deletion of D13S319 at 13q14.3 is detected in 100 nuclei and a homozygous deletion is also seen in 100 nuclei. There are no nuclei with a normal signal pattern. **Note:** different signal patterns are present in an **equal number** of nuclei for the same probe set, both represent loss and so the least complex clone is given first.

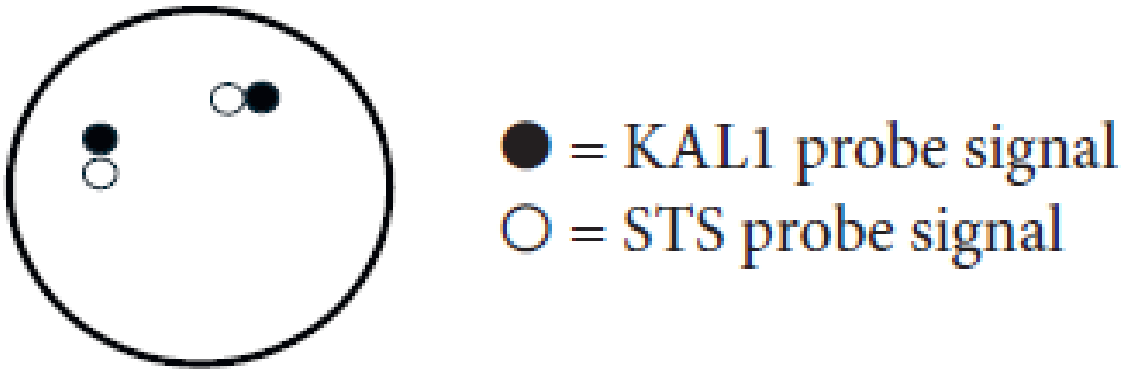
7.3.4 Relative Position of Signals

a. To indicate relative signal positions in the interphase nucleus, the result is given in two sets of parentheses, one following immediately after the other.
b. The total number of signals is given in the first set of parentheses and the relative position of the signals to one another using (**con**) and (**sep**) is given in the second set of parentheses.

7.3.4.1 Adjacent Probes

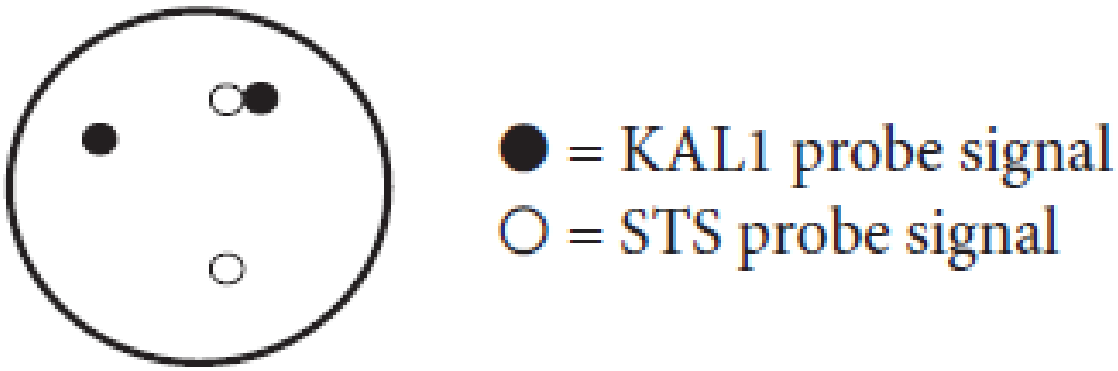
7.3.4.1.1 Normal Result

i. nuc ish (KAL1,STS)×2This is a normal result for *in situ* hybridization in a female. The hybridization signals for the KAL1 probe (*ANOS1*) and STS probe signals are normally adjacent because of close physical association of the respective loci (*ANOS1* and *STS*) on the X chromosome. There is a normal signal pattern of two signals for each probe in a female.



7.3.4.1.2 Abnormal Result

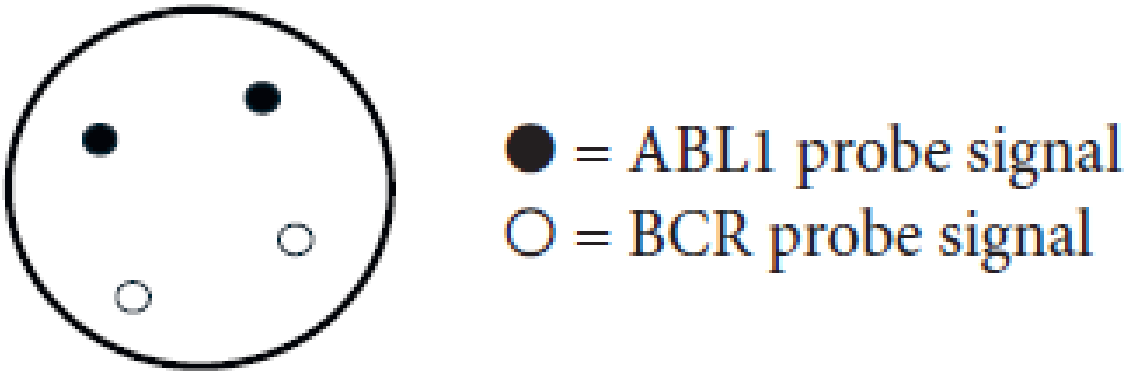
i. nuc ish (KAL1,STS)×2(KAL1 sep STS)×1Interphase *in situ* hybridization shows two signals for each probe. One KAL1 probe signal (*ANOS1* gene) and one STS probe signal are separated, presumably by chromosomal rearrangement and the other signals show the normal juxtaposition.



7.3.4.2 Dual-Fusion Probes

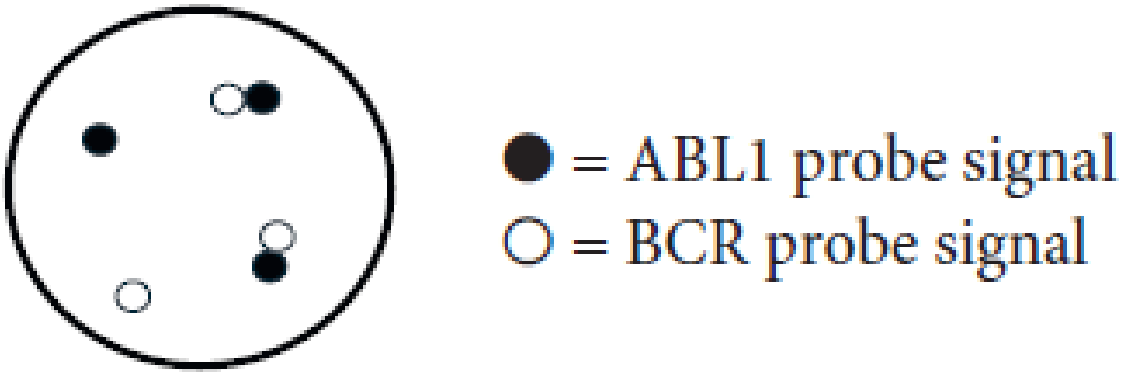
7.3.4.2.1 Normal Signal Pattern

i. nuc ish (ABL1,BCR)×2[200]No abnormality is detected by interphase *in situ* hybridization with a dual-color, dual-fusion ABL1/BCR probe set in a neoplastic sample. The *ABL1* and *BCR* genes reside on two separate chromosomes and rearrangement is not apparent in 200 nuclei. The expected copy number for each (×2) is given. **Note:** the ABL1 probe is listed before the BCR probe because they are listed in chromosome order.

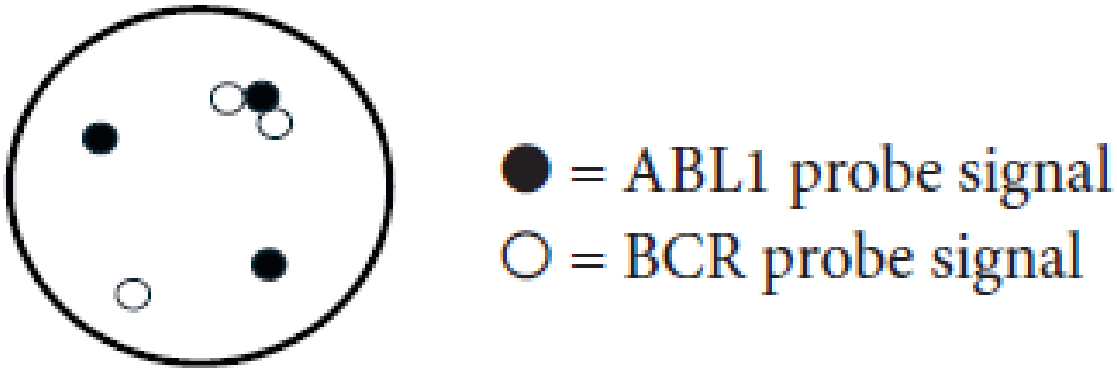


7.3.4.2.2 Abnormal Signal Pattern

i. nuc ish (ABL1,BCR)×3(ABL1 con BCR)×2[200]Interphase *in situ* hybridization of a neoplastic sample using a dual-color, dual-fusion ABL1/BCR probe set shows an abnormal pattern in 200 nuclei. There are three signals for each probe. There are two conjoined ABL1 and BCR probe signals, consistent with a reciprocal translocation between chromosomes 9 and 22 and formation of the *BCR*::*ABL1* fusion gene and the reciprocal *ABL1*::*BCR*. **Note:** signals associated with *BCR*::*ABL1* and *ABL1*::*BCR* are indistinguishable using this probe set.



ii. nuc ish (ABL1,BCR)×3(BCR con ABL1 con BCR)×1[100]Interphase *in situ* hybridization of a neoplastic sample using a dual-color, dual-fusion ABL1/BCR probe set shows an atypical rearrangement resulting one conjoined BCR/ABL1/BCR signal in 100 nuclei. This signal pattern could occur if 3′*ABL1* is inserted into *BCR*. RT-PCR for the *BCR*::*ABL1* chimeric transcript is recommended. There are also two isolated ABL1 probe signals and one isolated BCR probe signal.

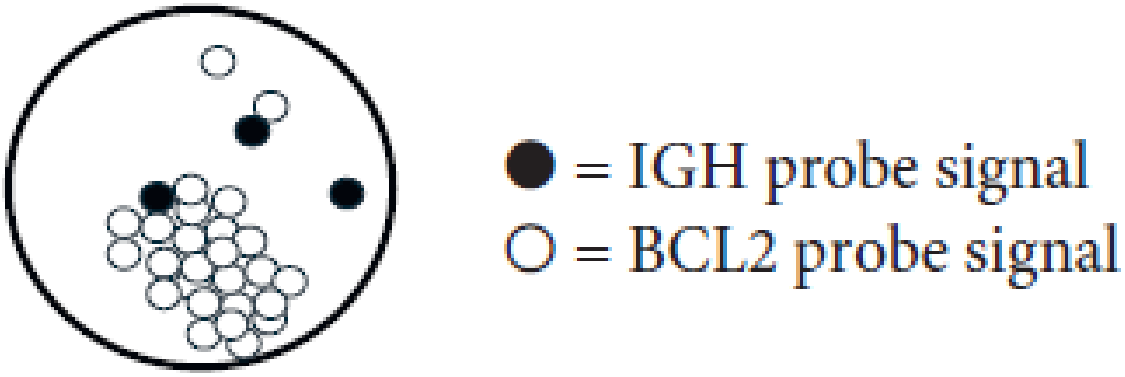


iii. nuc ish (ABL1,BCR)×2(ABL1 con BCR)×1[100]Interphase *in situ* hybridization of a neoplastic sample using a dual-color, dual-fusion ABL1/BCR probe set shows one conjoined ABL1 and BCR signal, most likely representing the *BCR*::*ABL1* fusion gene, one isolated ABL1 signal and one isolated BCR signal. This hybridization pattern is consistent with loss of, most likely, the reciprocal ABL1::BCR fusion signal in 100 nuclei.

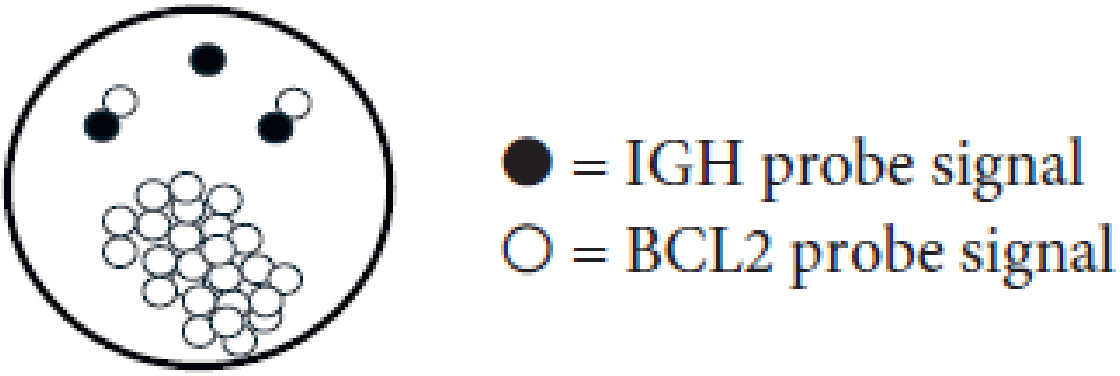
iv. nuc ish (ABL1×2,BCR×3)(ABL1 con BCR)×1[100]Interphase *in situ* hybridization of a neoplastic sample using a dual-color, dual-fusion ABL1/BCR probe set shows one conjoined ABL1 and BCR probe signal. There is also one isolated ABL1 probe signal and there are two isolated BCR probe signals. This result is consistent with *BCR*::*ABL1* fusion gene formation and loss of the *ABL1* gene from one chromosome, most likely the der(9)t(9;22).

v. nuc ish (ABL1,BCR)×4(ABL1 con BCR)×3[200]Interphase *in situ* hybridization of a neoplastic sample using a dual-color, dual-fusion ABL1/BCR probe set shows three conjoined ABL1 and BCR probe signals in 200 nuclei.

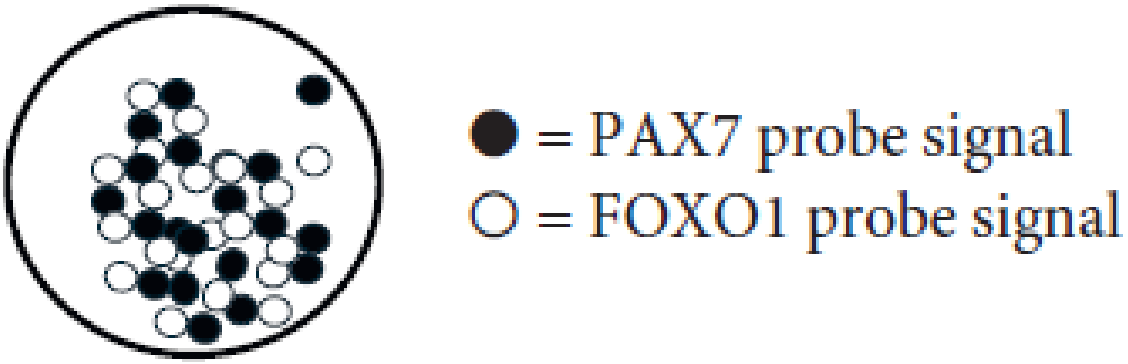
vi. nuc ish (IGH×3,BCL2×2,BCL2amp)(IGH con BCL2)×1(IGH con BCL2amp)×1[200]Interphase *in situ* hybridization of a neoplastic sample using a dual-color, dual-fusion IGH/BCL2 probe set shows three IGH probe signals and two BCL2 probe signals. There is also an amplified signal for the BCL2 probe in 200 nuclei. One IGH probe signal is conjoined with an amplified BCL2 probe signal. One IGH and one non-amplified BCL2 signal are conjoined.



vii. nuc ish (IGH×3,BCL2×2,BCL2amp)(IGH con BCL2)×2[180]Interphase *in situ* hybridization of a neoplastic sample using a dual-color, dual-fusion IGH/BCL2 probe set shows an amplified BCL2 probe signal that is not conjoined with an IGH probe signal. Two conjoined IGH and BCL2 probe signals and one additional IGH probe signal are also present.



viii. nuc ish (PAX7×1,PAX7amp,FOXO1×1,FOXO1amp)(PAX7 con FOXO1)amp[100]Interphase *in situ* hybridization of 100 nuclei of a neoplastic sample using a dual-color, dual-fusion PAX7/FOXO1 probe set shows one normal signal for the PAX7 and FOXO1 probes. There are also multiple copies of conjoined PAX7 and FOXO1 probe signals that are too numerous to count.



ix. nuc ish (3′BCL6×2,5′BCL6×1)(3′BCL6 con 5′BCL6)×1[77/100],(MYC)×3[80/100],(MYC×2∼3,IGH×2∼4)[100],(3′BCL2×2∼3, 5′BCL2×2)(3′BCL2 con 5′BCL2)×1[78/100]Interphase *in situ* hybridization of a neoplastic sample shows two signals for 3′BCL6 and one signal for 5′BCL6. One 3′BCL6 probe signal and one 5′BCL6 probe signal are conjoined leaving one isolated 3′BCL6 probe signal. The isolated 3′BCL6 probe signal may be evidence of an interstitial deletion or unbalanced rearrangement involving the *BCL6* gene. There are three MYC probe signals identified using both a single break-apart MYC probe and a dual-color, dual-fusion MYC/IGH probe set. The IGH probe shows two to four signals. There is one normal BCL2 probe signal (with 3′ and 5′ components connected), one to two isolated 3′BCL2 probe signals and one isolated 5′BCL2 probe signal. **Note:** ranges of signal number may be given to simplify otherwise complex results, e.g., (MYC×2∼3,IGH×2∼4) can be given to indicate the signal patterns (MYC×2,IGH×3), (MYC×2,IGH×4), (MYC×3,IGH×2), (MYC,IGH)×3 and (MYC×3,IGH×4). Similarly, (3′BCL2×2∼3,5′BCL2×2)(3′BCL2 con 5′BCL2)×1 indicates that nuclei have a single fusion and either two or three copies of 3′BCL2.

x. nuc ish (MYH11,CBFB)×3(MYH11 con CBFB)×2[100/200]Interphase *in situ* hybridization of a neoplastic sample using a dual-color, dual-fusion MYH11/CBFB probe set shows two conjoined MYH11 and CBFB signals in 100 of 200 interphase nuclei. The signal pattern shows no abnormality in the remaining 100 nuclei.

xi. nuc ish (ABL2)×2[200],(PDGFRB)×2[200],(ABL1,BCR)×3(ABL1 con BCR)×2[120/330]/(ABL1,BCR)×4(ABL1 con BCR)×3[120/330],(KMT2A)×2[200],(ETV6,RUNX1)×2[240],(IGH)×3[90/200],(TCF3)×2[150]Interphase *in situ* hybridization of a neoplastic sample using multiple probes and probe sets. The dual-color, dual-fusion ABL1/BCR probe set shows conjoined ABL1 and BCR signals that are consistent with *BCR*::*ABL1* fusion gene formation in 120 interphase nuclei. A further 120 interphase nuclei in the same

hybridization show gain of conjoined ABL1 and BCR signals, and 90 nuclei show a normal signal pattern for the ABL1 and BCR probes. There is also gain of an IGH signal in 90 of 200 nuclei scored. All other probes show a normal signal pattern. **Note:** probes are listed in chromosome order and where different abnormal signal patterns are present in an equal number of nuclei for the same probe set the least complex clone is described first.

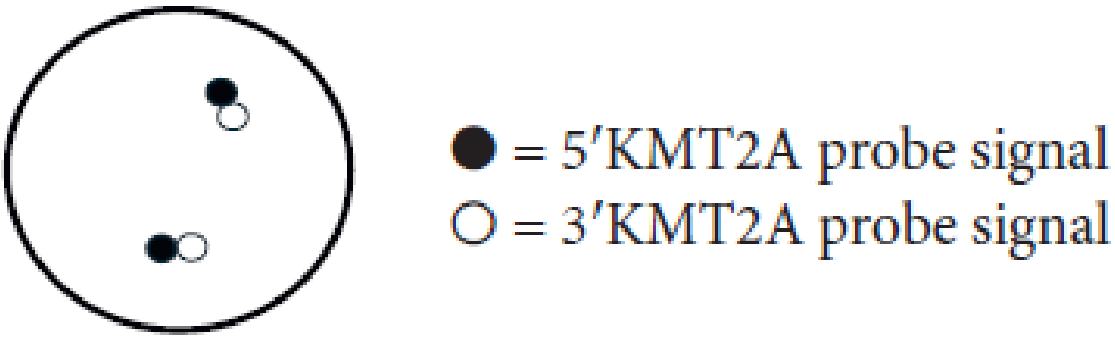
xii. 46,XY[20].ish 13q14(DLEU)×2 [10],13q34(LAMP1)×2 [10],14q32(IGH)×2 [6],16q23(MAF)×2 [6].nuc ish (DLEU×1,LAMP1×2)[17/200],(IGH,MAF)×3(IGH con MAF)×2[15/200]Karyotype of a neoplastic sample shows no abnormality. Metaphase *in situ* hybridization shows a normal result for two probes on chromosome 13 (DLEU and LAMP1) and a normal result for the dual-color, dual-fusion IGH/MAF probe set. Interphase *in situ* hybridization identified a small clone with an interstitial 13q deletion involving 13q14, and a clone of similar size with conjoining of IGH and MAF probe signals. **Note:** metaphases of the neoplastic clone(s) are not observed, and the clones are identified only by interphase *in situ* hybridization.

7.3.4.3 Break-Apart Probes

a. The normal signal pattern for break-apart probes is given using the probe designation without indicating the 5′ and 3′ components. For these probes the normal situation is the presence of two fusion signals.
b. For abnormal results, the total number of probe signals is given in the first set of parentheses and the relative position of the 5′ and 3′ signals to one another using (**sep**) and (**con**) is given in the second set of parentheses.

7.3.4.3.1 Normal Signal Pattern

i. nuc ish (KMT2A)×2[200]Interphase *in situ* hybridization of a neoplastic sample with a dual color break-apart KMT2A probe shows two KMT2A probe fusion signals in 200 interphase nuclei, no disruption of the *KMT2A* gene is detected. **Note:** the probe designation, without indicating the 5′ and 3′ components, is recommended in the normal setting even though it is acknowledged that the break-apart probes consist of a 5′ and a 3′ region.

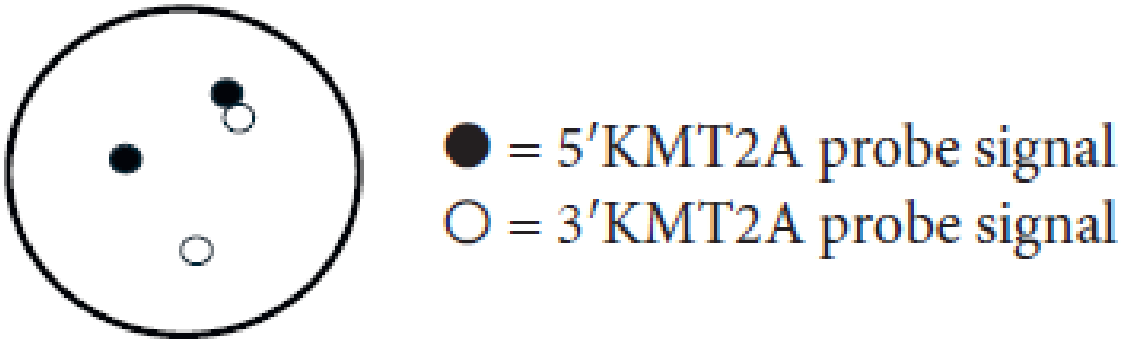


ii. nuc ish (CBFB)×2[200]Interphase *in situ* hybridization of a neoplastic sample with a dual color break-apart CBFB probe shows two CBFB probe fusion signals in 200 nuclei, no disruption of the *CBFB* gene is detected.

7.3.4.3.2 Abnormal Signal Pattern

Abnormal nuclei show separation of the two signal components of break-apart probes.

i. nuc ish (KMT2A)×2(5′KMT2A sep 3′KMT2A)×1 [200]Interphase *in situ* hybridization of 200 nuclei in a neoplastic sample with a dual color break-apart KMT2A probe shows two KMT2A probe signals. There is one intact 5′KMT2A/3′KMT2A probe signal and one signal has separated into the 5′KMT2A probe and the 3′KMT2A probe components, presumably because of a translocation involving the *KMT2A* gene. **Note:** that 5′ and 3′ probes are given for an abnormal result.

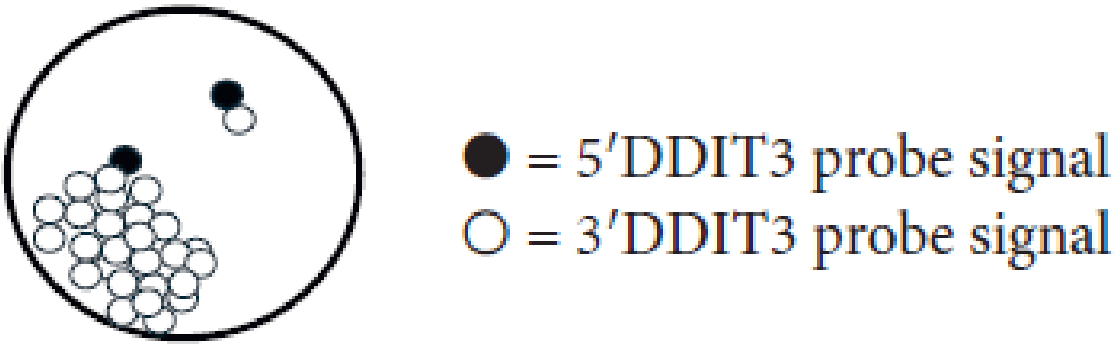


ii. nuc ish (5′KMT2A×2,3′KMT2A×1)(5′KMT2A con 3′KMT2A)×1[180]Interphase *in situ* hybridization of 180 nuclei in a neoplastic sample shows two 5′KMT2A probe signals and one 3′KMT2A probe signal. There is one intact 5′KMT2A/3′KMT2A signal and one isolated 5′KMT2A signal presumably because of a deletion involving 3′KMT2A or because there is a translocation resulting in *5′KMT2A-3′* partner gene, with loss of the reciprocal derivative chromosome.

iii. nuc ish (3′ALK×2,5′ALK×1)(3′ALK con 5′ALK)×1[65/100]Interphase *in situ* hybridization of a neoplastic sample with a dual color break-apart ALK probe shows one intact 3′ALK/5′ALK probe signal and an isolated 3′ALK probe signal. These abnormalities are detected in 65 of 100 interphase nuclei. No abnormality is detected in 35 nuclei. **Note:** the probe components are listed from **pter** to **qter** according to their position on the normal chromosome 2.

iv. nuc ish (3′IGH×0,5′IGH×2)[145/200]Interphase *in situ* hybridization of a neoplastic sample with a dual color break-apart IGH probe shows two signals for the 5′IGH probe and no signals for the 3′IGH probe, listed as they appear **pter** to **qter** on the normal chromosome 14. This abnormality is detected in 145 of 200 interphase nuclei. No abnormality is detected in 55 nuclei. **Note:** the relative position of the 3′ and 5′ components of the probe cannot be given since no 3′IGH probe signal is present.

v. nuc ish (3′DDIT3×2,5′DDIT3×1,5′DDIT3amp)×1(3′DDIT3 con 5′DDIT3)×1(3′DDIT3 con 5′DDIT3amp)×1[192/200]Interphase *in situ* hybridization of a neoplastic sample with a dual-color break-apart DDIT3 probe shows an abnormal *DDIT3* signal pattern with amplification of the 5′DDIT3 probe signal in 192 of 200 nuclei, *i.e.*, there are two signals for the 3′DDIT3 probe, one single signal for the 5′DDIT3 probe and an amplified 5′DDIT3 probe signal. There is normal colocalization of one of the 3′DDIT3 probe signals and the single 5′DDIT3 probe signal. There is also colocalization of a of 3′DDIT3 probe signal with the amplified 5′DDIT3 probe signal. No abnormality is detected in eight nuclei. **Note:** the 3′DDIT3 probe is listed before the 5′DDIT3 probe because it lies closer to **pter** on the normal chromosome.



vi. nuc ish (3′IGH×2,5′IGH×3)(3′IGH con 5′IGH)×1[210/250]Interphase *in situ* hybridization of a neoplastic sample with a dual-color break-apart IGH probe shows an *IGH* rearrangement with an extra 5′IGH signal using the IGH break-apart probe in 210 of 250 nuclei. No abnormality is detected in 40 nuclei. **Note:** the probe components are listed from **pter** to **qter** as they would lie on the normal chromosome 14.

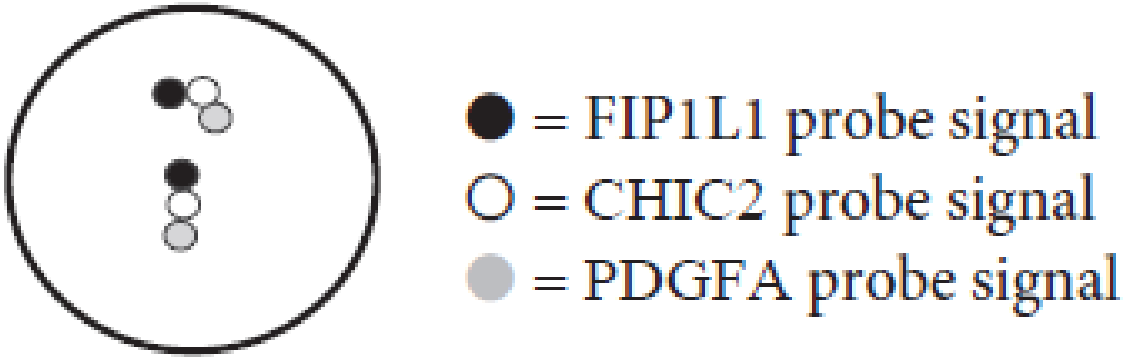
vii. nuc ish (CBFB)×2(5′CBFB sep 3′CBFB)×1[198]Interphase *in situ* hybridization of a neoplastic sample with a dual-color break-apart CBFB probe shows two CBFB probe signals, but one has separated into the 5′CBFB probe and 3′CBFB probe, presumably because of an inversion or translocation. This signal pattern is present in all 198 nuclei examined.

viii. nuc ish (CDKN2C×2,CKS1B×3)[90/100],(FGFR3×2,IGH×3)[93/100],(MYC)×2[100],(CCND1×2,IGH×3)[85/100],(ATM,TP53)×2[100],(IGH)×2(3′IGH sep 5′IGH)×1[95/100],(IGH,MAF)×3(IGH con MAF)×2[87/100],(IGH×3,MAFB×2)[91/100]Interphase *in situ* hybridization of a neoplastic sample shows gain of 1q21.3 (CKS1B locus specific probe) in 90 nuclei and conjoined IGH/MAF probe signals with an IGH/MAF dual-color, dual-fusion probe in 87 nuclei. The IGH dual-color break-apart probe shows separate 3′IGH and 5′IGH signals in 95 nuclei. An additional IGH probe signal is seen with the IGH/FGFR3, IGH/CCND1 and IGH/MAFB dual-color, dual-fusion probes. The CDKN2C, MYC, ATM and TP53 probes show a normal signal pattern.

7.3.4.4 Tricolor Probes

7.3.4.4.1 Single Chromosome Normal Signal Pattern

i. nuc ish (FIP1L1,CHIC2,PDGFRA)×2[200]Interphase *in situ* hybridization of a neoplastic sample with a tricolor deletion/translocation probe set shows two FIP1L1, CHIC2, PDGFRA probe fusion signals in all 200 interphase nuclei, no disruption of the *CHIC2* gene is detected.

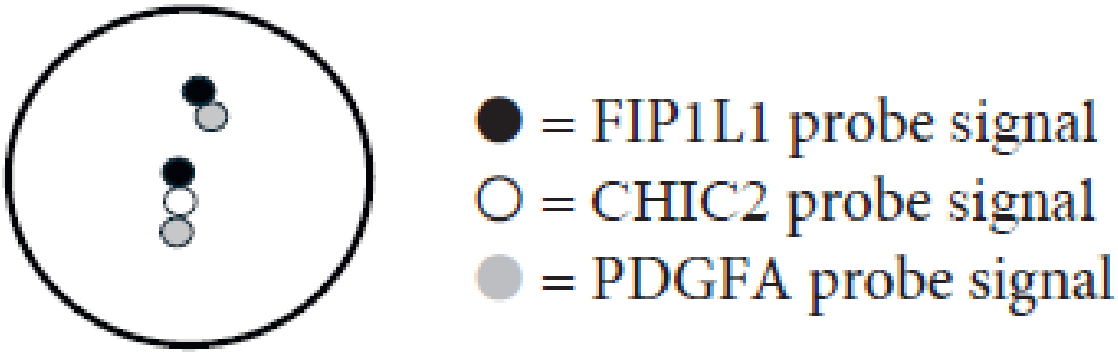


7.3.4.4.2 Single Chromosome Abnormal Signal Pattern

i. nuc ish(GOLIM4×1,MECOM×2,MYNN×2)[55/200]Interphase *in situ* hybridization of a neoplastic sample with a tricolor deletion/translocation probe set shows deletion of a proximal region of the long arm of one chromosome 3 including the *GOLIM4* gene in 55 of 200 nuclei. There are two MECOM and two MYNN probe signals. No abnormality is detected in 145 nuclei.

ii. nuc ish (GOLIM4×2,MECOM×3,MYNN×2)(GOLIM4/MECOM sep MECOM/MYNN)×1[35/100]Interphase *in situ* hybridization of a neoplastic sample with a tricolor deletion/translocation probe set shows one intact set of adjacent GOLIM4, MECOM, and MYNN probe signals in 35 of 100 nuclei. Due to a rearrangement with a breakpoint within the *MECOM* gene, there is also one GOLIM4 signal connected to one MECOM signal that is separated from a MECOM signal connected to a MYNN signal. No abnormality is detected in 65 nuclei.

iii. nuc ish (FIP1L1×2,CHIC2×1,PDGFRA×2)(FIP1L1 con PDGFRA)×1[150/200]Interphase *in situ* hybridization of a neoplastic sample with a tricolor deletion/translocation probe set shows one intact set of FIP1L1, CHIC2, and PDGFRA probe signals, and interstitial deletion including the *CHIC2* gene resulting in one conjoined FIP1L1 and PDGFRA probe signal in 150 of 200 nuclei. This result is consistent with formation of the *FIP1L1*::*PDGFRA* fusion gene. No abnormality is detected in 50 nuclei.



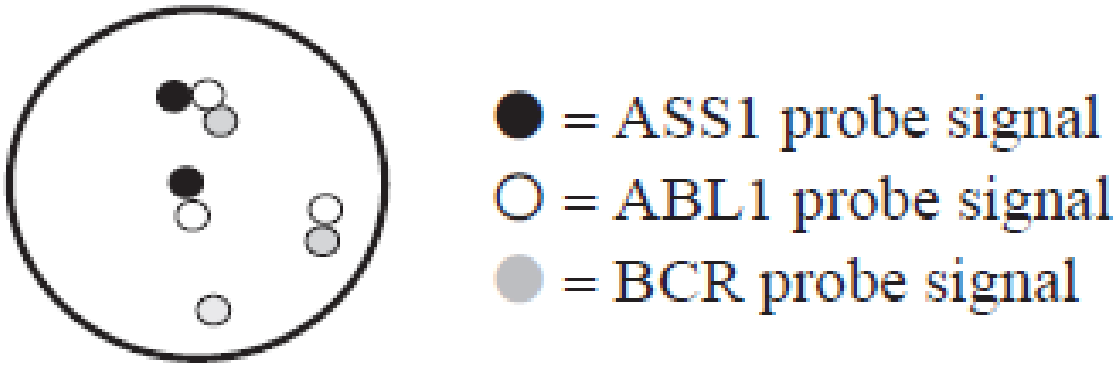
iv. nuc ish (FIP1L1,CHIC2,PDGFRA)×2(FIP1L1/CHIC2 sep PDGFRA)×1[150/200]Interphase *in situ* hybridization of a neoplastic sample with a tricolor deletion/translocation probe set shows one intact set of FIP1L1, CHIC2, and PDGFRA probe signals, along with one PDGFRA signal that has become separated from the FIP1L1/CHIC2 probe signal by a translocation at 4q12, in 150 of 200 nuclei. No abnormality is detected in 50 nuclei.

7.3.4.4.3 Two or More Chromosomes Normal Signal Pattern

i. nuc ish (ASS1,ABL1,BCR)×2[100]Interphase *in situ* hybridization of a neoplastic sample shows a normal signal pattern with a tricolor ASS1/ABL1/BCR deletion, dual-fusion probe set in 100 nuclei. **Note:** relative positions of signals are not provided for a normal result.

7.3.4.4.4 Two or More Chromosomes Abnormal Signal Pattern

i. nuc ish (ASS1×2,ABL1×3,BCR×3)(ASS1/ABL1 con BCR)×1(ABL1conBCR)×1[90/100] Interphase *in situ* hybridization of a neoplastic sample with a tricolor ASS1/ABL1/BCR deletion, dual-fusion probe set shows a conjoined BCR and ABL1 signal. There is one normal ASS1/ABL1 signal and one normal BCR signal. The rearranged signals are one ASS1/ABL1/BCR conjoined signal consistent with the *ABL1*::*BCR* reciprocal fusion gene; and one BCR/ABL1 conjoined signal consistent with the *BCR*::*ABL1* fusion gene. The abnormal signal pattern is seen in 90 nuclei and no abnormality is detected in ten nuclei.



ii. nuc ish (D8Z2×2,MYC×3,IGH×3)(MYC con IGH)×2[100/200],(IGH×3,BCL2×2)[100/200]Interphase *in situ* hybridization of a neoplastic sample using a tricolor, dual-fusion IGH/MYC and D8Z2 probe set shows two D8Z2 signals and two conjoined MYC and IGH signals in 100 of 200 nuclei scored. In a separate hybridization with a dual-color, dual-fusion IGH/BCL2 probe set, three IGH probe signals and two BCL2 probe signals are seen in 100 nuclei of 200 nuclei scored. Taken together these hybridization signal patterns are consistent with an *IGH*::*MYC* rearrangement and the *BCL2* gene is unrearranged. **Note:** the D8Z2 control probe is given as it confirms chromosome 8 copy number.

7.4 Multiple Copies of the Same Gene in Neoplasia

a. When the signals can be counted, the number of signals should be listed in the ISCN description.
b. Where there are too many probe signals to enumerate the exact copy number, the **greater than** (>) sign may be used to show the minimum number of copies present.
c. When the signals are too numerous to score **amp** may be used if it is clinically relevant and meets the counting criteria.

i. ish dmin(MYCN)×3~15[20]Metaphase *in situ* hybridization of 20 nuclei of a neoplastic sample shows double minutes involving *MYCN*, in three to 15 copies per metaphase.

ii. ish 8q24(MYC)×>25[5]/8q24(MYC)×2[10]
or
ish 8q24(MYC)amp[5]/8q24(MYC)×2[10]Metaphase *in situ* hybridization shows gain of multiple MYC probe signals in five metaphases of a neoplastic sample, and a normal signal pattern in ten metaphases. The signals could not always be enumerated, but there are more than 25 MYC probe signals in the abnormal metaphases. Alternatively, **amp** may be used to describe the high-level gain of MYC probe signals.

iii. ish ider(21)(q10)dup(21)(q22q22)(RUNX1++,RUNX1++)[5]Metaphase *in situ* hybridization confirms an isoderivative chromosome 21 with duplication of 21q22 identified in a neoplastic sample. There are two signals for the RUNX1 probe in each arm of the isoderivative chromosome. **Note:** a comma between the two probes in the ISCN description indicates that they are non-tandem (see Section 7.2.1).

iv. ish ider(21)(q10)add(21)(q11.2)(RUNX1amp,RUNX1amp)[3]An isochromosome derived from chromosome 21 with additional uncharacterized material in a neoplastic sample. Metaphase *in situ* hybridization shows an increase in RUNX1 probe signals fulfilling the clinical definition of *RUNX1* amplification. There is amplification of *RUNX1* on each chromosome arm.

v. ish der(21)(RUNX1)amp[4]Metaphase *in situ* hybridization shows that a derivative chromosome 21 in a neoplastic sample has an increase in RUNX1 probe signals so numerous that they cannot be quantified in the four metaphases analyzed.

vi. nuc ish (MYCN)×12∼>20[200]Interphase *in situ* hybridization of a neoplastic sample shows 12 to more than 20 MYCN probe signals in 200 nuclei. A control probe, D2Z1, is also used and its inclusion is optional in the ISCN description as the MYCN probe is informative.

vii. nuc ish (MYCN)amp[200]Interphase *in situ* hybridization of a neoplastic sample shows several *MYCN* probe signals too large to be quantified. A control probe, D2Z1, is also used, but is not included in the ISCN description as the MYCN probe signal pattern is informative.

viii. nuc ish (D17Z1,ERBB2)×4∼5[100/200]Interphase *in situ* hybridization of a neoplastic sample shows four to five signals for the D17Z1 and ERBB2 probes in 100 of 200 nuclei. The control probe is given in the ISCN description as it confirms polysomy for chromosome 17. No abnormality is detected in 100 nuclei.

ix. nuc ish (D17Z1×2,ERBB2×10∼20)[100/200]Interphase *in situ* hybridization of a neoplastic sample shows ten to 20 ERBB2 probe signals in 100 nuclei and two signals for the alpha satellite 17 probe, D17Z1. The control probe is given in the ISCN description as it confirms there are only two copies of chromosome 17. No abnormality is detected in 100 nuclei.

x. nuc ish (D17Z1×2∼3,ERBB2amp)[100/200]/(D17Z1,ERBB2)×3[20/200]Interphase *in situ* hybridization of a neoplastic sample shows copy gain of D17Z1 and amplification of ERBB2 probe signals. In addition, three signals each for both D17Z1 and ERBB2 are seen in 20 nuclei and two signals for each observed in 80 nuclei.

xi. nuc ish (D17Z1,ERBB2)amp[156/200]/(D17Z1,ERBB2)×4[20/200]Interphase *in situ* hybridization of a neoplastic sample shows signal amplification of the D17Z1 and ERBB2 probes. Four D17Z1 and ERBB2 probe signals are observed in 20 nuclei and the remaining 24 nuclei show the normal two signals for each probe.

7.5 Enumeration Probes

For enumeration probes the abbreviated system (karyotype format) is used (see Section 4.7).

i. ish 8(D8Z2)×3[20]/8(D8Z2)×2[30]Metaphase *in situ* hybridization in a prenatal sample shows three signals for the chromosome 8 pericentromeric alpha satellite probe, D8Z2, in 20 metaphases and two signals for this probe in 30 metaphases. These results are consistent with mosaic trisomy chromosome 8.

ii. ish 8(D8Z2)×3[25]/8(D8Z2)×2[25].nuc ish (D8Z2)×3[52/100]*In situ* hybridization shows three D8Z2 probe signals in 25 metaphases and two D8Z2 probe signals in another 25 metaphases; interphase *in situ* hybridization confirms the presence of an extra D8Z2 probe signal in 52 of 100 nuclei of this neoplastic specimen. These results are consistent with a clone with trisomy 8.

iii. 45,X[3]/46,XY[12].ish X(DXZ1×1,SRY×0)[32]/X(DXZ1)×1,Y(SRY)×1[68]Karyotype shows two cell lines in a male: one cell line with 45,X and the other with an apparently normal male karyotype. For determining the sex chromosome complement, it is appropriate to indicate the status of *SRY* in both cell lines. The cell line with a single X chromosome is confirmed by metaphase *in situ* hybridization to have no signals for *SRY*. The 46,XY cell line is confirmed to have a single X chromosome and one appropriately located *SRY* gene on the Y chromosome. A **multiplication** (×) sign is used instead of **plus** (+) sign as this is a normal signal pattern for the single X chromosome. **Note:** the normal cell line is listed last.

iv. nuc ish (DXZ1×2,DYZ3×1,D18Z1×3),(RB1,D21S259/D21S341/D21S342)×3
or
nuc ish (DXZ1×2,DYZ3×1,D18Z1×3),(RB1,D21S259)×3Interphase *in situ* hybridization shows two probe signals for the X chromosome, one probe signal for the Y chromosome, and three probe signals for chromosomes 13, 18 and 21. This finding is consistent with a triploid result, 69,XXY. **Note:** the chromosome 21 probe contig shows each probe listed, separated by slant lines in the first example. In the second example a description of the other chromosome 21 contig probes must be given in the text of the report.

7.6 Mosaic and Chimera Signal Pattern

For general rules concerning reporting mosaicism and chimerism and for an explanation of the use of **double slant line** (//) in chimeras, see Section 4.5.3.

i. nuc ish (DXZ1)×2[400]//Interphase *in situ* hybridization shows 400 nuclei all representing the female recipient post sex-mismatched stem cell transplant. No donor nuclei are detected.

ii. //nuc ish (DXZ1,DYZ3)×1[400]Interphase *in situ* hybridization shows 400 nuclei all representing the male donor post sex-mismatched allogeneic stem cell transplant. No recipient nuclei are detected.

iii. nuc ish (DXZ1)×2[50]//(DXZ1,DYZ3)×1[350]Interphase *in situ* hybridization using X and Y alpha satellite probes shows 50 recipient XX nuclei and 350 donor XY nuclei post sex-mismatched allogeneic stem cell transplant.

iv. nuc ish (DXZ1)×2[50]/(DXZ1×1,DYZ3×0)[10]//(DXZ1,DYZ3)×1[300] or (DXZ1)×2[50]//(DXZ1,DYZ3)×1[300]/(DXZ1×1,DYZ3×0)[10]Interphase *in situ* hybridization using X and Y alpha satellite probes shows 50 recipient XX nuclei and 300 donor XY nuclei post sex-mismatched allogeneic stem cell transplant. Ten nuclei with a single X chromosome are detected. The origin of the single X chromosome cell line is unknown and could be derived from either the recipient XX (shown in the first option) or donor XY (shown in the second option) cell line. **Note**: the smallest cell line is listed last for recipient and donor.

v. mos 46,X,+r[15]/45,X[10].ish r(X)(wcpX+,DXZ1+)[10]Karyotype shows two cell lines in a female: one with 46 chromosomes including a small ring chromosome and another cell line with 45,X. Metaphase *in situ* hybridization using the whole X chromosome paint and the X alpha satellite probe, shows that the ring chromosome is derived from the X chromosome.

vi. 46,X,+r.ish r(X)(wcpX+,DXZ1+)[15]/r(X)(wcpX+,DXZ1+,DXZ1+)[10]Karyotype shows a cell line with a single X chromosome and a small ring chromosome. Metaphase *in situ* hybridization with a whole X chromosome paint shows that the ring is derived from the X chromosome. Probe DXZ1, for the X alpha satellite, shows the ring to be monocentric in some metaphases and dicentric in other metaphases. **Note:** if the non-tandem duplication of the DXZ1+ signal pattern is due to dynamic mosaicism then it is not reported in the ISCN description.

vii. ish del(14)(q21.2q21.2)(RP11–453F20–)dn[6]/14q21.2(RP11–453F20)×2[4]Metaphase *in situ* hybridization using a locus specific probe, RP11–453F20 confirms a *de novo* cryptic deletion within band 14q21.2 in six of the ten metaphases. This deletion had originally been identified by microarray.

viii. ish del(14)(q21.2q21.2)(RP11–453F20–)dn[16]/dup(14)(14q21.2q21.2)(RP11–453F20++)mat[4]Metaphase *in situ* hybridization using a locus specific probe, RP11–453F20 confirms a *de novo* cryptic deletion within band 14q21.2 in 16 of 20 metaphases, and a duplication within band 14q21.2, inherited from the mother, in four of the 20 metaphases. The abnormality of this subband has previously been identified by microarray.

ix. 47,XX,+mar[10]/46,XX[20].ish der(15)(:p11.2→q11.2:)(D15S11+,SNRPN+,D15S10–,GABRB3–)[5]/15q11.2q12(D15S11,SNRPN,D15S10,GABRB3)×2[20]Karyotype shows mosaicism for a marker chromosome of unknown origin in a female. Metaphase *in situ* hybridization identifies the marker as an abnormal chromosome 15 that includes the region defined by probes for D15S11 (15q11.2) and the *SNRPN* (15q11.2) gene.

x. ish 21(D21S259/D21S341/D21S342)×3[20]/21(D21S259/D21S341/D21S342)×2[30]Metaphase *in situ* hybridization using a locus specific probe contig for chromosome 21, shows mosaicism in a female with three chromosomes 21, each with a single copy of the Down syndrome critical region in 20 of 50 metaphases analyzed. All loci of the contig probe are listed in this example. **Note:** if all three signals for

D21S259/D21S341/D21S342 are present on a single chromosome 21 the result will be ish der(21)(q22.13)(D21S259/D21S341/D21S342+++).

xi. nuc ish chi (DXZ1,DYZ3)×1[32/50]/(DXZ1)×2[18/50]Interphase *in situ* hybridization shows one copy of the X chromosome and one copy of the Y chromosome in 32 of 50 nuclei, and 18 nuclei with two copies of the X chromosome. This is consistent with a XY/XX chimera although further studies are needed for confirmation. The larger of the cell lines is listed first.

xii. ish chi X(DXZ1)×2[5]/X(DXZ1)×1,Y(SRY)×1[5]Metaphase *in situ* hybridization using probes for DXZ1 and SRY in a chimeric individual shows two cell lines in five metaphases each, one cell line with two X chromosomes and the other with one X and one Y chromosome. The cell lines are given in chromosome order.

xiii. nuc ish (DXZ1×2,DYZ3×1,D18Z1×2)[150/200],(RB1×2,D21S270/D21S1425/D21S341×3)Interphase *in situ* hybridization shows a signal pattern consistent with an XXY sex chromosome complement in 150 of 200 nuclei and the remaining 50 nuclei show a signal pattern consistent with an XY sex chromosome complement. All nuclei scored show a normal result for RB1 and D18Z1 and are non-mosaic for trisomy 21. **Note:** cell numbers are not given for a non-mosaic constitutional interphase result.

xiv. mos 47,XY,+21[10]/46,XY[5].ish 21(D21S259/D21S341/D21S342)×3[15]/21(D21S259/D21S341/D21S342)×2[5].nuc ish (D21S259/D21S341/D21S342)×3[35/50]Karyotype, metaphase *in situ* hybridization and interphase *in situ* hybridization show mosaic trisomy 21 in a male. The normal cell line is not given but is apparent from the denominator of the interphase (**nuc ish**) result.

xv. mos 45,X[7]/47,XYY[5]/46,XY[8].ish X(DXZ1×1,SRY×0)[10]/X(DXZ1)×1,Y(SRY)×2[8]/X(DXZ1)×1,Y(SRY)×1[12].nuc ish (DXZ1×1,DYZ3×0)[12/50]/(DXZ1×1,DYZ3×2)[6/50]/(DXZ1,DYZ3)×1[32/50]Karyotype shows three cell lines: a cell line with 45,X, a cell line with one X chromosome and two copies of the Y chromosome, and the remaining 12 metaphases with a normal male karyotype. The normal cell line is given last in the karyotype, **ish** and **nuc ish** nomenclature, and the abnormal cell lines are listed with the largest first.

8 Microarray

8.1 Introduction

Chromosomal microarray is a genome-wide investigation for the detection of copy number change. In platforms that are supplemented with single nucleotide polymorphism (SNP) probes, zygosity and some forms of ploidy can be determined. Most microarray platforms cover only nonrepetitive regions. As such, the acrocentric short arms, centromeric and telomeric regions, and regions of heterochromatin are not detected by microarray.

Positional structural chromosome information is not provided by this technology and elucidation of the nature of the underlying rearrangement by alternative methods such as conventional karyotype or FISH may be required.

8.1.1 General Principles

a. For general cytogenomic rules that are also applicable to microarray, see Chapter 4. For targeted microarray result nomenclature, see Chapter 10.
b. If *no abnormality* is detected by microarray, the results are expressed beginning with **arr** to designate microarray, then a space followed by the opening parenthesis. Sex chromosomes are listed first, followed by a **comma** (**,**), before the autosomes and the closing parenthesis. This is followed by the **multiplication** (×) sign and the copy number. The genome build is only given if the nucleotide coordinates are reported (see Sections 4.4.5 and 8.2.1).
c. An *abnormal* result in which nucleotide coordinates are given, is expressed beginning with **arr** to designate microarray, no space, the specified **genome build** (*e.g.,* **[GRCh38]** referring to the Genome Reference Consortium Human Build 38 assembly) in **square brackets** (**[ ]**), then a space followed by chromosome band and nucleotides. Only the abnormal genomic regions are described.

- The aberrations of sex chromosomes are listed first, followed by autosomes which are listed from lowest to highest number chromosome.
- The nucleotides are listed within parentheses from **pter** to **qter** with an **underscore** (_), to indicate the segment between the listed nucleotides. This is followed by the **multiplication** (×) sign and copy number of the aberration.
- Multiple aberrations are each separated by a **comma** (**,**). The nomenclature for reporting abnormal results is detailed in Section 4.4.
- The normal sex chromosome complement is generally not given in the ISCN description for an autosomal abnormality, although if it is clinically relevant it should be included in the interpretive text.

- When describing abnormalities involving sex chromosomes, the normal sex chromosome may be given for clarity.

d. For interstitial deletions or duplications where both breakpoints are within the same chromosome band, the breakpoint band is given only once in the ISCN description.

e. To indicate a mixed cell population, the proportion of cells with the aberration can be estimated from the fractional copy number and included in **square brackets** (**[ ]**) following the copy number. Alternatively, the range of copy numbers can be indicated using a **tilde** (**~**).

f. When mixed cell populations can be distinguished for *constitutional and unrelated clones*, the largest cell line/clone is listed first. For *related clones in neoplasia*, the least complex clone is listed first.

g. In neoplastic samples the proportion of the sample with each abnormality is given in **square brackets** (**[ ]**) when the abnormality is detected at less than 100% of the sample. When the abnormality is apparently present in 100% of the sample, then it is optional to include [1.0].

h. The proportion of the sample with an abnormality is estimated from the profile and is not adjusted for the tumor load.

i. Three systems are used in the microarray format (see Section 4.7.2):

- The abbreviated system describes the abnormality/abnormalities *without* using the genome build and nucleotides.
- The short system includes the genome build, chromosome bands and nucleotides within the abnormality.
- The extended system describes the span of the nucleotides within the abnormality and the normal flanking nucleotides. Commas are not used in the nucleotides in the extended system.

j. In the abbreviated system, the result is expressed as **arr** followed by a space, then the nomenclature of the abnormal result within parenthesis. The nomenclature rules are given in Section 4.7.2.

k. Gains and losses are reported relative to the normalized ploidy, and it may not be possible to distinguish between a one copy gain in a high proportion of the sample and a two copy gain in a low proportion of the sample. Similarly, it may be necessary to use a different method to determine the ploidy and/or mosaicism of a sample, *e.g*., to discern tetraploidy from diploidy, and/or triplication from duplication.

l. The descriptive narrative, or interpretive comment in the report must indicate the platform used and the resolution. For targeted microarray analysis, see Chapter 10.

m. If **shallow genome sequencing** is undertaken, the term **sseq** is used instead of **arr**.

n. Some of the ISCN examples in this chapter do not represent observed data but are provided to demonstrate the nomenclature principles.

8.2 Examples of Microarray Nomenclature

8.2.1 Normal Results

i. arr (X,1–22)×2Microarray analysis shows no abnormality in a female profile.

ii. arr (X,Y)×1,(1–22)×2Microarray analysis shows no abnormality in a male profile.

iii. arr (1–22)×2Microarray analysis shows no abnormality in the sample and the sex chromosomes are undisclosed.
iv. 46,U.arr (1–22)×2The karyotype and microarray analysis show no abnormality. The sex chromosomes are undisclosed.

8.2.2 Abnormal Copy Number Results

Structural chromosome information is not provided by this technology and elucidation of the nature of the rearrangement by alternative methods such as conventional karyotype or FISH may be necessary.

i. arr (X)×2,(Y)×1Microarray analysis shows a male profile with two copies of an X chromosome and one Y chromosome. This finding is consistent with Klinefelter syndrome.
ii. arr (X)×1,(Y)×2Microarray analysis shows a male profile with a single X chromosome and gain of a Y chromosome. The normal X chromosome is given in the ISCN description for clarity.
iii. arr (X)×2,(Y)×1,(1–22)×3SNP microarray analysis is consistent with triploidy, 69,XXY.
iv. arr (X,1–22)×3SNP microarray analysis is consistent with triploidy, 69,XXX.
v. arr (X,18)×3Microarray analysis in a female is consistent with a single copy gain of chromosomes X and 18. **Note:** where more than one chromosome is involved, these are separated by a **comma** (**,**).
vi. sseq (X,18)×3Shallow genome sequencing in a female is consistent with a single copy gain of chromosomes X and 18.
vii. arr (8,21)×3Microarray analysis is consistent with a single copy gain of chromosomes 8 and 21.
viii. arr (16q)×3Microarray analysis shows a single copy gain of the entire long arm of chromosome 16.
ix. arr (18)×3
or
arr[GRCh38] 18p11.32q23(102,328_79,093,443)×3Microarray analysis shows a single copy gain of the entire chromosome 18, consistent with trisomy 18.
x. arr (21)×3
or
arr[GRCh38] 21q11.2q22.3(13,531,865_46,914,745)×3Microarray analysis shows a single copy gain of the entire long arm of chromosome 21. **Note:** most microarrays do not cover the repetitive short arm sequences of the acrocentric chromosomes and the short arm is therefore not reported in the nomenclature. Chromosome analysis is needed to determine whether this is a translocation type trisomy or nondisjunction trisomy of chromosome 21.
xi. arr (X,1–19,21,22)×3SNP microarray analysis is consistent with a near-triploidy in a female with two copies of chromosome 20.
xii. arr[GRCh38] 15q11.1q13.2(20,366,669_30,226,235)×4Microarray analysis shows a two copy gain of proximal long arm of chromosome 15, resulting in tetrasomy of 15q11.1 to 15q13.2. Distinguishing a supernumerary marker chromosome or an

interchromosomal insertion from a triplication of this region requires conventional karyotyping or metaphase FISH.

xiii. arr[GRCh38] Xq28(155,708,407_156,005,042)×1 or Yq12(56,894,927_57,191,562)×1Microarray analysis shows a single copy loss of the pseudoautosomal region (PAR2) that is found at either Xq28 or Yq12. It cannot be determined if the loss is from the X chromosome or the Y chromosome in a male. FISH or chromosome analysis is required to confirm the location of loss.

xiv. arr[GRCh38] Xp22.33 or Yp11.31p11.2(559,968_917,321)×3Microarray analysis of a male with a single copy gain within the pseudoautosomal region (PAR1) of either Xp or Yp. **Note:** in GRCh38 the nucleotide positions are identical for this region on both X and Y chromosomes.

xv. arr[GRCh38] (X)×2,Yp11.32p11.2(11,091_3,295,603)×1Microarray analysis shows the presence of a single copy of a segment of the short arm of the Y chromosome, with no detectable loss from the two X chromosomes nor autosomes. FISH or chromosome analysis is required to confirm the structural nature of the gain that includes *SRY*. **Note:** the normal sex chromosomes are given in the nomenclature for sex determination.

xvi. arr[GRCh38] Yq11.23(24,741,599_24,873,358)×0,20q13.2q13.33(53,224,067_63,743,732)×3Microarray analysis shows a male profile with an interstitial loss within Y chromosome at band Yq11.23 and a gain of the distal long arm of chromosome 20 involving bands 20q13.2 to 20q13.33.

xvii. arr[GRCh38] 1p36.33p36.32(827,048_3,736,354)×3,1q41q44(221,649,655_247,175,095)×1Microarray analysis shows an apparently terminal gain of part of the short arm of chromosome 1 and an apparently terminal loss of part of the long arm of chromosome 1. This result may indicate a duplication/deletion recombinant chromosome derived from a parental inversion. Further testing is needed to establish the structural nature of the rearrangement. **Note:** microarray shows gain and loss of the most distal microarray markers of 1p36.33 and 1q44 respectively, and are presumed to be terminal.

xviii. arr[GRCh38] 20q13.13q13.33(51,001,876_64,323,572)×1,22q13.32q13.33(48,533,211_50,776,669)×3Microarray analysis shows an apparently terminal single copy loss of part of the long arm of chromosome 20 and an apparently terminal single copy gain of part of the long arm of chromosome 22 as covered by the microarray. This finding may represent the inheritance of an unbalanced derivative chromosome from a parental translocation and chromosome analysis of both parents is indicated.

xix. arr[GRCh38] 4q32.2q35.1(163,146,681_183,022,312)×1
or
arr[GRCh38] 4q32.2q35.1(163002425×2,163146681_183022312×1,184322231×2)Microarray analysis shows an interstitial loss within the long arm of chromosome 4 from bands 4q32.2 to 4q35.1. The extended system shows the flanking nucleotides that do not show a copy number loss. This defines the maximum and minimum deleted region. Commas are not used in the nucleotides in the extended system. **Note:** in the

extended system of nomenclature, the copy number and **multiplication** (×) sign are designated for the nucleotides within the parentheses.

xx. arr[GRCh38] 11p12(37,741,458_39,209,912)×3
or
arr[GRCh38] 11p12(37003221×2,37741458_39209912×3,39752007×2)Microarray analysis shows a single copy gain involving the short arm of chromosome 11 within band 11p12. The gain is approximately 1.47 Mb in size. The extended system shows the next neighboring proximal and distal nucleotides with normal copy number. This defines the maximum and minimum region of the duplication. Commas are not used in the extended ISCN description.

xxi. arr[GRCh38] 6q21q25.1(113,900,000_149,100,000)×1,(21)×3Microarray analysis shows interstitial loss in the long arm of chromosome 6 involving bands 6q21 to 6q25.1 and a single copy gain (trisomy) of chromosome 21.

xxii. arr[GRCh38] 9p24.3p13.1(204,166_38,756,057)×1,18q21.33q22.1(63,877,984_64,683,663)×1,21q11.2q21.1(13,600,026_20,175,986)×3Microarray analysis shows three abnormalities: a single copy loss within the short arm of chromosome 9, an interstitial loss of a segment of the long arm of chromosome 18 and gain of part of the long arm of chromosome 21. **Note:** chromosomes are listed in numerical order, regardless of whether they show a gain or loss.

xxiii. arr[GRCh38] 14q31.1(82,695,844_82,855,387)×1,14q32.33(105,643,093_106,109,395)×3Microarray analysis shows two separate interstitial deletions involving chromosome 14 in bands 14q31.1 and 14q32.33. **Note:** the abnormalities are shown from **pter** to **qter**, regardless of whether they are gains or losses.

xxiv. arr[GRCh38] 18p11.32p11.21(102,328_15,079,388)×1,18q22.3q23(69,172,132_79,093,443)×1Microarray analysis shows an apparently terminal single copy loss of the short arm of chromosome 18 and an apparently terminal single copy loss of the long arm of chromosome 18. This most likely indicates a ring chromosome 18, although FISH or chromosome analysis is indicated for confirmation.

8.2.3 Inheritance

When known, the parental origin of the abnormality may follow the copy number (×1, ×3, *etc*.). There is no space between the copy number and the inheritance abbreviation (**dn, mat, pat, inh, dmat, dpat, dinh, umat, upat**).

i. arr[GRCh38] Xq25(126,228,413_126,535,347)×0matMicroarray analysis in a male with an interstitial loss of the long arm of the X chromosome within band Xq25. This deletion is inherited from the mother.

ii. arr[GRCh38] Xq25(126,228,413_126,535,347)×1matSame abnormality as the above example in a female.

iii. arr[GRCh38] Xp22.31(6,467,202_8,091,950)×0matMicroarray analysis in a male with an interstitial loss of the short arm of the X chromosome within band Xp22.31 that is inherited from the mother.

iv. arr[GRCh38] (Y)×1,Xp11.22(53,215,290_53,986,534)×2matMicroarray analysis in a male with a gain of the short arm of the X chromosome within band Xp11.22 that is inherited from the mother. **Note:** the normal Y chromosome is given for clarity of the sex chromosome complement.

v. arr[GRCh38] Xp11.22(53,215,290_53,986,534)×3matMicroarray analysis in a female with a gain of the short arm of the X chromosome within band Xp11.22 that is inherited from the mother.

vi. arr[GRCh38] 4q32.2q35.1(163,146,681_183,022,312)×1dnMicroarray analysis shows an interstitial loss of the long arm of chromosome 4 involving bands 4q32.2 to 4q35.1. The heterozygous loss is apparently *de novo* in origin.

vii. arr[GRCh38] 17p11.2(16,512,256_20,405,113)×3dnMicroarray analysis shows a single copy gain of the short arm of chromosome 17 within band 17p11.2. The gain is at least 3.89 Mb in size and is apparently *de novo* in origin.

viii. arr[GRCh38] 4q28.2(128,184,801_129,319,376)×3mat,16p11.2(29,581,254_30,066,186)×3patMicroarray analysis shows a gain of a segment of the long arm of chromosome 4 within band 4q28.2 that is inherited from the mother, and a gain of a segment of the short arm of chromosome 16 within band 16p11.2 that is inherited from the father.

ix. arr[GRCh38] 9p24.3(1,310,386_1,709,409)×1mat,9p22.3p22.2(16,455,330_16,763,471)×1dn,18q21.33q22.1(62,747,805_67,920,791)×1dnMicroarray analysis shows three abnormalities: an interstitial single copy loss within 9p24.3 is determined, by parental studies, to be of maternal origin. The single copy loss of 9p22.3 to 9p22.2 and a single copy loss of 18q21.33 to 18q22.1 are both apparently *de novo*. **Note:** the inheritance of each is listed after the specific gain or loss and the two abnormalities on chromosome 9 are listed from **pter** to **qter**.

x. arr[GRCh38] 16p12.1p11.2(28,475,372_29,662,636)×3pat,16p11.2(29,662,635_30,188,030)×4matpatMicroarray analysis shows a single copy gain of 16p12.1 to 16p11.2 inherited from the father and a two copy gain within 16p11.2 inherited from both the mother and father.
Father: arr[GRCh38] 16p12.1p11.2(28,475,372_30,188,030)×3
Mother: arr[GRCh38] 16p11.2(29,662,635_30,188,030)×3

xi. arr[GRCh38] 22q11.21(18,929,329_21,111,370)×4mat patMicroarray analysis shows a gain of two copies of part of the long arm of chromosome 22 within band 22q11.21. One gain is inherited from the mother and the other is inherited from the father, *i.e.*, the individual has inherited the abnormality from each parent.

xii. arr[GRCh38] 22q11.21(18,929,329_21,111,370)×6dinhMicroarray analysis shows gain of four copies of the part of the long arm of chromosome 22 within band 22q11.21. The parental origin of the duplications cannot be specified where both parents are duplication carriers, as there are multiple recombinant and segregation possibilities that could account for the six copies.

xiii. arr[GRCh38] 10q26.13q26.3(122,454,932_133,620,799)×3dmat,14q32.12q32.33(94,042,298_106,874,940)×1dmat,22q11.21(20,363,826_21,107,318)×3Microarray analysis shows an apparently terminal gain of the long arm of chromosome 10 of bands 10q26.13 to

10q26.3 and an apparently terminal loss of the long arm of chromosome 14 of bands 14q32.12 to 14q32.33 that are determined to be derived from a known maternal translocation. Microarray testing of both parents is required to determine the origin of the gain on chromosome 22.

8.2.4 Multiple Techniques

For the rules on describing nomenclature where multiple techniques are applied, see Section 4.6.

i. 47,XX,del(6)(q14q16),+21c[20].arr[GRCh38] 6q14.1q16.3(78,848,613_104,293,334)×1,(21)×3cThe karyotype and microarray of a neoplastic sample shows a deletion in the long arm of chromosome 6 in 100% of the sample tested in a patient with constitutional trisomy 21 (Down syndrome). **Note:** it is optional to include the indication of clonality. If included it would be written as: 47,XX,del(6)(q14q16),+21c[20].arr[GRCh38] 6q14.1q16.3(78,848,613_104,293,334)×1[1.0],(21)×3c

ii. 46,X,der(Y)t(Y;20)(q11.23;q13.2).arr[GRCh38] Yq11.23q12(24,741,599_57,191,562)×0,20q13.2q13.33(53,224,067_63,743,732)×3 Microarray analysis shows an apparently terminal loss of part of the long arm of the Y chromosome and an apparently terminal gain of part of the long arm of chromosome 20. This is consistent with the finding by conventional karyotype of a derivative Y chromosome from an unbalanced translocation involving chromosomes Y and 20. **Note:** the sex chromosome abnormality is listed first. There is no normal Y chromosome in this individual.

iii. 46,XY,der(20) t(Y;20) (q11.23;q13.2).arr[GRCh38] Yq11.23q12(24,741,599_57,191,562)×2,20q13.2q13.33(53,224,067_63,743,732) ×1Microarray analysis shows an apparently terminal gain of the part of the long arm of the Y chromosome and an apparently terminal loss of part of the long arm of chromosome 20. This is consistent with the finding by conventional karyotype, of a derivative chromosome 20 resulting from an unbalanced translocation involving chromosomes Yq11.23 and 20q13.2. **Note:** the sex chromosome abnormality is listed first. There is a normal Y chromosome in addition to the derivative chromosome 20 in this individual.

iv. 46,XX.arr[GRCh38] Xp22.31(6,923,924_7,253,485)×3,5q14.3(88,018,766_89,063,989)×1The karyotype shows a normal female. Microarray analysis shows a single copy gain of part of the short arm of the X chromosome and a single copy interstitial loss of part of the long arm of chromosome 5. **Note:** the sex chromosome abnormality is listed first.

v. 46,XY,r(14)(p13q32).arr(X,Y)×1,(1–22)×2The karyotype shows a ring chromosome 14, with breakpoints in the short arm at 14p13 and in the distal long arm at 14q32. Microarray shows a male profile and no abnormality is detected. **Note:** most microarrays do not cover the short arm of acrocentric chromosomes or telomeric regions of chromosomes. This is shown by the normal microarray nomenclature in this example.

vi. 46,XY,der(8)(:p21.2→p23.1::p23.1→qter).arr[GRCh38] 8p23.3p23.1(214,984_7,149,893)×1,8p23.1p21.2(12,625,585_23,768,948)×3The karyotype shows an inverted duplication of the short arm of chromosome 8 for the segment 8p23.1 to 8p21.2. There is a known loss of the short arm telomere associated with this recurrent rearrangement and it is often derived from a paracentric inversion of chromosome 8 involving bands 8p23.1 to 8p21.2. Microarray confirms the deletion of the distal short arm of chromosome 8 involving the segment 8p23.3 to 8p23.1 and a gain of the segment 8p23.1 to 8p21.2.

vii. 46,XY,t(2;10)(q23;p15).ish t(2;10)(306F7+;306F7−).arr[GRCh38] 2q22.3q24.1(146,608,141_157,717,565)×1The karyotype shows an apparently balanced translocation between the long arm of chromosome 2 at 2q23 and the short arm of chromosome 10 at 10p15. Subtelomere FISH shows the chromosome 10p subtelomere located on the derivative chromosome 2 and absent from the derivative chromosome 10. Microarray shows an interstitial deletion in the long arm of chromosome 2 that aligns with the translocation breakpoint on chromosome 2. **Note:** the microarray refines the breakpoint on chromosome 2, but as this is not evident in hindsight in the conventional karyotype preparations at 400bphs, the conventional karyotype breakpoints are not revised.

viii. 46,X,der(Y)t(X;Y)(p22.33;q11.221).arr[GRCh38] Xp22.33(10,001_15,937,465)×2,Yq11.221q11.23(14,027,925_25,031,382)×0The karyotype and microarray analysis show a male profile with a single copy gain of part of the short arm of the X chromosome and loss of part of the long arm of the Y chromosome, resulting from an unbalanced translocation involving Xp and Yq.

ix. ish der(X)t(X;Y)(p22.33;p11.2)(DXZ1+,SRY+).arr[GRCh38] Xp22.33(251,879_2,746,231)×1,Yp11.32p11.2(11,091_3,295,603)×1Microarray analysis is interpreted in the context of metaphase FISH. An unbalanced translocation derived from a rearrangement between the short arms of the X and Y chromosomes is detected. This has resulted in loss of distal Xp and gain of the short arm of the Y chromosome involving PAR1 including *SRY*.

x. 46,XX.ish der(X)(qter→q28::p22.32→qter)(EST Cdy 16c07+,DXYS129−,SHOX−,DXZ1+,EST Cdy 16c07+).arr[GRCh38] Xp22.33p22.32(253,119_4,759,611)×1,Xq28(155,285,628_156,005,042)×3An apparently normal female karyotype. However, subtelomere FISH shows gain of the Xq subtelomere, present on both ends of the derivative X chromosome, and loss of the Xp subtelomere. SNP microarray shows a female profile with a derivative X chromosome with terminal deletion of Xp22.32 and duplication of Xq28. The deletion of Xp includes the *SHOX* gene. **Note:** the order is written relative to the orientation of the segment containing the centromere.

xi. 46,XY.ish der(X)(qter→q28::p22.32→qter)(EST Cdy 16c07+,DXYS129−,SHOX−,DXZ1+,EST Cdy 16c07+).arr[GRCh38] Xp22.33p22.32(253,119_4,759,611)×0mat,Xq28(155,285,628_156,005,042)×2matT he derivative X chromosome described in the previous example is inherited in a male fetus.

xii. 47,XY,+mar.arr[GRCh38] 1p13.1p11.2(117,053,799_121,604,818)×3dnMicroarray analysis shows a single copy gain of the short arm of chromosome 1, spanning approximately 4.6 Mb and likely identifying the marker chromosome. Most

microarray platforms will not detect the pericentromeric alpha-satellite DNA and the centromeric bands are rarely included in the nomenclature of rings and markers. FISH is required to confirm the involvement of the centromere. An amended result after FISH analysis could be written as:
47,XY,+r.arr[GRCh38] 1p13.1p11.2(117,053,799_121,604,818)×3dn.ish r(1)(p13.1q1?1)(D1Z1+)
or
47,XY,+r
arr[GRCh38] 1p13.1p11.2(117,053,799_121,604,818)×3dn
ish r(1)(p13.1q1?1)(D1Z1+)

xiii. 47,XY,+mar dn.arr[GRCh38]
1p12p11.2(117,596,421_121,013,236)×3,15q25.1q26.3(78,932,946_100,201,136)×3
Microarray analysis shows two apparently *de novo* aberrations: a single copy gain of part of the short arm of chromosome 1 and a single copy gain of part of the long arm of chromosome 15. This could represent a marker comprised of material from chromosomes 1 and 15, and FISH is needed for confirmation.

xiv. 46,XX.arr[GRCh38]
3p12.2(80,395,073_83,498,191)×3inh,12p12.1(23,543,231_23,699,047)×1dnNormal female karyotype with an inherited gain of chromosome 3 within 3p12.2 by microarray analysis, an apparently *de novo* interstitial loss of part of the short arm of chromosome 12 within band 12p12.1.

xv. arr[GRCh38]
8q23.1q24.3(105,171,556_146,201,911)×3,15q26.2q26.3(96,062,102_100,201,136)×1Microarray analysis shows a single copy gain of the long arm of chromosome 8 involving 8q23.1 to 8q24.3 and a single copy loss of the long arm of chromosome 15 involving 15q26.2 to 15q26.3. Terminal gain and loss may be indicative of an unbalanced translocation. However, microarray does not provide positional information. Following subsequent chromosome analysis, FISH analysis and determination of maternal inheritance, the nomenclature can be written as follows:
46,XY,der(15)t(8;15)(q23.1;q26.2)dmat.arr[GRCh38]
8q23.1q24.3(105,171,556_146,201,911)×3,15q26.2q26.3
(96,062,102_100,201,136)×1.ish der(15) t(8;15) (RP11–1143I12+,RP11–14C10−)
or
46,XY,der(15)t(8;15) (q23.1;q26.2)dmat
arr[GRCh38]
8q23.1q24.3(105,171,556_146,201,911)×3,15q26.2q26.3(96,062,102_100,201,136)×1
ish der(15) t(8;15)(RP11–1143I12+,RP11–14C10−)
Note: karyotyping detected the balanced rearrangement in the mother, thus **dmat** is placed after the karyotype in the nomenclature in this example (see Section 4.6).

xvi. 46,XY,rec(18)dup(18q)inv(18)(p11.32q21)dpat.arr[GRCh38]
18p11.32(102,328_2,326,882)×1, 18q21.31q23(56,296,522_76,093,443)×3The karyotype shows an abnormal chromosome 18 that is interpreted in the context of a microarray and a paternal karyotype. Microarray analysis shows loss of part of the short arm of chromosome 18 and gain of part of the long arm of chromosome 18. Karyotype analysis of the individual's father demonstrated a balanced pericentric

inversion. Thus, this example is a duplication/deletion recombinant chromosome derived from an inversion in the father.

xvii. 47,XX,+mar.arr[GRCh38] 21q11.2q21.1(13,461,349_17,308,947)×4,21q22.3(46,222,759_46,914,885)×3Micro array analysis shows a two copy gain of 21q11.2 to 21q21.1 and a single copy gain of 21q22.3, indicating that the marker chromosome is the result of a complex rearrangement involving two different segments of chromosome 21. This results in tetrasomy for part of a proximal region of the long arm of chromosome 21 and trisomy for a more distal part of the long arm of chromosome 21.

xviii. 47,XX,+mar[18]/46,XX[9].arr[GRCh38] 21q11.2q22.3(13,461,349_46,914,885)×3[0.8]Microarray analysis of a neoplastic sample shows a gain of 21q11.2 to 21q22.3 is present in 80% of the sample and likely represents the marker chromosome.

xix. 47,XY,+mar1[12]/48,XY,+mar1,+mar2[8].ish mar1(D7Z1+)[10],mar2(D20Z1+)[5].arr[GRCh38] 7q11.21(62,510,570_65,410,986)×3[1.0],20p11.23q13.12(18,998,717_41,675,280)× 3[0.4]The karyotype shows two cell lines. One cell line has one marker (mar1) and one cell line has two different markers (mar1 and mar2). Mar1 is present in all cells. FISH shows mar1 is derived from chromosome 7 and mar2 is derived from chromosome 20. The origin and level of mosaicism for both markers is confirmed by microarray.

xx. 46,XX,t(14;18)(q32;q21.1)[1]/46,idem,r(7)(p13q32)[8]/46,XX[1].arr[GRCh38] 7p22.3p13(43,376_44,487,561)×1[0.8],7q32.3q36.3(131,973,640_159,327,017)×1[0. 8]Microarray of a neoplastic sample shows apparently terminal deletions of the short and long arms of chromosome 7, consistent with the ring chromosome 7 observed by karyotyping. A balanced translocation involving chromosomes 14 and 18 seen on the karyotype is not detected by microarray.

xxi. 46,X,der(X)(Xpter→Xq27::4p16.1→4pter),der(4)(Xqter→Xq27::4p15.3→4q12::13 q31→13qter),der(11)(11pter→11q25::4q13.1→4q26:),der(13)(13pter→13q31::4qter →4q27::11q25→11qter). arr[GRCh38] 4p16.1p15.32(7,143,522_16,904,765)×1,4q31.1(139,194,590_140,075,273)×1,11q22 .1q22.2(101,653,515_102,364,410)×1The karyotype shows a complex rearrangement involving chromosomes X, 4, 11 and 13. The microarray analysis shows segments of copy number loss on chromosomes 4 and 11.

8.2.5 Mixed Cell Populations and Uncertain Copy Number

i. arr (X)×1[0.6]
or
arr[GRCh38] Xp22.33q28(168,546_155,233,730)×1[0.6]Microarray analysis shows a single copy loss of the X chromosome in approximately 60% of the sample in a female.

ii. arr (X)×1~3
or
arr[GRCh38] Xp22.33q28(168,546_155,233,730)×1~3Microarray analysis of a female shows loss of the X chromosome in a proportion of cells that is

undetermined. **Note:** microarray cannot differentiate between 45,X/46,XX cell lines and 45,X/47,XXX cell lines. FISH or karyotype is indicated.

iii. arr (X)×1,(Y)×0[0.6]
or
arr (X)×1,(Y)×0∼1Microarray analysis shows loss of the Y chromosome in 60% of the sample in a phenotypic male. **Note:** the limitation of microarray is that it cannot differentiate between 45,X/46,XY cell lines or 45,X/47,XYY cell lines. FISH or karyotype is indicated.

iv. arr[GRCh38] (X)×1[0.8],Xq26.2q28(133,301,245_152,723,000)×1Microarray analysis in a female shows 80% of the sample has only one apparently normal X chromosome, while the remaining 20% contains a normal X chromosome and an X chromosome with a deletion of Xq26.2 to Xq28. This equates to heterozygous loss of Xq26.2 to Xq28 in 100% of the sample.

v. arr[GRCh38]
1p36.11p35.3(25,889,422_28,493,687)×3mat,11p12p11.12(41,444,865_49,146,935)×1dn[0.5]Microarray analysis shows inheritance of a maternal single copy gain within chromosome 1 involving the segment 1p36.11 to 1p35.3 and mosaicism for a single copy loss within chromosome 11 involving the segment 11p12 to 11p11.12. The loss within chromosome 11 is of apparently *de novo* origin.

vi. arr[GRCh38]
Xp22.33p11.23(701_48,643,784)×1[0.8],Xp11.23q21.1(48,645,844_77,165,813)×1[0.2],Xq21.1q28(77,173,853_155,270,560)×1[0.8]Microarray analysis in a female shows mosaicism for loss of the terminal short arm of the X chromosome at Xp22.33 to Xp11.23 and the terminal long arm at Xq21.1 to Xq28 in 80% of the sample. A single copy loss for the segment Xp11.23 to Xq21.1 is detected in approximately 20% of the sample. This finding is suggestive of a mosaic ring X chromosome with both 45,X and 46,XX cell lines. FISH or chromosome analysis is needed to determine the structural nature of the abnormality.

vii. arr[GRCh38] (X,1–7,9–12)×1,13q12.11q14.2(19,438,807_48,800,573)×1,13q14.2(48,986,461_49,176,936)×0,13q14.2q34(49,176,999_115,095,706)×1,(15–20,22)×1Microarray analysis of a neoplastic sample shows a near haploid genome and single copies of the X chromosome and chromosomes 1 to 7, 9 to 12, 15 to 20 and 22. The result for chromosome 13 shows a region of single copy loss and a region within 13q14.2 with a mixture of biallelic loss and single copy loss. Chromosomes 8, 14, and 21 are present in two copies. **Note:** microarray cannot determine whether the two heterozygous deletions occur in *cis* or in *trans*.

viii. ish mos del(2)(q11.2q13)(RP11–478D22–)[10]/2q12.1(RP11–478D22)×2[20].arr[GRCh38] 2q11.2q13(100,982,729_112,106,760)×1[0.4]FISH and microarray analyses show a mosaic deletion in the long arm of chromosome 2. By microarray, approximately 40% of the sample has the deletion.

ix. 47,XY,+mar[5]/46,XY[20].ish der(2)(p11.2q13) (RP11–478D22+)[5]/2q12.1(RP11–478D22)×2[25].arr[GRCh38] 2p11.2q13(90,982,729_112,106,760)×3[0.2]FISH and karyotype analyses demonstrate a mosaic marker chromosome derived from chromosome 2. By microarray approximately 20% of the sample has three copies of chromosome 2p11.2 to 2q13.

x. arr[GRCh38] (5,6)×3[0.3],7q34(138,904,207_140,533,785)×>2[?]SNP microarray analysis of a neoplastic sample shows three copies of chromosomes 5 and 6 in 30% of the sample. There is a cell line with gain of a region within 7q34, but the copy number is uncertain. There is allelic imbalance demonstrated in the B allele frequency (BAF) plot for this region, but it is not possible to determine the copy number precisely. **Note:** a **question mark** within **square brackets** (**[?]**) is used to indicate that the proportion of the sample tested that has the gain, is unknown. Where clinically relevant, copy number should be confirmed by another method.

xi. arr[GRCh38] 7p11.2(54,290,345_55,087,100)amp[?]Microarray analysis of a neoplastic sample shows amplification of a region in 7p11.2. The exact copy number is too large to be enumerated accurately by microarray. **Note:** a **question mark** within **square brackets** (**[?]**) is used to indicate that the proportion of the sample tested that has the amplification, is unknown.

xii. arr[GRCh38] 2p24.3(15,911,477_15,976,076)amp[?],(8)×3[0.8],(21)×4[0.8]Microarray analysis of a neoplastic sample shows amplification of 2p24.3 including the *MYCN* gene, the proportion of cells with the amplification is unknown. One additional copy of chromosome 8 and two additional copies of chromosome 21 are present in 80% of the sample. **Note:** alternative methods are required to determine if there is evidence of clonal evolution. This is a limitation of microarray technology.

xiii. arr[GRCh38] 11q22.3q23.2(104,669,588_113,439,979)×1[0.3],13q14.13q14.3(46,290,874_51,390,298)×1[0.8]Microarray analysis of a neoplastic sample shows a deletion in the long arm of chromosome 11 of 11q22.3 to 11q23.2 in approximately 30% of the sample and a deletion in the long arm of chromosome 13 of 13q14.13 to 13q14.3, in approximately 80% of the sample.

xiv. arr[GRCh38] 12p13.33p11.1(84,917_34,382,567)×2∼4Microarray analysis shows a two copy gain of the short arm of chromosome 12, resulting in tetrasomy 12p. Although this result likely indicates mosaicism for an additional isochromosome of the short arm of chromosome 12 such as those found in Pallister-Killian syndrome, FISH or chromosome analysis is needed for confirmation. The **tilde** (**∼**) is used to indicate that the number of copies of this region varies from two to four.

xv. arr[GRCh38] 13q14.2(49,913,857_49,938,728)×1[0.9],13q14.2q14.3(49,957,631_50,801,835)×0[0.9],13q14.3(50,805,629_51,137,300)×1[0.9]
or
arr[GRCh38] 13q14.2(49,913,857_49,938,728)×1∼2,13q14.2q14.3(49,957,631_50,801,835)×0∼2,13q14.3(50,805,629_51,137,300)×1∼2Microarray analysis of a neoplastic sample shows three contiguous deletions in the long arm of chromosome 13 resulting in a region of homozygous loss with flanking regions of heterozygous loss. **Note:** microarray cannot determine whether the heterozygous deletions and the smaller biallelic deletion occur in the same or different clone. The deletions are listed from **pter** to **qter**.

xvi. arr[GRCh38] 9p24.3p21.3(133,828_21,975,007)×1[0.8],9p21.3(21,976,403_22,003,224)×0[0.8],9

p21.3p12(22,004,154_39,158,239)×1[0.8],9q21.11q34.3(68,358,779_138,394,717)×3[0.8]Microarray analysis of a neoplastic sample shows heterozygous loss of part of the short arm of chromosome 9, biallelic loss of 9p21.3 including part of the *CDKN2A* and *CDKN2B* genes and gain of part of the long arm of chromosome 9 involving 9q21.11 to 9q34.3. The clonal population with the copy number changes constitutes 80% of the sample.

8.2.6 Nomenclature Specific to Single Nucleotide Polymorphism (SNP) Microarray

SNP microarray platforms can detect regions of homozygosity that may represent ancestral homozygosity, parental consanguinity, uniparental disomy, and in neoplastic disease, regions of acquired loss of heterozygosity.

a. The zygosity of chromosomal regions may be defined as **heterozygous** (**htz**) or **homozygous** (**hmz**).
b. SNP microarrays can be used to detect abnormalities relative to genome ploidy and given using the symbols, <n>, <2n>, <3n>, *etc*.
c. Uniparental disomy where the parental origin has been determined can be designated by **umat** or **upat**.

i. arr (X,1–22)×2hmzComplete hydatidiform mole that represents a monospermic fertilization of an empty ovum. There is no maternal complement.
ii. arr (X,1–22)×2hmz htzComplete hydatidiform mole represents a dispermic fertilization of an empty ovum with both sperm carrying an X chromosome. There is no maternal complement. **Note:** in this abbreviated system (microarray format) of nomenclature, **hmz htz** indicates that there are alternating stretches of homozygosity and heterozygosity across the stated chromosomes. The **hmz** is given before **htz** following the alphabetical order rule.
iii. arr (X,Y)×1,(1–22)×2hmz htzComplete hydatidiform mole represents a dispermic fertilization of an empty ovum with one sperm carrying an X chromosome and the other carrying a Y chromosome. There is no maternal complement.
iv. arr <4n>(7)×3[0.9]SNP microarray of a neoplastic sample shows loss of one copy of chromosome 7 relative to the tetraploid genome in 90% of cells.
v. arr chi (X,1–22)×2[0.7]/(X,1–22)×2[0.3]SNP microarray shows a pattern consistent with an XX/XX chimera where the haplotypes are different. The largest cell line is listed first. **Note:** this is consistent with a tetragametic chimera.
vi. arr chi (X,1–22)×2hmz[0.6]/(X,Y)×1,(1–22)×2[0.4]SNP microarray shows a pattern consistent with an XX/XY chimera where there is homozygosity of the XX cell line. The largest cell line (60%) is given first. **Note:** this is consistent with an androgenetic or parthenogenetic chimera.
vii. arr chi (X,Y)×1[0.7],(18)×3[0.7]/(X,1–22)×2[0.3]SNP microarray analysis shows a pattern consistent with an XY/XX chimera. A male complement in 70% and a female complement in 30% of the sample is observed. An additional copy of chromosome 18 is also detected in 70% of the sample, presumably in the male complement, although confirmation of this finding is required. **Note:** the normal female cell line and sex chromosome complement are indicated for clarity. A prenatal karyotype confirmed the presence of trisomy 18 in the male cell line.

viii. arr (X,Y)×1(1–22)×2[0.4]//(X,1–22)×2[0.6]SNP microarray analysis of a male recipient after transplantation with a female donor. **Note:** the recipient is given first.

ix. arr[GRCh38] 11q13.4q21(74,685,586_94,929,516)×2hmzSNP microarray analysis shows homozygosity in the long arm of chromosome 11 involving the segment 11q13.4 to 11q21 that is approximately 20.2 Mb in size.

x. arr[GRCh38] 15q24.3q26.1(77,800,856_91,327,974)×2hmz upat,16p11.2(28,848,540_29,033,424)×1matSNP microarray analysis shows a segment of homozygosity of approximately 13.5 Mb on chromosome 15 involving 15q24.3 to 15q26.1 and a single copy loss in chromosome 16 within 16p11.2 of approximately 0.18 Mb. Comparison of the SNP genotypes between the patient and both parents, shows paternal uniparental disomy for the segment of homozygosity on chromosome 15 and maternal inheritence of the 16p11.2 deletion.

xi. arr (15q,21q)×2hmz upat
or
arr[GRCh38] 15q11.2q26.3(23,123,715_101,888,908)×2hmz upat,21q11.21q22.3(14,595,263_48,084,819)×2hmz upatSNP microarray analysis shows homozygosity for the entire long arms of chromosomes 15 and 21. Comparison of the SNP genotypes between the patient and both parents, shows paternal uniparental isodisomy for both of the regions of homozygosity. **Note**: the multiple regions of homozygosity may be grouped within a parenthesis: arr[GRCh38] (15q11.2q26.3(23,123,715_101,888,908),21q11.21q22.3(14,595,263_48,084,819))×2hmz upat

xii. arr (7)×2htz umatSNP microarray of the proband and both parents with comparison of SNP genotypes shows uniparental maternal heterodisomy of chromosome 7.

xiii. arr (7)×2hmz htz umatSNP microarray of the proband and both parents with comparison of SNP genotypes, shows alternating segments of maternal isodisomy and maternal heterodisomy for chromosome 7.

xiv. arr[GRCh38] 1p33(47,231,951_47,312,561)×1,9p24.3p21.3(14,326_21,826,388)×2hmz,9p21.3(21,827,193_21,993,275)×0,9p21.3p13.2(21,994,102_36,530,622)×2hmz,(17q)×3SNP microarray shows loss of chromosome 1 within band 1p33, regions of copy neutral loss of heterozygosity in bands 9p24.3 to 9p21.3 and 9p21.3 to 9p13.2, a biallelic deletion within band 9p21.3 including *CDKN2A* and a gain of the long arm of chromosome 17.

xv. arr[GRCh38] 11p15.5p15.4(2,265,338_6,275,434)×2hmz c,19q13.33q13.43(49,759,500_58,586,384)×2hmzSNP microarray analysis of a neoplastic sample is consistent with a constitutional region of homozygosity on the short arm of chromosome 11 and an acquired loss of heterozygosity of the long arm of chromosome 19. The clonal population is 100% of the sample. **Note:** the region of homozygosity on chromosome 11 is shown to be biparental.

xvi. arr[GRCh38] 1p36.33p36.31(632,287_5,983,870)×3hmz,1p36.31p36.13(5,984,115_17,694,600)×2hmzSNP microarray analysis shows duplication of chromosome 1 at 1p36.33 to 1p36.31. There is a region of homozygosity involving the segment 1p36.33 to 1p36.13 that includes the duplicated segment 1p36.33 to 1p36.31 as shown by the B allele frequency (BAF) pattern.

xvii. arr[GRCh38] 2q33.1q37.1(197,557,641_230,542,167)×1,(12)×3,(22)×2hmz.nuc ish (IGH,BCL2)×3(IGH con BCL2)×2[200]Microarray analysis of a neoplastic sample shows deletion of chromosome 2, involving the segment 2q33.1 to 2q37.1, trisomy 12 and loss of heterozygosity for chromosome 22. The clonal population is 100% of the B-cell enriched sample. Interphase FISH shows *IGH*::*BCL2* fusion.

xviii. arr (X,3,7,9q,13–17,19,20,22)×1[1.0]SNP microarray analysis indicates a near-haploid profile in a neoplastic sample from a female. Chromosomes 1, 2, 4 to 6, 8, 9p, 10 to 12, 18, and 21 show a heterozygous state, representing the normal copy number and therefore are not specified. Whereas chromosomes X, 3, 7, 13 to 17,19, 20, 22 and 9q show one copy compared to the heterozygous state. Based on only SNP microarray data, it is not always possible to determine whether this concerns a near-haploid complement or a mixture of near-haploid and doubled near-haploid complements. **Note:** the near-haploid complement represents 100% of the sample.

xix. arr (X)×2hmz,(1,2)×4,(3)×2hmz,(4–6)×4,(7)×2hmz,(8,9p)×4,(9q)×2hmz,(10–12)×4,(13–17)×2 hmz,(18)×4,(19,20)×2hmz,(21)×4,(22)×2hmzSNP microarray results from a neoplastic sample indicate that all chromosomes are abnormal compared to normal diploidy, either by abnormal copy number or loss of heterozygosity. The clonal population is 100% of the sample. This finding may represent doubling of the near-haploid clone in the example above.

xx. arr (X,Y)×1~2[0.3],(1–13)×2hmz[0.3],(14)×2~4[0.3],(16–20)×2hmz[0.3],(21)×2~4[0.3],(22)×2hmz[0.3]SNP microarray analysis of a neoplastic sample shows a doubled near-haploid complement in a male. Chromosomes X, Y, 14 and 21 show copy number gain in 30% of the sample. In addition, there is homozygosity for chromosomes 1 to 13, 16 to 20, and 22 present in 30% of the sample.

xxi. arr[GRCh38] 12q11~q13.13(37,482,598_51,172,567)×2hmz[0.2~0.3],12q13.13q24.33(51,172,758_133,201,059)×2hmz[0.3]SNP microarray analysis of a neoplastic sample shows the region of chromosome 12 between 12q11 and 12q13.13 displays mosaic copy neutral loss of heterozygosity (CN-LOH), and there is gradual increase in separation of the B allele frequency heterozygous plot indicating that there are numerous subclones with slightly differing breakpoints. The **tilde** (**~**) between the chromosomal breakpoints indicates a range to demonstrate these multiple subclone breakpoints. The proporton of the clones, as calculated from the BAF, ranges from approximately 20–30% of the sample. The contiguous region from 12q13.13 to 12q24.33 displays CN-LOH in approximatley 30% of the sample with no discernible subclonal variation.

xxii. arr[GRCh38] 17p13.3~p13.1(158,756_7,281,077)×1[0.7~0.9],17p13.1p11.2(7,281,162_17,542,789)×1[0.9]SNP microarray analysis of a neoplastic sample demonstrates loss of a segment of the short arm of chromosome 17 with a range of deletion breakpoints between 17p13.3 and 17p13.1, as indicated by the use of **tilde** (**~**) in the breakpoint designation. There is a change in the clonal population across this region from 70% to 90% of the sample. Deletion of the region between 17p13.1 and 17p11.2 appears as a single event with no detectable subclonal variation.

xxiii. arr[GRCh38] 17p13.3~p13.1(158,756_7,281,077)×1~2,17p13.1p11.2(7,281,162_17,542,789)×1~2

The same microarray profile as given directly above, but the precise proportion of cells in the subclones is unknown in this neoplastic sample.

xxiv. arr[GRCh38] 13q14.13q14.2(45,815,660_49,850,541)×2hmz[0.4],13q14.2q14.3(49,864,100_51,118,038)×0[0.40],13q14.3q34(51,118,412_114,338,054)×2hmz[0.40]SNP microarray analysis of a neoplastic sample shows loss of heterozygosity for most of the long arm of chromosome 13 in a clonal population of 40% of the sample. A deletion within the homozygous region results in a biallelic loss.

xxv. arr[GRCh38] 13q14.13q14.2(45,815,660_49,850,541)×2hmz[?],13q14.2q14.3(49,864,100_51,118,038)×0~2,13q14.3q34(51,118,412_114,338,054)×2hmz[?]SNP microarray analysis of a neoplastic sample where the proportion of the population with the abnormalities involving 13q14.3 to 13q34 could not be determined.

xxvi. arr[GRCh38] 1p33(47,234,490_47,297,731)×1,7p14.1(38,254,348_38,331,733)×0,9p24.3p21.3(192,128_21,816,759)×2hmz,9p21.3(21,818,110_21,993,965)×0,9p21.3p21.1(21,994,102_33,103,874)×2hmz,10q22.1q26.3(69,872,653_133,613,032)×2hmzSNP microarray in a neoplastic sample shows heterozygous loss within the short arm of chromosome 1 within band 1p33 and biallelic loss within band 7p14.1. There are segments of copy neutral loss of heterozygosity in bands 9p24.3 to 9p21.3 and 9p21.3 to 9p21.1 and a biallelic deletion within band 9p21.3 that includes *CDKN2A*. In addition, there is CN-LOH of chromosome 10 between 10q22.1 to 10q26.3. *STIL*::*TAL1* fusion in 1p33 and the *TRG* rearrangement in 7p14.1 can be confirmed using alternative methods.

xxvii. arr <2n>(X,4,6,8,10,11)×3[0.3],(14)×4[0.3],(17,18)×3[0.3],(21)×4[0.3]A near triploid microarray profile for a neoplastic sample with the following banded karyotype: 58<2n>,XX,+X,+4,+6,+8,+10,+11,+14,+14,+17,+18,+21,+21[5]/46,XX[15]
Since it is biologically relevant in this case, the abnormal microarray profile is described relative to the diploid genome and the clonal population is present in 30% of the sample.

xxviii. arr[GRCh38] 15q11.1q14(19,794,748_38,740,478)×2htz umat,15q14q22.2(38,957,053_59,002,774)×2hmz umat,15q22.2q26.3(59,003,816_101,349,386)×2htz umatSNP microarray analysis shows chromosomes 15 with heterozygous contributions of the maternal genome flanking a segment of homozygous contribution of the maternal genome. Both maternal uniparental heterodisomy and isodisomy are present for chromosome 15 and there are no paternal copies of chromosome 15.

8.2.7 Complex Array Results

a. The abbreviation **cx** for complex chromosome rearrangement is used where there are *numerous* rearrangements across the entire genome or within a region of a chromosome, or numerous copy number gains and/or losses and/or loss of heterozygosity (LOH)/absence of heterozygosity (AOH), within a chromosome region.

b. The **complex** (**cx**) abbreviation is used where the definition of chromothripsis or chromoanasynthesis is not met.

i. arr (X,1–22)cxMicroarray analysis shows multiple complex rearrangements across the entire genome in a female.

ii. arr (1–22)cxMicroarray analysis shows multiple complex rearrangements in chromosomes 1 to 22. The sex chromosomes appear normal and are therefore not shown.

iii. arr (X,Y,1–22)cxMicroarray analysis shows multiple complex rearrangements across the entire genome in a male.

iv. arr <4n>(X,1–22)cxMicroarray analysis of a neoplastic sample shows a highly complex tetraploid genome with multiple aberrations involving many chromosomes and chromosomal regions.

v. arr[GRCh38] 3p26.3q12.1(19,817_98,667,822)cx[0.5]Microarray analysis of a neoplastic sample shows a complex pattern of copy number changes in the long arm of chromosome 3 in approximately 50% of the sample.

vi. arr[GRCh38] 1p13.3~q44(108,110,616_244,524,345)×1cxMicroarray analysis in a neoplastic sample shows multiple deletions in a chromosomal region on chromosome 1 between bands 1p13.3 to 1q44. **Note:** the number of deletions does not meet the definition of chromothripsis.

vii. arr[GRCh38] 5q23.2(122,370,756_123,372,153)×3,(7q)×5~6,(17)cxMicroarray analysis of a medulloblastoma sample with gain of chromosome 5 at 5q23.2 including the S*NCAIP* gene, high copy gain of the long arm of chromosome 7 including *CDK6* and multiple aberrations of chromosome 17.

viii. arr[GRCh38] (3)cx,(8p)×1[0.8],11q22.3~q24.1(103,435,986_121,769,727)×1[0.5],13q14.12q21.31(45,111,555_61,907,840)×1[0.3],17p13.3p11.2(150,208_17,289,901)×1[0.8]Microarray analysis of a neoplastic sample shows multiple aberrations of chromosome 3 plus deletions of 8p, 11q, 13q and 17p. The proportion of abnormalities is different amongst the sample population, *i.e.*, deletion of the short arm of chromosome 8 at 80%, deletion of 11q22.3 to 11q24.2 at 50%, 13q14.1 to 13q21.31 at 30% and 17p13.3 to 17p11.21 at 80%. **Note:** it is a limitation of microarray that it cannot determine whether the abnormalities are in the same or different clones.

c. In complex array results, as may be the case in neoplastic samples, the laboratory may choose to display results in table form instead of in an ISCN description. The information in the table must include the chromosomes and bands corresponding to the variant, the type of variant (loss, gain, amplification or region of homozygosity), the designated genome build and the genomic coordinates of the variant. An example table is given below (Table 9). The inclusion of a table does not replace the written description/interpretive comment.

i. arr[GRCh38] 2p25.3p13.3(12,770_51,077,428)×2~3,6p21.1p12.1(44,186,302_57,106,710)×1~2,6q14.1q23.3(79,737,355_137,811,379)×1~2,9p22.1p21.1(19,701,167_29,655,000)×1~2,10q26.13q26.3(125,607,675_133,612,882)×2~3,11q21q24.1(93,957,093_123,939,048)×1,13q14.2q14.3(49,885,788_50,932,461)×1,22q12.1q13.33(27,370,796_50,759,338)×2~3

or

arr (2,6,9,10,11,13,22)cxMicroarray analysis of a neoplastic sample shows a highly complex molecular profile with mosaicism for gains and losses involving chromosomes 2, 6, 9, 10, 11, 13 and 22 with apparently 100% clonality. Each may be designated in

the ISCN description or as a **complex karyotype** (**cx**), with a description in the interpretation. Alternatively, the aberrations may be presented in a table.

ii.

Table 9. Tabulation of a highly complex microarray result.

Chromosome/ band	Genomic coordinates [GRCh38]	Size, Mb	Type	Copy number	Proportion[a]	Comments[b]
2p25.3p16.3	10,001_50,391,884	50.4	Gain	5	25%	*MYCN*
6q	Whole long arm	109	Loss	1	40%	*FOXO3*
8p23.3q21.13	224,944_75,033,615	74.8	Loss	1	25%	
9q21.11q34.3	68,220,553_138,174,185	69.9	CN-LOH[c]	2	40%	*NOTCH1*
17p13.3p11.2	150,208_21,609,771	21.5	Loss	1	40%	*TP53*
18	Whole chromosome	80.3	Gain	3	25%	

[a] Indicates the proportion of the sample with the clone.
[b] Relevant genes or additional information relevant to the disease as required.
[c] Copy neutral loss of heterozygosity.

8.2.7.1 Chromoanagenesis

Complex genome rearrangements grouped under chromoanagenesis, *i.e.*, **chromoanasynthesis** (**cha**), **chromoplexy** (**cpx**), and **chromothripsis** (**cth**), may be challenging to differentiate as multiple overlapping genome instability and repair mechanisms may be present in an individual sample. Illustrations of these highly complex events are described in Figure 10. The mechanism for chromoplexy is shown in Figure 10 for comparison although it is not detected by microarray technology.

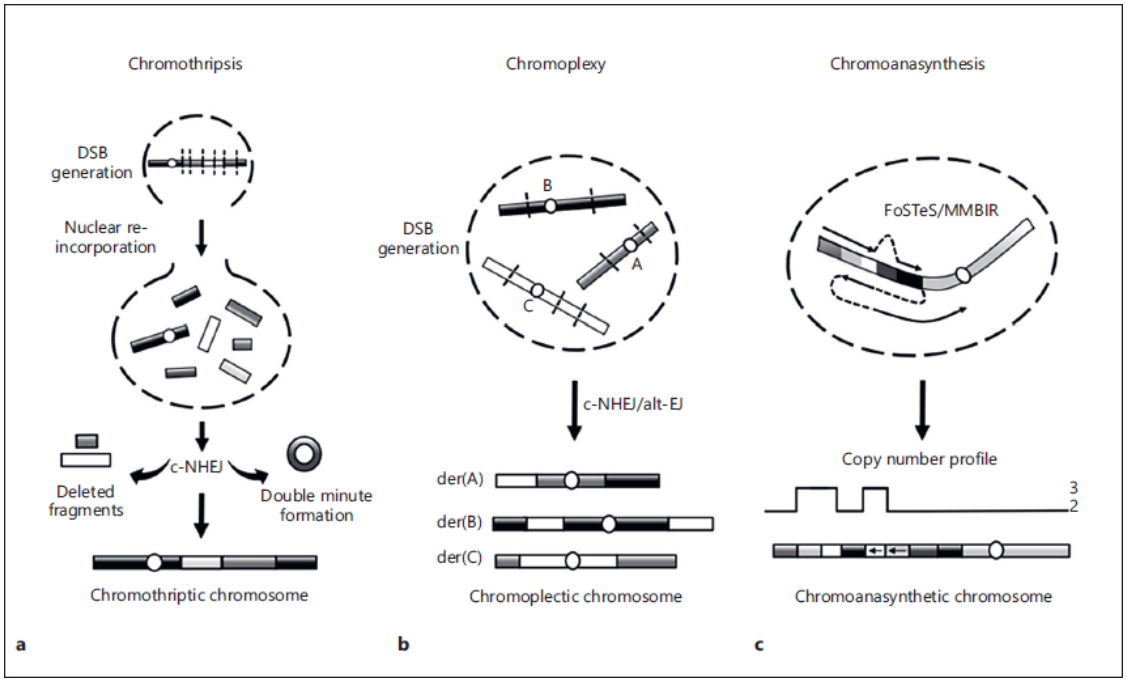


Fig. 10. *Characteristics of chromothripsis, chromoplexy, and chromoanasynthesis-derived structural variants.* ***a*** *In chromothripsis, a chromosome in a micronucleus can undergo massive DNA damage and result in multiple double-strand breaks (DSBs, depicted with dashed black lines). When the micronucleus is re-incorporated into the nucleus during mitosis, the DSBs undergo repair through Non-Homologous End Joining (c-NHEJ), where chromosome segments are randomly stitched back together, lost, or become double minutes. Functionally relevant segments could become double minutes and undergo amplification, as has been observed in MYC and other oncogene-containing segments in various cancer cases (Stephens et al., 2011; Rausch et al., 2012; Cheng et al., 2016).* ***b*** *In chromoplexy, different DSBs can be repaired with or without DNA loss at the breakpoints and be arranged into various derivative configurations, as shown here by the rearrangements of example derivative chromosomes A, B, and C. Chromoplexy is illustrated here for side-by-side comparisons with chromothripsis and chromoanasynthesis, and nomenclature for chromoplexy is illustrated in Chapter 9.* ***c*** *In chromoanasynthesis, a normal chromosome can undergo DNA segment re-synthesis (dashed lines to show template switches and solid arrows to show replication) mediated by replication processes such as fork-stalling and template switching (FoSTeS) and microhomology-mediated break-induced replication (MMBIR). These mechanisms lead to templated insertions that exhibit higher copy-number and may be arranged in different orientations (depicted in light grey and darker grey with black arrows signifying inverted sequence orientation). Notice the chromoanasynthesis chromosome has a copy-number profile exhibiting intercalating duplication-normal-duplication copy-number states, as seen in previous studies (Liu et al., 2011).* ***Note:*** *this figure and legend were adapted from Zepeda-Mendoza and Morton (2019).*

8.2.7.1.1 Chromothripsis

Chromothripsis (**cth**) is a single catastrophic event by which multiple rearrangements originate through random shattering and reshuffling of clustered chromosome regions and reassembly is primarily by classical non-homologous end joining (c-NHEJ). This is observed by the formation of derivative chromosomes with multiple and complex rearrangements and in microarray, regions of alternating copy number states between one and two copies (Zepeda-Mendoza and Morton, 2019; Lin et al., 2023; Xue and Durocher, 2023).

i. arr (1p)cthMicroarray analysis (abbreviated system, microarray format) shows multiple alternating changes (disomy and losses within the region) in the short arm of chromosome 1. Only the short arm of chromosome 1 is involved.
ii. arr (1,13)cthMicroarray analysis (abbreviated system, microarray format) shows chromothripsis involving chromosomes 1 and 13.
iii. arr[GRCh38] (1)cth,6q25.1q27(149,100,000_170,899,992)×1,(13)cthMicroarray analysis of a neoplastic sample shows chromothripsis of chromosomes 1 and 13, loss of chromosome 6 within bands 6q25.1 to 6q27. The clonal population is 100% of the sample.
iv. arr[GRCh38] 2p24.3p21(13,057,600_46,159,159)cth[0.9]Microarray analysis shows chromothripsis occurring within the region 2p24.3 to 2p21. The clonal population is approximately 90% of the sample.
v. arr[GRCh38] (2)cth[1.0],13q13.1(31,916,090_32,275,782)×1~2,13q14.11q14.3(39,748,868_53,284,167)×1[1.0],13q31.3(92,010,808_93,313,573)×1[1.0]Microarray analysis of a neoplastic sample shows chromothripsis of chromosome 2 and multiple deletions of chromosome 13, where the clonal population of the 13q13.1 deletion is approximately 100% of the sample.
vi. arr[GRCh38] 21q11.2q22.11(13,004,599_30,731,780)×2~4,21q22.11q22.3(30,801,359_42,723,271)amp[?],21q22.3(42,782,774_46,709,983)×1~2Microarray analysis of a neoplastic sample with a previously identified intrachromosomal amplification of chromosome 21 (iAMP21). There are fluctuations of copy number gain between bands 21q11.2 to 21q22.11, amplification between bands 21q22.11 to 21q22.3 including *RUNX1* and an apparently terminal single copy loss involving 21q22.3. **Note:** the copy number profile of iAMP21 is consistent with the breakage-fusion-bridge cycle followed by chromothripsis. Due to the complexity of copy number change the size of the clonal population of subclones cannot be determined.

8.2.7.1.2 Chromoanasynthesis

Chromoanasynthesis (**cha**) is a phenomenon whereby multiple combinations of structural variants including deletions, duplications, triplications, inversions, and translocations are generated without the clustered breakpoints of chromothripsis. This occurs through errors in DNA replication, namely fork stalling and template switching (FoSTeS) and microhomology-mediated break-induced replication (MMBIR) (Zepeda-Mendoza and Morton, 2019).

i. arr (6)chaMicroarray analysis shows multiple changes of copy number of chromosome 6.
ii. arr[GRCh38] 17p13.3q11.2(1,304,173_29,909,627)cha[0.5]Microarray analysis shows multiple changes of copy number, affecting most of the short arm of chromosome 17. Chromoanasynthesis is evident in approximately 50% of the sample.

8.3 Polar Bodies

First and second polar bodies as well as the secondary and the fertilized oocyte are the result of meiotic division (reduction division) and normally do not contain chromosomes, but one or two chromatids (the same is true for secondary and tertiary spermatozoa). This section describes nomenclature for chromatid loss and gain in polar bodies or respective oocytes identified by the cytogenomic techniques of **microarray** (**arr**) and **shallow genome sequencing** (**sseq**).

a. If shallow genome sequencing is used, replace **arr** with **sseq** for normal and abnormal results.
b. As the resolution of shallow genome sequencing is approximately 5-10 Mb, the normal result can be described, acknowledging limitations of the technique.
c. Following meiosis 1, the **first polar body** (**PB1**) consists of two chromatids, usually from a single chromosome for chromosomes X and 1–22.
d. At fertilization, meiosis 2 is completed forming the **second polar body** (**PB2**) which consists of only one chromatid for X and 1–22.
e. When describing normal or abnormal PB results, the term **chromatid** (**cht**) is used.
f. **PB1** nomenclature is given in relation to a normal haploid set of two chromatids for X,1–22.
g. **PB2** nomenclature is given in relation to the number of chromatids where the normal haploid set is one chromatid for X,1–22.
h. These terms however, are also appropriate to describe the respective oocytes. It should also be noted that although both polar bodies are analyzed, the deduced result of the oocyte is needed to make a diagnosis (*i.e.*, whether or not the oocyte is chromosomally normal so it can be fertilized for further development into an embryo).
i. Polar bodies 1 and 2 have different numbers of chromatids, and the microarray/sseq profiles regarding copy number are interpreted accordingly.

8.3.1 Normal Polar Body Results

Polar body 1

i. arr cht(X,1–22)×2Microarray analysis shows 23 chromatids relative to a haploid set of two chromatids.
ii. sseq cht(X,1–22)×2Shallow genome sequencing shows 23 chromatids relative to a haploid set of two chromatids.

Polar body 2

i. arr cht(X,1–22)×1Microarray analysis shows 23 chromatids relative to a haploid set of one chromatid.
ii. sseq cht(X,1–22)×1Shallow genome sequencing shows 23 chromatids relative to a haploid set of one chromatid.

8.3.2 Abnormal Polar Bodies PB1

The normal copy number is ×2 (two chromatids) for PB1.

i. arr cht(X)×1Microarray analysis shows loss of one X chromatid relative to a haploid set of two chromatids.
ii. arr cht(X)×1,cht(5)×0Microarray analysis shows loss of one X chromatid and loss of both chromatids 5 relative to a haploid set of two chromatids.
iii. arr cht(8,19)×3Microarray analysis shows gain of one chromatid 8 and a gain of one chromatid 19 relative to a haploid set of two chromatids. There are three chromatids in total for each aneuploidy. Parentheses can be used to group abnormalities of the same copy number.
iv. arr cht(4)×0,cht(17)×4,cht(18)×0,cht(22)×3Microarray analysis shows loss of both chromatids 4 and 18, gain of two chromatids 17, and gain of one chromatid 22 relative to a haploid set of two chromatids.
v. arr cht(4,14)×0,cht(17)×4,cht(22)×3Microarray profile shows loss of both chromatids 4 and 14, gain of two chromatids 17, and gain of one chromatid 22 relative to a haploid set of two chromatids.

8.3.3 Abnormal Aneuploidy PB2

The normal copy number is ×1 (one chromatid) for PB2.

i. arr cht(X)×0Microarray analysis shows loss of the X chromatid relative to a haploid set of one chromatid.
ii. arr cht(13)×2,cht(21)×0Microarray analysis shows gain of one chromatid 13 and loss of one chromatid 21 relative to a haploid set of one chromatid.
iii. arr cht(13,18,21)×2Microarray analysis shows gains of one chromatid each for 13, 18 and 21 relative to a haploid set of one chromatid.
iv. arr cht(13)×2,cht(14,18)×0,cht(21)×2Microarray analysis shows gains of one chromatid each for 13 and 21, and loss of chromatids 14 and 18 relative to a haploid set of one chromatid.

8.3.4 Abnormal Structural PB1

i. arr[GRCh38] cht1p36.3p12(1,059,622_119,772,865)×1,cht1q12q44(143,822,876_248,903,579)×3, cht(21)×4Microarray analysis shows loss of the chromatid region 1p36.3 to 1p12, gain of the chromatid region 1q12 to 1q44, and gain of two chromatids for 21 relative to a haploid set of two chromatids.
ii. arr[GRCh38] cht7p22.3q33(576,616_137,975,092)×0dmat,cht13q12.11q31.1(19,238,580_80,007,319)×4dmatMicroarray analysis shows loss of two chromatids for region 7p22.3 to 7q33 and gain of two chromatids for region 13q12.11 to 13q31.1 relative to a haploid set of two chromatids. The mother has a balanced reciprocal translocation, 46,XX,t(7;13)(q33;q31.1).
iii. arr[GRCh38] cht8p23.3q11.21(175,733_49,909,509)×3,cht(21)×0Microarray analysis shows gain of part of one chromatid for region 8p23.3 to 8q11.21 and loss of two chromatids for 21 relative to a haploid set of two chromatids.

8.3.5 Abnormal Structural PB2

i. arr[GRCh38] cht1p36.3p12(1,059,622_119,772,865)×2,cht1q12q44(143,822,876_248,903,579)×0, cht(21)×0Microarray analysis shows gain of chromatid region 1p36.3 to 1p12, loss of chromatid region 1q12 to 1q44, and loss of chromatid 21 relative to a haploid set of one chromatid.
ii. arr[GRCh38] cht7p22.3q33(576,616_137,975,092)×3,cht13q12.11q31.1(576,616_137,975,092)×0, cht13q31.1q34(576,616_137,975,092)×2Microarray analysis shows gain of two chromatid regions for 7p22.3 to 7q33, loss of chromatid region 13q12.11 to 13q31.1 and gain of chromatid region 13q31.1 to 13q34 relative to a haploid set of one chromatid.
iii. arr[GRCh38] cht8p23.3q11.21(175,733_49,909,509)×0,cht(21)×3Microarray analysis shows loss of chromatid region 8p23.3 to 8q11.21 and gain of two chromatids for 21 relative to a haploid set of one chromatid.

9 Genome Mapping

9.1 Introduction

In addition to detection of both balanced and unbalanced structural variation, genome mapping can detect copy number changes analogous to chromosomal microarray analysis (Levy et al., 2022; Smith et al., 2022; Iqbal et al., 2023; Sahajpal et al., 2023). The nomenclature for genome mapping (Moore et al., 2023) uses elements of karyotype, microarray and region-specific nomenclature to describe the observed structural and copy number variation.

The ISCN description of genome mapping results does not indicate the platform used (*i.e.*, optical or electronic genome mapping), the labelling strategy (*e.g.*, DLE-1), the type of genome assembly (*e.g.*, rare variant, *de novo*, or guided), the version of bioinformatic pipeline, and whether any custom filter settings are in use, therefore these must form part of the descriptive narrative in the report. If classification is performed via a filtered list of genes, the genes may be indicated in the interpretative section of the report or by a statement indicating that the list is available upon request.

9.2 General Principles

a. The nucleotides listed are not necessarily those of the actual breakpoint, but rather indicate the extent of the fragment as determined by the position(s) of the labelled DNA motif within the variant region and closest to the chromosomal breakpoint(s). For this reason, the enzyme labelling strategy must be stated in the techniques section of the report.
b. The principles of genome mapping nomenclature are the same for constitutional and neoplastic samples.
c. Only results that are abnormal, based upon the laboratory's reporting procedures, are included in the ISCN description. The exception is that normal sex chromosomes may be reported for the purpose of sex determination.
d. Assessment of copy number in genome mapping can be difficult because the technology does not sample single cells but rather assesses DNA from many cells. **Note:** gains and losses are reported relative to the normalised ploidy. It may not be possible to distinguish between a one copy gain in a high proportion of the sample and a two copy gain in a low proportion of the sample.

Even when enrichment strategies have been performed in neoplastic samples the proportion of the sample with an abnormality given in the ISCN description may not be representative of the true level of the abnormality in the neoplasm, *e.g.*, an abnormality in 80% of tumor cells would be in only 40% of the clinical sample if the tumor load is 50%. This is a limitation of the test.

e. The proportion of abnormality within the sample cannot be used to determine subclone composition using this technology.
f. The gene fusion definition has been harmonized between ISCN, the Human Genome Organisation (HUGO) Gene Nomenclature Committee, Variant Interpretation for Cancer Consortium (VICC) Gene Fusion Specification, and Human Genome Variation Society (HGVS). Gene fusions occur when two or more genes join and result in a chimeric transcript and/or a novel interaction between a rearranged regulatory element with the expressed product of a partner gene (a regulatory fusion) (see Section 4.4.6.1).

9.3 Nomenclature Rules

a. For general cytogenomic rules that are also applicable to genome mapping see Chapter 4.
b. For nomenclature to describe targeted genome mapping see Section 10.6.
c. There is a space after the technique, **ogm** or **ogm[GRCh38**], and before the rest of the ISCN description of the result (see Section 4.4.1).
d. Results are reported in a single line of nomenclature. However, complex results can be presented in a table for clarity (see Tables 10 and 11).
e. Regardless of whether there is a structural abnormality or a copy number gain or loss, the aberrations are listed in numerical order from lowest to highest numbered chromosome. The sex chromosome abnormalities are listed first with the X before the Y unless only the X chromosome is abnormal, then the normal Y is listed first (see Section 4.3).
f. The band designations and aberrant nucleotides are listed from **pter** to **qter** (as determined by the orientation of the region containing the centromere), consistent with the public databases of current genome builds on UCSC or Ensembl genome browsers (www.genome.ucsc.edu or www.ensembl.org).
g. Genome mapping nomenclature uses the karyotype format and the microarray format. The karyotype format ISCN is used when the structural nature of the abnormality is apparent. It is possible to use both formats within the ISCN description although, for each chromosome, the nomenclature must consistently use either one format or the other. Within the nomenclature formats different systems are used (see Section 4.7):

- The abbreviated system (microarray format) is used for aneuploidy and chromoanagenesis where only the chromosome is given and no nucleotides. Copy number is given for aneuploidy but not for chromoanagenesis.
- The short system (karyotype format) defines the structural abnormality by the chromosome breakpoints and nucleotides. Copy number is not included.
- The short system (microarray format) defines abnormalities by the chromosome breakpoints and nucleotides. Copy number is included.
- The detailed system (karyotype format) describes abnormal chromosomes in their entirety from **pter** to **qter**. In this system, when describing a **derivative** (**der**)

chromosome, it is not necessary to use the terms **del**, **dup**, **ins**, **inv** or **t** because the structure is apparent from the nucleotide coordinate sequence. Copy number is not included.

- The extended system (microarray format) includes the span of the nucleotides involved in the abnormality as well as the flanking uninvolved nucleotides. Commas are not used in the nucleotides. Copy number is included.

h. **Commas** (**,**) in nucleotide numbers are optional but improve readability. It is recommended not to include commas in the extended form where the maximal and minimal extent of the copy number variant (CNV) is given (see Section 4.4.5).

i. An **underscore** (**_**) indicates that the gain, loss, or inversion encompasses the segment between the listed nucleotides. A **tilde** (**~**) between two nucleotide coordinates indicates uncertainty of the breakpoint.

j. A **semicolon** (**;**) separates nucleotides that are aberrant due to translocation in the short system (karyotype format) and a **double colon** (**::**) separates the nucleotides to indicate breakage and reunion in the detailed system (karyotype format). It is also used to indicate breakage and reunion of chromosomes where it is uncertain if the change is intrachromosomal or interchromosomal (see Section 9.4.2.5).

k. To indicate a mixed cell population, the proportion of cells in the sample with the copy number variant (CNV) is estimated from the fractional copy number and is included in **square brackets** (**[ ]**) following the copy number.

l. When mixed cell populations can be distinguished for constitutional and unrelated clones, the largest cell line/clone is listed first. For related clones in neoplasia, the least complex clone is listed first.

m. For structural changes, the **variant allele frequency** (**VAF**) may be included after the abnormality in **square brackets** (**[ ]**) and annotated **VAF** to distinguish it from the proportion of the sample calculated using the fractional copy number, *e.g*., [VAF0.2]. Alternatively, it may be included in the text description within the report or in the tabular form. **Note:** for neoplastic samples the **VAF** in the sample may not represent the level of abnormality in the tumor.

n. Listing of gene(s) is not mandatory in the genome mapping nomenclature but when given, the gene(s) listed are not italicised. Only those participating in fusion gene formation (whether resulting in chimeric gene products or involving regulatory elements) or that are investigated by targeted assays, are reported (see Sections 9.4.2.3 and 9.4.2.5). Genes involved in fusion gene formation are separated by a **double colon** (**::**), while all others are separated by a **comma** (**,**) (Bruford et al., 2021).

o. In karyotype format nomenclature the gene(s) is indicated in **parentheses** (**( )**) immediately after the abnormality and before the **square brackets** (**[ ]**) indicating the proportion of the sample or **VAF**. Loss or gain of critical genes is indicated by a **minus** (−) or **plus** (+) sign after the gene symbol in the karyotype format (see Section 9.4.2.3) and the **double colon** (**::**) indicates gene fusion. In microarray format nomenclature the gene(s) is indicated in **parentheses** (**( )**) immediately after the abnormality and before the copy number. The **minus** (−) and **plus** (+) signs are not used in the microarray format. For intragenic deletion or duplication no gene symbol is used in the ISCN description as the entire gene is not involved, but it may be appropriate to name the gene in the text of the report (see Section 9.4.2.3). Genes of no known clinical significance to the referral type and those not involved in structural change are not listed.

p. If genome mapping further clarifies the karyotype and, in retrospect, the abnormality can be visualized with banding, the karyotype may be amended to reflect this new genome mapping information. If the abnormality is cryptic and cannot be visualized by banding, the abnormality is **not** listed in the banded karyotype. Conversely, if genome mapping does not confirm a change visible by karyotype then the karyotypic abnormality may still be reported if a further review of the karyotype confirms its presence (see Section 4.6).
q. Genome mapping analysis can demonstrate a relative gain or loss of DNA although analysis by another technique may be necessary to report ploidy. Genome mapping does not always allow discrimination between homologous chromosomes.

9.4 Nomenclature Examples

All examples below use **genome build GRCh38**. The genome build must be stated if nucleotide coordinates are present in the nomenclature, but is not required if only whole chromosome, or chromosome arm aneuploidy is reported without nucleotide coordinates.

9.4.1 Normal Results

If no clinically significant abnormality is detected using genome mapping the sex chromosomes are given first and are separated from the autosomes. There is a space between **ogm** and the opening parenthesis.

i. ogm (X,1–22)×2Genome mapping in a female with no abnormality detected.
ii. ogm (X,Y)×1,(1–22)×2Genome mapping in a male with no abnormality detected.
iii. ogm (1–22)×2Genome mapping with no abnormality detected and the sex is not disclosed.
iv. 46,U.ogm (1–22)×2Karyotype and genome mapping show no abnormality and the sex chromosomes are undisclosed.

9.4.2 Abnormal Results

Some of the examples in this chapter do not represent observed genome mapping data but are provided to demonstrate nomenclature principles (*i.e.*, the nucleotide coordinates may not be the same as would be obtained from experimental data).

9.4.2.1 Aneuploidy of Whole Chromosomes or Chromosome Arms

i. ogm (X)×1[0.6]Genome mapping shows loss of the X chromosome in 60% of the sample in a female. **Note:** the abbreviated system (microarray format) of nomenclature is used in the description of whole chromosome aneuploidy.
ii. ogm (X)×0[0.5],(Y)×1Genome mapping shows loss of the X chromosome in 50% of the neoplastic sample in a male.
iii. ogm (X,21)×3Genome mapping shows three copies of chromosomes X and 21.

iv. ogm (21,22)×3[0.2]Genome mapping shows three copies of chromosomes 21 and 22 in approximately 20% of a neoplastic sample.

v. ogm (X)×1Genome mapping shows the presence of a single X chromosome and is consistent with 45,X in a constitutional sample.

vi. ogm (X)×1,(Y)×0[0.8]Genome mapping shows the presence of a single X chromosome and is consistent with acquired loss of the Y chromosome in 80% of a neoplastic sample. **Note:** inclusion of the X chromosome is optional in neoplasia.

vii. ogm (X)×2,(Y)×1Genome mapping shows the presence of two X chromosomes and one Y chromosome, consistent with an XXY chromosome complement in a constitutional sample.

viii. ogm (X)×1,(Y)×2Genome mapping shows gain of the Y chromosome in a male, consistent with an XYY sex chromosome complement.

ix. ogm (X)×2[0.5],(Y)×1,(8,21)×3[0.5]Genome mapping shows gain of chromosomes X, 8 and 21 in approximately 50% of this neoplastic sample in a male. The normal Y chromosome is given so it is clear that this is a male with gain of an X chromosome.

x. ogm (17p)×1[0.7],(17q)×3[0.7]Genome mapping shows loss of the entire short arm of chromosome 17 and gain of the entire long arm of chromosome 17 in approximately 70% of a neoplastic sample.

9.4.2.2 Deletion

The abbreviation (**del**) is used to denote both terminal and interstitial **deletions** and is used when the chromosomal structure can be ascertained. Alternatively, the microarray format may be used by indicating the copy number (*e.g.*, ×1). If using the karyotype format, deletions within a chromosome band are given with the band listed twice, whereas the band is listed only once in the microarray format (see Table 4 in Section 4.7). Schematic representation of an interstitial deletion identified by genome mapping is shown in Figure 11. A comment may be made in the text of the report to discuss the size variation between the actual deletion and the deletion reported in the ISCN description.

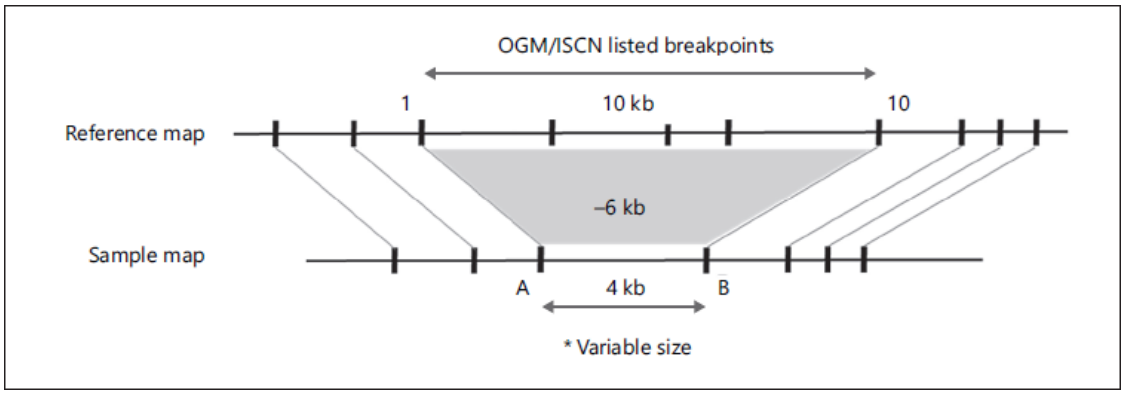


Fig. 11. *Schematic representation of an interstitial deletion identified by genome mapping (Courtesy of Dr. H. Barseghyan). The reference map breakpoints 1 and 10 are listed in the ISCN however, these labels are aligned to sample map locations A and B, with a total distance between them of 4 kb, indicating that the actual deletion size is equal to 6 kb (difference between reference and sample maps). In general, it is not necessary to include this remnant DNA in the genome mapping nomenclature, but a comment may be made in the text of the report to explain the discrepancy between the ISCN breakpoints and the actual size of the deletion when required. ****Variable size*** *refers to the deletion specific distance between points A and B.*

i. ogm[GRCh38] 17q11.2(30,273,120_32,477,675)×1[0.5]
or
ogm[GRCh38] del(17)(q11.2q11.2)(30,273,120_32,477,675)[0.5]Genome mapping shows an interstitial deletion of 2.2 Mb within 17q11.2 in approximately 50% of the neoplastic sample. The loss includes the *NF1* gene. **Note:** inclusion of the *NF1* gene in the ISCN description is not mandatory, but if included, it is placed in **parentheses** (**( )**) immediately before the **square brackets** (**[ ]**) containing the proportion of the abnormality in the sample, *e.g.*,ogm[GRCh38] 17q11.2(30,273,120_32,477,675)(NF1)×1[0.5]orogm[GRCh38] del(17)(q11.2q11.2)(30,273,120_32,477,675)(NF1−)[0.5]

ii. ogm[GRCh38] 11q14.1q22.3(80,488,887_108,177,359)×1
or
ogm[GRCh38] del(11)(q14.1q22.3)(80,488,887_108,177,359)Genome mapping shows an interstitial deletion between bands 11q14.1 and 11q22.3 involving nucleotides 80,488,887 to 108,177,359. The actual size of the deletion is 27,684 kb, whereas the size obtained from the two adjacent fluorescent label positions is 27,688 kb as there is 4 kb of residual DNA between the fluorescent label positions. See Figure 11 for a diagrammatic explanation.

iii. ogm[GRCh38] 22q11.21(18,858,640_21,290,760)×1
or
ogm[GRCh38] 22q11.21(18855621×2,18858640_21290760×1,21294586×2)
or
ogm[GRCh38] del(22)(q11.21q11.21)(18,858,640_21,290,760)Genome mapping shows a 2.4 Mb interstitial deletion within 22q11.21. The expanded system (microarray format) shows that the next neighboring proximal nucleotide that does not show a loss is 3 kb away and the next neighboring distal nucleotide that does not indicate that a loss is 3.8 kb away from the alteration. **Note:** demarcating commas are not used in the nucleotide coordinates in the expanded system as the nucleotide coordinates and copy number designation become confused.

iv. ogm[GRCh38] 17p13.3p13.1(66,653_8,010,821)×1[0.7]
or
ogm[GRCh38] del(17)(p13.1)(pter_8,010,821)[0.7]Genome mapping shows an apparently terminal deletion of chromosome 17 with the breakpoint in 17p13.1 at nucleotide 8,010,821. The deletion is present in 70% of this neoplastic sample.

v. ogm[GRCh38] Xq25(126,228,413_126,535,347)×0mat
or
ogm[GRCh38] Xq25(126225312×1,126228413_126535347×0,126538250×1)mat
or
ogm[GRCh38] del(X)(q25q25)(126,228,413_126,535,347)matGenome mapping shows an interstitial deletion of Xq25 involving loss of nucleotides between 126,228,413 and 126,535,347 of maternal origin in a male. If the normal Y chromosome is not given in the ISCN, then the report text must indicate the sex. The second option demonstrates the expanded system (microarray format) showing the maximal extent of the deletion. **Note:** for further explanation of the nomenclature for inheritance refer to Section 9.4.2.6.

vi. ogm[GRCh38] 6q21q25.1(113,900,000_149,100,000)×1[0.5],(21)×3c
or
ogm[GRCh38] del(6)(q21q25.1)(113,900,000_149,100,000)[0.5],(21)×3cGenome mapping of a neoplastic sample shows an interstitial loss in the long arm of chromosome 6 from 6q21 to 6q25.1 in 50% of the sample. There is a single copy gain (trisomy) of chromosome 21 that is constitutional. **Note:** copy number loss due to structural abnormality may be presented in a microarray format nomenclature (**×1**) or karyotype format nomenclature (**del**). Whole chromosome aneuploidy is reported using the (abbreviated system) microarray format.

vii. ogm[GRCh38]
del(13)(q14.2q14.3)(50,121,221_52,453,910)[0.4],del(13)(q14.3q14.3)(50,502,914_51,002,914)[0.2]Genome mapping shows two overlapping interstitial deletions involving the long arm of chromosome 13 in a CLL sample. There is a larger deletion of 13q14.2 to 13q14.3 involving loss of approximately 2.3 Mb from one chromosome 13 in approximately 40% of the sample and a smaller deletion of approximately 500 kb within 13q14.3 of the other homologue in approximately 20% of the sample. For clarity **single underlining** (**_**) may be used to distinguish homologous chromosomes in the short system (karyotype format).

viii. ogm[GRCh38]
13q14.2q14.3(50,121,221_50,502,913)×1[0.4],13q14.3(50,502,914_51,002,914)×1[0.6],13q14.3(51,002,939_52,453,910)×1[0.4]Genome mapping shows the same interstitial deletions involving the long arm of chromosome 13 as seen in the previous example. The homologues could not be distinguished, and so the three segments are listed from **pter** to **qter** using the short system (microarray format). **Note:** in the microarray format description of the deletion within 13q14.3, the band is not repeated (see Table 4).

ix. ogm[GRCh38]
Xq24q28(118,930,414_155,233,098)×2[0.3],1p32.3(51,400,687_51,477,088)×1[0.3],(1q)×3[0.3],(5,7,9,19)×3[0.5]Genome mapping of a neoplastic sample from a male shows gain of Xq24 to Xq28 in 30% of the sample; an interstitial deletion of part of the short arm of chromosome 1 in 30% of the sample; gain of the entire long arm of chromosome 1 in 30% of the sample, and trisomies of chromosomes 5, 7, 9 and 19 in 50% of the sample. **Note:** it is a limitation of genome mapping that it cannot determine whether the abnormalities are in the same or different clones.

The above example could be written in tabular form (Table 10).

Table 10. Example of genome mapping results written in tabular form.

Chromosome/ chromosome region/band	Nucleotide coordinates GRCh38	Size, kb	Abnormality type	Reported gene(s)*	Copy number	Proportion of the sample	Comment
Xq24q28	118,930,414_155,233,098	36,302	Gain		2	30%	
1p32.3	51,400,687_51,477,088	76	Loss	*CDKN2C*	1	30%	Adverse risk
1q	Whole arm		Gain	*CKS1B*	3	30%	Adverse risk
5,7,9,19	Whole chromosome		Gain		3	50%	

*Note: only those genes known to be of specific diagnostic or prognostic significance are reported.

x. ogm[GRCh38] 5q14.3q35.1(88,421,659_170,088,529)×1[0.9],(17)×1[0.3]
or
ogm[GRCh38]
del(5)(q14.3q35.1)(88,421,659_170,088,529)[0.9],(17)×1[0.3]Genome mapping of a neoplastic specimen shows an interstitial deletion of chromosome 5 from 5q14.3 to 5q35.1 in 90% of the sample and monosomy 17 in 30% of the sample.

xi. ogm[GRCh38]
9p21.3(21,150,533_21,671,683)×1[0.4],9p21.3(21,671,699_22,142,918)×0[0.6],9p21.3(22,143,009_22,277,637)×1[0.4].nuc ish (CDKN2A)×0[110/200]Genome mapping of a neoplastic sample shows interstitial deletion of both chromosome 9 homologues at 9p21.3, and the result is confirmed by *in situ* hybridization using a probe for *CDKN2A*. There are two segments of heterozygous loss that are present in 40% of the sample and one segment of homozygous loss in 60% of the sample. There is insufficient structural information to determine the extent of deletion on each homologue, therefore the segments of loss are listed as three distinct segments using the short system (microarray format).

xii. ogm[GRCh38]
del(9)(p21.3p21.3)(21,150,533_22,277,637)[0.4],del(9)(p21.3p21.3)(21,671,684_22,142,918)[0.2].nuc ish (CDKN2A)×0[40/200]Genome mapping of a neoplastic sample shows interstitial deletion of both chromosome 9 homologues at 9p21.3, and the result is confirmed by *in situ* hybridization using the probe for *CDKN2A*. One homologue showed an interstitial deletion in 40% of the sample while the other showed an interstitial deletion in 20%. For clarity single underlining may be used to distinguish between homologous chromosomes.

9.4.2.3 Duplication

The abbreviation (**dup**) is used for **duplications**. Alternatively, the microarray format may be used by indicating the copy number (*e.g.*, ×3).

i. ogm[GRCh38] 6q21q25.1(113,900,000_149,100,000)×3
or
ogm[GRCh38] dup(6)(q21q25.1)(113,900,000_149,100,000)Genome mapping

analysis shows duplication in the long arm of chromosome 6 from 6q21 to 6q25.1. The original orientation of the duplicated sequence is maintained. In this example the short system (microarray format) is shown first followed by the alternative short system (karyotype format). The position of the duplication is indicated in neither format, but it is assumed that it is a tandem duplication. **Note:** copy number changes may be presented either using microarray format (×3) or karyotype format (**dup**).

ii. ogm[GRCh38] der(6)(pter_q25.1::q21_qter)(pter_149,100,000::113,900,000_qter)Genome mapping analysis shows duplication in the long arm of chromosome 6 from 6q21 to 6q25.1. Breakage and reunion of the chromosome is indicated by the **double colon** (**::**). The original orientation of the duplicated sequence is maintained, and this is indicated by the order of the nucleotide coordinates in the detailed system (karyotype format) nomenclature. **Note:** this is described as a **derivative** (**der**) chromosome in the detailed system.

iii. ogm[GRCh38] der(6)(pter_q25.1::q25.1_q21::q25.1_qter)(pter_149,099,000::149,100,000_113,900,000::149,100,001_qter)Genome mapping analysis shows duplication in the long arm of chromosome 6 from 6q21 to 6q25.1 at the distal breakpoint (6q25.1). The orientation of the duplicated sequence is inverted, as indicated by the order of the nucleotide coordinates in the detailed system (karyotype format) nomenclature. **Note:** this is described as a **derivative** (**der**) chromosome in the detailed system.

iv. ogm[GRCh38] der(6)(pter_q21::q25.1_q21::q21_qter)(pter_113,900,000::149,100,000_113,900,000::113,900,001_qter)Genome mapping analysis shows duplication in the long arm of chromosome 6 from 6q21 to 6q25.1 at the proximal breakpoint (6q21). The orientation of the duplicated sequence is inverted, as indicated by the order of the nucleotide coordinates in the detailed system (karyotype format) nomenclature.

v. arr[GRCh38] Xq22.2(103,757,477_103,848,705)×3,Xq22.2(103,958,437_104,059,021)×3.ogm[GRCh38] der(X)dup(X)(q22.2q22.2)(103,849,669_103,757,512)dup(X)(q22.2q22.2)(103,958,981_104,060,016)Microarray analysis shows two regions of gain in the long arm of the X chromosome. Genome mapping confirms the duplications, shows that they are *in cis* and that the more proximal duplication is in an inverted orientation. The genome mapping ISCN is written in short system (karyotype format). **Note:** the order of the nucleotide coordinates shows the orientation and location of the inverted segment.

vi. ogm[GRCh38] 11q23.3(118,341,120_118,349,783)×3[0.6]
or
ogm[GRCh38] dup(11)(q23.3q23.3)(118,341,120_118,349,783)[0.6]Genome mapping shows intragenic duplication of part of *KMT2A* within 11q23.3 in 60% of a neoplastic sample. This represents a simple canonical *KMT2A* partial tandem duplication. *KMT2A* is not listed in the ISCN description because only part of the gene is duplicated (see Section 9.3).

vii. ogm[GRCh38] 11q23.3(118,341,120_118,526,842)(KMT2A)×3[0.6]
or
ogm[GRCh38]
dup(11)(q23.3q23.3)(118,341,120_118,526,842)(KMT2A++)[0.6]Genome mapping shows duplication of the *KMT2A* gene within 11q23.3 in 60% of a neoplastic sample. **Note:** the first option uses the short system (microarray format) and does not provide structural information. It shows that there are three copies of *KMT2A* in 60% of the sample. The second option uses the short system (karyotype format) and shows that there are two copies of *KMT2A* on one of the chromosome 11 homologues.

9.4.2.4 Insertion

The orientation of the **insertion** (**ins**) is indicated by the order of the bands and the nucleotide coordinates of the inserted region when the detailed system (karyotype format) of nomenclature is used. Insertions, for which the identity of the inserted material is unknown, are described by use of the abbreviations **ins** and **question mark** (**?**) and making use of a **tilde** (**~**) to reflect uncertainty of the breakpoint localization at the point of the insertion. As demonstrated in Figure 12, a 6 kb segment of unknown DNA is inserted between 1~4 kb of the reference. If the size of the unknown insertion is not provided in the report text, it is not possible for the reader of the nomenclature to know the size of the inserted material

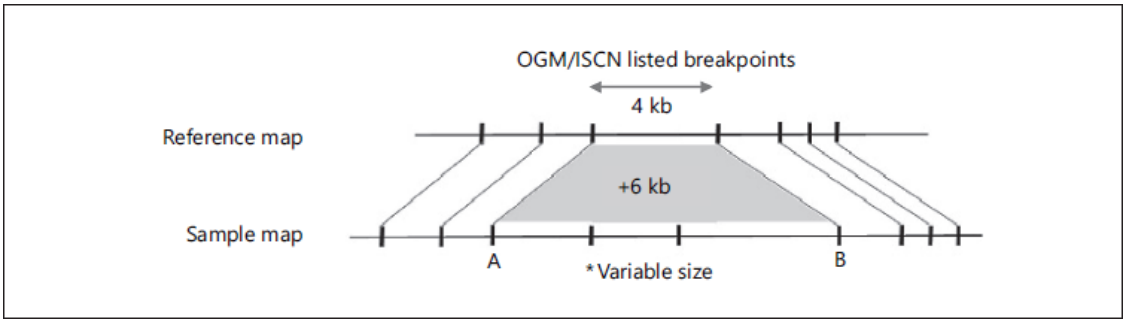


Fig. 12. *Schematic representation of a chromosomal insertion identified by genome mapping (courtesy of Dr. H. Barseghyan). * **Variable size** refers to the insertion specific distance between points A and B.*

9.4.2.4.1 Intrachromosomal Insertion

i. ogm[GRCh38]
ins(2)(p24.1p12p11.2)(19,795,841~19,799,854::80,780,708_87,576,955)
or
ogm[GRCh38]
der(2)(pter_p24.1::p12_p11.2::p24.1_p12::p11.2_qter)(pter_19,795,841~19,799,854::80,780,708_87,576,955::19,795,841~19,799,854_80,780,707::87,576,956_qter)Genome mapping shows that the short arm segment of approximately 6.8 Mb between bands 2p12 and 2p11.2 is inserted into the short arm at band 2p24.1 within a 4 kb

region. The original orientation of the inserted segment is maintained. The first option uses the short system (karyotype format) nomenclature and the second uses the detailed system (karyotype format). **Note:** the nucleotides at the insertion point are separated from the inserted nucleotides by a **double colon** (**::**) even though the insertion is intrachromosomal. To describe the chromosome using the detailed system, it is described as a **derivative** (**der**) chromosome.

ii. ogm[GRCh38]
ins(2)(p24.1p11.2p12)(19,795,841~19,799,854::87,576,955_80,780,708)
or
ogm[GRCh38]
der(2)(pter_p24.1::p11.2_p12::p24.1_p12::p11.2_qter)(pter_19,795,841~19,799,854::87,576,955_80,780,708::19,795,841~19,799,854_80,780,707::87,576,956_qter)Same insertion example as above, except that the orientation of the bands within the segment have been reversed in their new position, *i.e.*, band 2p11.2 is now closer than band 2p12 to 2pter.

iii. ogm[GRCh38]
der(2)(pter_p24.1::p11.2_p12::p11.2_p12::p24.1_p12::p11.2_qter)(pter_19,795,841~19,799,854::87,576,955_80,780,708::87,576,955_80,780,708::19,795,841~19,799,854_80,780,708::87,576,955_qter)Same insertion example as above with the inserted segment in an inverted orientation. The inserted segment is duplicated.

9.4.2.4.2 Interchromosomal Insertion

i. ogm[GRCh38] der(2)ins(2;?)(q35;?)(219,823,156~219,844,642;?)Genome mapping shows that approximately 45.5 kb of material of unknown origin is inserted into the long arm of chromosome 2 at band 2q35 within a 21.5 kb region. **Note:** the inserted segment may be unknown either because of substantial rearrangement or because it is composed of repetitive sequence.

ii. ogm[GRCh38]
ins(18;13)(q12.2;q22.2q13.3)(37,636,503~37,640,279;77,743,263_35,366,781)Genome mapping shows an insertion of bands 13q13.3 to 13q22.2, from nucleotides 35,366,781 to 77,743,263, into band 18q12.2, between nucleotides 37,636,503 and 37,640,279, in an inverted orientation.

iii. ogm[GRCh38]
ins(X;7)(p21.1;q21.11q22.3)(36,850,248~36,855,273;77,950,039_107,500,419)Genome mapping shows an insertion of bands 7q21.11 to 7q22.3, involving nucleotides 77,950,039 to 107,500,419, into Xp21.1 between nucleotides 36,850,248 and 36,855,273. In the derivative X chromosome, band 7q21.11 is closer to Xpter and band 7q22.3 is closer to the chromosome X centromere.

iv. ogm[GRCh38]
der(X)ins(X;7)(p21.1;q22.3q21.11)(36,850,248~36,855,273;107,500,419_77,950,039)Genome mapping shows a derivative X chromosome resulting from a duplication of a segment from 7q21.11 to 7q22.3 that is inserted into Xp21.1. In the derivative X the band 7q22.3 is closer to Xpter and band 7q21.11 is closer to X centromere. There are two normal copies of chromosome 7.

v. ogm[GRCh38] der(17)dup(17)(p13.3p13.3)(2,252,518_2,372,750)ins(17;3)(p13.3;q29q29)(2,372,750~2,376,439;197,617,365_197,768,658)Genome mapping shows a derivative chromosome 17 resulting from two rearrangements. There is a duplication within 17p13.3 from nucleotide 2,252,518 to 2,372,750 and an insertion of an additional copy of the region within 3q29, from nucleotides 197,617,365 to 197,768,658, into band 17p13.3. The orientation of the inserted segment from chromosome 3, relative to pter and qter, is maintained.

vi. ogm[GRCh38] der(4)del(4)(q22.2q22.2)(93,645,428_93,651,467)ins(4;15)(q22.2q22.2;q25.1q26.3)(93,651,468~93,652,173;80,402,705_98,589,048)Genome mapping shows a derivative chromosome 4 resulting from an interstitial deletion within 4q22.2 involving nucleotides 93,645,428 to 93,651,467; an insertion of a duplicated region from 15q25.1 to 15q26.3 of nucleotides 80,402,705 to 98,589,048, into chromosome 4 within 4q22.2 between nucleotides 93,651,468 and 93,652,173. The inserted segment from chromosome 15 is in the same orientation relative to pter of the recipient chromosome. There is one derivative chromosome 4 with both an interstitial deletion within 4q22.2 and an insertion from chromosome 15, one normal chromosome 4, and two normal chromosomes 15.

9.4.2.5 Inversion and Translocation

a. The same rules apply to genome mapping as are applied to karyotype descriptions of translocations however, the nucleotide coordinates at the chromosome breakpoints are indicated and the formation of fusion genes or the involvement of other significant genes may be indicated.
b. In the case of gene fusions that alter regulation (*e.g., IGH*::*MYC*) the regulatory element (reported first in the ISCN description) and regulated element are given even if the break occurs outside the gene region.
c. Fusion genes that form a chimeric transcript are reported with the 5′ gene first, followed by the 3′ gene.
d. It can be difficult to discriminate between homologous chromosomes in genome mapping, and inversions may appear identical to translocations between homologues. Examples viii and ix demonstrate the specific nomenclature to deal with this issue.
e. Genome mapping may call a reciprocal translocation with a region of uncertainty, or displacement of the breakpoint on the two hybrid maps. This region of uncertainty can be indicated by use of the **tilde** (**~**).

i. ogm[GRCh38] t(6;7)(q21;q32.1)(108,985,886~108,982,237;128,310,022~128,313,239)Genome mapping shows a reciprocal translocation between chromosomes 6 and 7. The chromosomes and breakpoints are separated by a **semicolon** (**;**) as are the nucleotides. **Note:** the use of a **tilde** (**~**) to demonstrate the region of uncertainty of the breakpoints.

ii. ogm[GRCh38] t(3;12)(q26.2;p13.2)(169,465,210~169,466,001;11,801,652~11,804,643)(MECOM::ETV6)[VAF0.3]Genome mapping analysis of a neoplastic sample shows a

translocation between 3q26.2 (between nucleotides 169,465,210 and 169,466,001) and 12p13.2 (between nucleotides 11,801,652 and 11,804,643) resulting in fusion of the *MECOM* gene cluster and *ETV6*. The translocation is present at a VAF of 30%.

If the above example is confirmed by interphase triple color fluorescence *in situ* hybridization then the result would be:

iii. ogm[GRCh38]
t(3;12)(q26.2;p13.2)(169,465,210~169,466,001;11,801,652~11,804,643)(MECOM::ETV6)[VAF0.3].nuc ish (GOLIM4×2,MECOM×3,MYNN×2)(GOLIM4/MECOM sep MECOM/MYNN)×1[150/200],(ETV6)×2(5′ETV6 sep 3′ETV6)×1[145/200]
or
ogm[GRCh38]
t(3;12)(q26.2;p13.2)(169,465,210~169,466,001;11,801,652~11,804,643)(MECOM::ETV6)[VAF0.3]
nuc ish (GOLIM4×2,MECOM×3,MYNN×2)(GOLIM4/MECOM sep MECOM/MYNN)×1[150/200],(ETV6)×2(5′ETV6 sep 3′ETV6)×1[145/200]**Note**: genome mapping and ISH nomenclature may be presented in either order, separated by a period (.), or onseparate lines without a period.

iv. ogm[GRCh38]
t(6;12;21)(q24.3;p13.2;q22.12)(146,851,704~146,853,248;11,869,907~11,870,531;34,923,303~34,925,677)(ETV6::RUNX1)[VAF0.4]Genome mapping analysis of a neoplastic sample showed a three-way translocation between 6q24.3 (between nucleotides 146,851,704 and 146,853,248), 12p13.2 (between nucleotides 11,869,907 and 11,870,531) and 21q22.12 (between nucleotides 34,923,303 and 34,925,677) resulting in fusion of the *ETV6* gene and *RUNX1*. The VAF may be reported in (**[ ]**) or be indicated in the interpretive text of the report.

v. ogm[GRCh38]
7p12.2(50,325,186_50,390,021)×1[0.8],t(9;22)(q34.12;q11.23)(130,840,573~130,841,562;23,246,875~23,249,247)(BCR::ABL1)[VAF0.45]
or
ogm[GRCh38]
del(7)(p12.2p12.2)(50,325,186_50,390,021)[0.8],t(9;22)(q34.12;q11.23)(130,840,573~130,841,562;23,246,875~23,249,247)(BCR::ABL1)[VAF0.45]Genome mapping shows a 65 kb interstitial deletion within band 7p12.2 in approximately 80% of the sample. This deletion includes part of the *IKZF1* gene. The translocation t(9;22) that results in a *BCR*::*ABL1* fusion gene is also present and its VAF should be indicated in the ISCN description, the text of the report or in a table (see Table 11). In the first ISCN description the chromosome 7 deletion is given using the short system (microarray format) and the translocation between chromosomes 9 and 22 is given using the short system (karyotype format). In the alternative description both abnormalities are given using short system (karyotype format). **Note:** genes with intragenic deletions are not included in the ISCN description (see Section 9.3).

Table 11. Example of genome mapping results written in tabular form.

Chromosome / chromosome region/band	Nucleotide coordinates GRCh38	Size, kb	Abnormality type	Reported gene(s)*	Copy number	Proportion of the sample/ VAF	Comment
7p12.2p12.2	50,325,186_50,390,021	65	Loss	*IKZF1*	1	80%	Intragenic deletion
t(9;22) (q34.12;q11.23)	130,840,573~130,841,562; 23,246,875~23,252,247		Translocation	*BCR::ABL1*	1	VAF0.45	Fusion gene

*Note: only those genes known to be of specific diagnostic or prognostic significance are reported.

vi. ogm[GRCh38]
del(6)(q21q21)(106,685,000_108,976,886),t(6;7)(q21;q32.1)(108,979,887~108,982,237;128,310,022~128,312,239)Genome mapping shows an interstitial deletion within 6q21 and a reciprocal translocation between chromosomes 6 and 7. It is unclear whether the deletion is in the same chromosome 6 homologue that is involved in the translocation with chromosome 7.
If the deletion is on the same chromosome 6 homologue near the translocation breakpoint, this would change the ISCN description to der(6) and the abnormalities would be listed **pter** to **qter**.
If the deletion involves the other chromosome 6 homologue then the abnormalities are given in alphabetical order.
Note: when it is uncertain whether abnormalities occur *in cis* or *in trans*, the nomenclature is written as if the abnormalities are *in trans*.

vii. ogm[GRCh38]
t(1;17)(p36.23;p13.3)(8,781,440~8,783,345;2,208,744~2,208,947)(RERE::SMG6)[VAF0.3],del(6)(q12q23.3)(63,771,696_135,674,891)[0.5],del(12)(p13.2)(pter_12,722,843)[0.5]Genome mapping of a neoplastic sample shows a reciprocal translocation between chromosomes 1 and 17 resulting in a *RERE*::*SMG6* fusion gene. The VAF of the *RERE*::*SMG6* fusion gene is 30%. There is an interstitial deletion of 6q in 50% of this neoplastic sample. There is also an apparently terminal deletion of 12p (from 12pter to 12p13.2) including the *ETV6* gene, in 50% of the sample.

viii. ogm[GRCh38]
inv(16)(p13.11q22.1)(15,724,261~15,727,746_67,088,684~67,091,199) or t(16;16)(p13.11;q22.1)(15,724,261~15,727,746;67,088,684~67,091,199)(CBFB::MYH11) [VAF0.35]
or
ogm[GRCh38]
16::16(p13.11::q22.1)(15,724,261~15,727,746::67,088,684~67,091,199)(CBFB::MYH11)[VAF0.35]Genome mapping shows the recurrent inv(16) or t(16;16) in this

neoplastic sample, but the mechanism is not apparent because the technology does not allow the homologous chromosomes 16 to be distinguished. Nomenclature for this special case of either inversion or translocation is provided by use of the **double colon** (**::**), *i.e.*, 16::16, to indicate breakage and rejoining without showing the mechanism.

ix. ogm[GRCh38]
inv(13)(q12.12q14.11)(23,515,291~23,516,483_44,050,358~44,051,942) or
t(13;13)(q12.12;q14.11)(23,515,291~23,516,483;44,050,358~44,051,942)
or
ogm[GRCh38]
13::13(q12.12::q14.11)(23,515,291~23,516,483::44,050,358~44,051,942)Genome mapping shows a paracentric inversion or translocation involving the long arm of chromosome 13, but the mechanism is not apparent because the technology has not allowed the homologous chromosomes 13 to be distinguished. Nomenclature for this special case of either inversion or translocation is provided by use of the **double colon** (**::**) to indicate breakage and rejoining without showing the mechanism.

x. ogm[GRCh38]
inv(18)(q12.1q12.2)(33,122,379~33,123,311_37,636,503~37,640,279)Genome mapping shows an inversion of chromosome 18 for which the chromosomal structure is apparent or is demonstrated by another technique.

xi. 46,XX,–12,+mar.ogm[GRCh38]
der(12)del(12)(p13.1p12.2)(14,574,829_20,872,573)inv(12)(p12.2q21.31)(20,872,784_84,975,818)del(12)(q21.31q23.3)(84,976,892_105,462,170)The karyotype shows a marker chromosome and genome mapping suggests that the marker is an abnormal chromosome 12 resulting from a pericentric inversion of chromosome 12 with deletions at both breakpoints. The derivative chromosome 12 is described in this example using the short system (karyotype format) nomenclature. **Note:** the abnormalities of the der(12) are given **pter** to **qter**.

xii. ogm[GRCh38]
dup(12)(pterp13.2)(pter_11,752,836),der(18)(18pter_18q12.1)(18pter_33,122,379~33,123,311)::(18q12.2_18q12.1)(37,640,279~37,636,503_33,123,311~33,122,379)::(18q12.2::13q22.3_13q13.3)(37,636,504~37,640,279::77,743,263_35,366,781)::(18q12.2_18qter)(37,636,504~37,640,279_18qter)Genome mapping shows an abnormal chromosome 12 with duplication of 12pter to 12p13.2, described in this example using the short system (karyotype format) nomenclature. An abnormal chromosome 18 is described in this example using the detailed system (karyotype format). The abnormal chromosome 18 has an inversion of 18q12.1 to 18q12.2 and an insertion of 13q13.3 to 13q22.2 at the distal 18q12.2 breakpoint. The inserted chromosome 13 segment is in an inverted orientation relative to pter of the recipient chromosome 18.

xiii. ogm[GRCh38] r(8)(p23.1q24.3)(::9,689,003_141,892,587::)Genome mapping shows a ring chromosome 8. Structural chromosome information is known.

xiv. ogm[GRCh38]
8pterp23.1(pter_9,689,003)×1,8::8(p23.1::q24.3)(9,689,564::141,891,598),8q24.3qter(141,892,587_qter)×1Same example as above but without structural information.

xv. ogm[GRCh38] r(18)(p11.31q23)(::3,995,832~3,993,827_77,086,852~77,089,748::)Genome mapping shows a ring chromosome 18. Structural chromosome information is known.

xvi. ogm[GRCh38] 18pterp11.31(pter_3,995,832~3,993,827)×1,18::18(p11.31::q23)(3,995,832~3,993,827::77,086,852~77,089,748),18q23qter(77,086,852~77,089,748_qter)×1Genome mapping shows the same abnormality as the above example but without structural information. The uncertainty of the breakpoints is indicated by the **tilde** (**~**).

9.4.2.6 Inheritance

The parental origin of the abnormality, if known, follows the copy number (**×1**, **×3**, *etc*.). There is no space between the copy number and the abbreviation for inheritance (**dn**, **mat**, **dmat**, **pat**, **dpat**, **inh**) or if the abbreviation for inheritance follows a parenthesis.

i. ogm[GRCh38] Xq25(126,228,413_126,535,347)×0mat
or
ogm[GRCh38] Xq25(126,231,505×1,126,228,413_126,535,347×0,126,537,900×1)matGenome mapping shows interstitial loss of the long arm of the X chromosome at band Xq25 in a male. The size of the fragment containing the hemizygous loss is at least 306.9 kb. The next neighboring proximal nucleotide that does not show a loss is approximately 3 kb away and the next neighboring distal nucleotide that does not show a loss is approximately 2.5 kb away from the deletion. This interstitial deletion is inherited from the mother.

ii. ogm[GRCh38] +der(22)t(11;22)(q23.3;q11.21)(116,696,681;17,400,001)dmatGenome mapping shows a supernumerary derivative chromosome 22 from a t(11;22) that is inherited from the mother who is shown to carry a balanced t(11;22) translocation.

iii. ogm[GRCh38] t(11;22)(q23.3;q11.21)(116,696,681;17,400,001)Genome mapping of the mother of the above example who carries a balanced t(11;22) translocation.

iv. ogm[GRCh38] 11q23.3qter(114,600,001_qter)×1dn,(21)×3dpatGenome mapping shows two abnormalities: a *de novo* apparently terminal deletion of part of the long arm of chromosome 11; and a trisomy of chromosome 21 that is known to be translocation-type trisomy 21 inherited from a previously identified Robertsonian translocation in the father. **Note:** Robertsonian translocations, *e.g.*, der(14;21) are not detectable by genome mapping.

v. ogm[GRCh38] 11q23.3qter(114,600,001_qter)×1dn,(21)×3dnGenome mapping shows two *de novo* abnormalities: an apparently terminal deletion of part of the long arm of chromosome 11 and trisomy 21.

vi. ogm[GRCh38] der(X)ins(X;7)(p21.1;q21.11q22.3)(36,849,611~36,850,248;77,950,039_107,500,419)dmatGenome mapping shows a derivative X chromosome resulting from an insertion of the segment from 7q21.11q22.3 into Xp21.1. On the abnormal X chromosome, band 7q21.11 is closer to Xpter and band 7q22.3 is closer to X

centromere. There are two normal copies of chromosome 7. This is inherited from the balanced ins(X;7) in the mother. The sex chromosome constitution of the offspring is not given.

9.4.2.7 Complex Genomes

The abbreviation (**cx**) for **complex** chromosome rearrangement is used for multiple complex rearrangements across the entire genome or within a region of the genome.

a. For a complex result, the sex chromosomes and autosomes are included in the same parenthesis.

i. ogm (1–22)cxGenome mapping shows multiple complex rearrangements in chromosomes 1 through 22. The sex chromosomes appear normal and are therefore not shown. **Note:** this example is using the abbreviated system (microarray format).

ii. ogm (X,1–22)cxGenome mapping shows multiple complex rearrangements across the entire genome in a female. **Note:** this example is using the abbreviated system (microarray format).

iii. ogm (X,Y,1–22)cxGenome mapping shows multiple complex rearrangements across the entire genome in a male.

iv. ogm[GRCh38] 3p26.3q12.1(61,495_98,386,666)cx[0.5]Genome mapping shows a complex pattern of chromosomal copy number changes in the short arm and proximal long arm of chromosome 3. It is seen in approximately 50% of the sample.

v. ogm[GRCh38] (X,8,12)cx[?],t(12;20)(p13.2;q13.33)(11,930,948;62,644,813)(ETV6::PRPF6)[VAF0.4],(19,20)cx[?]Genome mapping shows complex abnormalities involving chromosomes X, 8, 12, 19 and 20. The proportion of the sample with these abnormalities could not be determined. There is a translocation between chromosomes 12 and 20 that results in the formation of an *ETV6*::*PRPF6* fusion gene at a VAF of 40%.

vi. ogm[GRCh38] der(9)(9pter_9q34.3)(pter_136,394,716)::(5q34_5q35.1)(168,693,009_170,930,711)::(5q22.1_5q31.1)(110,670,173_131,637,622)::(5q35.1_5q35.3)(172,659,120_180,698,801)Genome mapping shows a derivative chromosome 9 in which the 9q34.3 to 9qter segment is replaced by three segments from chromosome 5 that are in a different order but are in the original orientation relative to pter of the der(9).

vii. 46,X,add(X)(p11.4)[16]/45,X[4].arr[GRCh38] Xp22.33p11.4(14,482_39,595,755)×1[0.2],Xp11.4q28(40,920,409_155,232,907)×1[1.0],11q12.3q25(63,578,458_134,868,407)×3[0.8].ogm[GRCh38] der(X)t(X;11)(p11.4;q12.3)(40,920,409;63,578,469)[0.8]/(X)×1[0.2]Karyotype analysis shows two different cell lines in a neoplastic sample: four metaphases with only one X chromosome and sixteen metaphases with one normal X chromosome and another X chromosome with additional material of unknown origin replacing Xpter to Xp11.4. Microarray analysis shows an apparently terminal deletion of the short arm of the X chromosome and gain of 11q12.3 to 11q25. Genome mapping shows that there is a derivative X chromosome from a t(X;11) in 80% of the sample. The der(X)t(X;11)

results in loss of Xpter to Xp11.4 and gain of 11q12.3 to 11qter in 80% of the sample. The remaining 20% of the sample has only one intact X chromosome, *i.e.*, it is apparent that one copy of Xpter to Xp11.4 is present in 20% of the sample and one copy of Xp11.4 to Xqter is present in 100% of the sample. The clones can be discerned in the genome mapping data because the karyotype is known. **Note:** the data are presented in the order in which the analyses are performed. The karyotype result is listed first but the microarray and genome mapping data may be listed in either order. The largest clone is listed first (see Sections 4.5.3 and 9.3).

viii. ogm[GRCh38]
der(3)(18qter_18q22.1)(18qter_64,508,657~64,495,812)::(18q22.1_q22.1)(64,599,393_64,508,657)::(18q21.2_18q21.31)(52,655,298~52,663,250_58,108,577~58,142,571)::(6q24.1_6q22.31)(141,757,829~141,750,150_122,094,992~122,080,291)::(18q12.2_18q21.2)(37,501,271~37,515,201_52,655,298~52,663,250)::(6q24.2_6q24.1)(143,185,339~143,182,042_141,757,829~141,750,150)::(3p14.2_3qter)(61,475,372~61,480,748_qter),der(6)(6pter_6q22.31)(pter_122,080,291~122,094,992)::(18q22.1_18q21.31)(64,508,657~64,495,812_58,142,571~58,108,577)::(3p14.2_3pter)(60,003,285~60,000,939_pter),der(18)(18pter_18q12.2)(pter_37,501,271~37,515,201)::(3p14.2_3p14.2)(61,480,748~61,475,372_60,032,856~60,009,391)::(6q24.2_6qter)(143,182,042~143,185,339_qter)Genome mapping shows complex rearrangements involving chromosomes 3, 6 and 18. Most of the short arm of the derivative chromosome 3 is replaced by rearranged sections of the chromosome 18 long arm (including a duplication within 18q22.1) and part of the chromosome 6 long arm. Part of the long arm of the derivative chromosome 6 is replaced by part of the long arm of chromosome 18 and part of the chromosome 3 short arm. The derivative chromosome 18 distal to q12.2 is replaced by material from the short arm of chromosome 3 and the long arm of chromosome 6. **Note:** for clarity in complex cytogenomic ISCN descriptions the karyotype format is used. Terms such as **dup** and **inv** are not employed in the description of a **derivative** chromosome using the detailed system (karyotype format) nomenclature. Structural changes such as **dup** and **inv**, are apparent from the nucleotide coordinates of the translocated segments that are written as they are oriented **pter** to **qter** on the derivative chromosome. The **pter** to **qter** orientation is determined by the orientation of the segment containing the centromere. A schematic diagram of the rearrangements is shown in Figure 13.

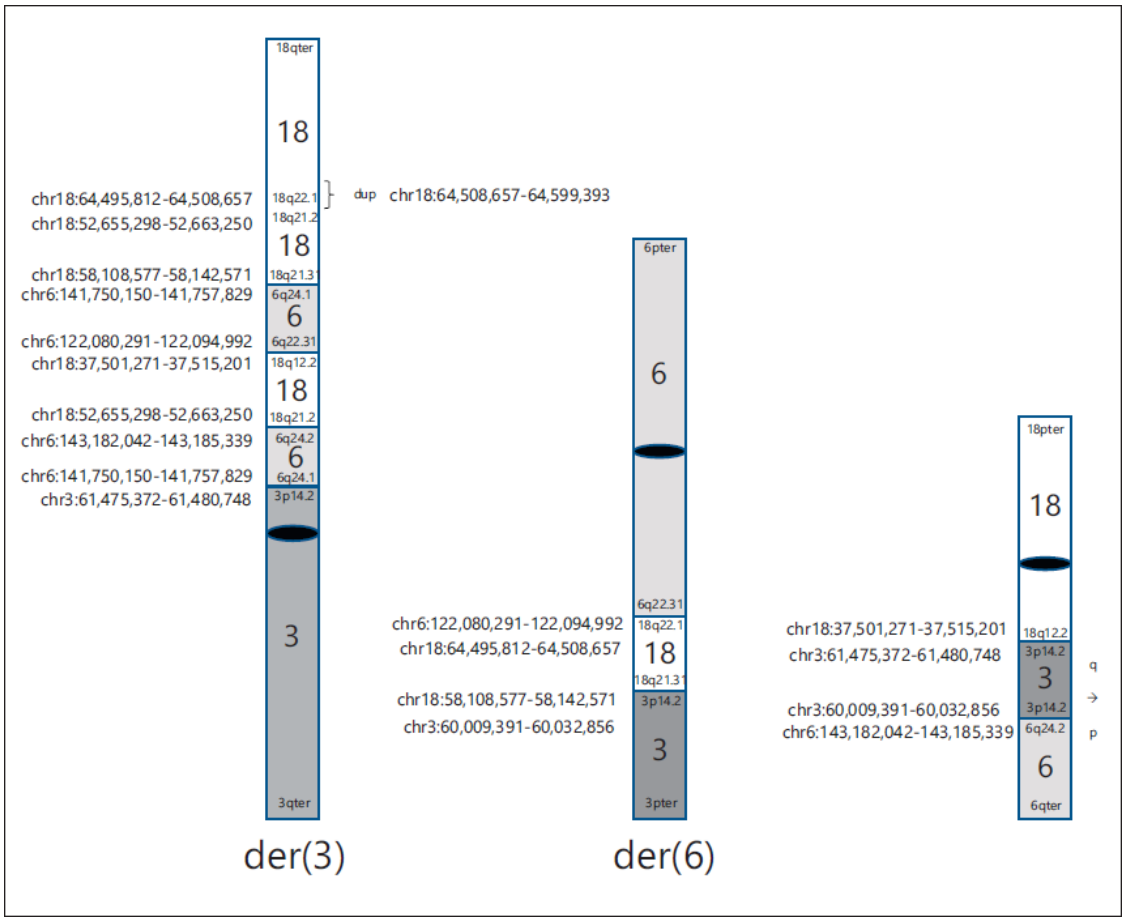


Fig. 13. *Schematic diagram of complex rearrangements of chromosomes 3, 6 and 18 (courtesy of Uwe Heinrich).*

9.4.2.7.1 Chromoanagenesis

Complex genome rearrangements grouped under **chromoanagenesis**, *i.e.*, **chromoanasynthesis** (**cha**), **chromothripsis** (**cth**) and **chromoplexy** (**cpx**), may be challenging to differentiate as multiple overlapping genome instability and repair mechanisms may be present in an individual sample. See Figure 10 for illustrations of these highly complex events that are described below by the simplified nomenclature. **Note:** genome mapping may not always differentiate

between chromothripsis and chromoanasynthesis; in this case, the term **complex** (**cx**) may be used with clarification provided in the interpretation.

9.4.2.7.1.1 Chromothripsis

Chromothripsis (**cth**) is a phenomenon by which multiple rearrangements originate through random shattering and reshuffling of clustered chromosome regions in a single catastrophic event (see Section 8.2.7.2).

i. ogm (2p)cthGenome mapping shows multiple alternating copy number changes in the short arm of chromosome 2 that are consistent with chromothripsis.
ii. ogm (5,8)cth[?]Genome mapping shows chromothripsis in chromosome 5 and chromosome 8. The proportion of the neoplastic sample with chromothripsis could not be determined as indicated by a **question mark** in **square brackets** (**[?]**).
iii. ogm[GRCh38] (5)cth,6q25.1q27(149,100,000_170,899,992)×1,(8)cth
or
ogm[GRCh38] (5)cth,del(6)(q25.1q27)(149,100,000_170,899,992),(8)cthGenome mapping shows chromothripsis of chromosomes 5 and 8 with a concomitant loss of part of the long arm of one chromosome 6 from 6q25.1 to 6q27.
iv. ogm[GRCh38] 2p24.3p21(13,197,725_46,386,298)cth[0.9]Genome mapping shows chromothripsis occurring within the region 2p24.3 to 2p21 in approximately 90% of the neoplastic sample.

9.4.2.7.1.2 Chromoanasynthesis

Chromoanasynthesis (**cha**) is a phenomenon by which multiple combinations of structural variants resulting in copy number changes (commonly duplications) (see Section 8.2.7.3).

i. ogm (3)chaGenome mapping analysis shows multiple changes of copy number, consistent with chromoanasynthesis involving chromosome 3.
ii. ogm[GRCh38] 17p13.3q11.2(1,207,467_28,236,645)cha[?]Genome mapping analysis shows multiple changes of copy number involving most of the short arm of chromosome 17. **Note:** it is not possible to determine the size of the clone with chromothripsis of chromosome 17, so the proportion of the sample bearing this abnormality is given as a **question mark** in **square brackets** (**[?]**).

9.4.2.7.1.3 Chromoplexy

Chromoplexy (**cpx)** is a phenomenon where derivative chromosomes are generated by the chimeric joining of DNA segments from two or more chromosomes. Chromosome reassembly is predicted to occur by c-NHEJ or alternative end joining (Alt-EJ) repair (Zepeda-Mendoza and Morton, 2019) (see Fig. 10).

i. ogm (1,2,3,4)cpxA four-way chromoplexy event between chromosomes 1, 2, 3, and 4 described using the abbreviated system (microarray format) of nomenclature.See

also Section 9.4.2.7 for an example of the detailed system (microarray format) of nomenclature that can also be applied to describe chromoplexy.

9.4.2.8 Multiple Techniques

Where multiple techniques are used, the karyotype is reported first, if performed, and other techniques may be reported in any order, *e.g.*, they may be presented in the order in which they are performed. The ISCN description for each subsequent technique is preceded by a **period** (**.**).

i. 47,XY,+mar dn.ogm[GRCh38] 1p12p11.2(117,596,421_121,013,236)×3Karyotype analysis detected a *de novo* marker. Genome analysis shows a single copy *de novo* gain of the short arm of chromosome 1 from bands 1p12 to 1p11.2, spanning approximately 3.4 Mb, likely identifying the marker chromosome. Genome mapping will not detect the heterochromatin near the centromeres and so the centromeric bands are rarely included in the nomenclature of rings and markers after genome mapping analysis. The centromere is probably included in the aberration and could be confirmed by *in situ* hybridization. An amended result after *in situ* hybridization analysis would be written as given in example ii.

ii. 47,XY,+mar dn.ish der(1)(D1Z1+).ogm[GRCh38] 1p12p11.2(117,596,421_121,013,236)×3Unidentified *de novo* marker chromosome is detected by karyotype analysis and confirmed to be of chromosome 1 origin by *in situ* hybridization. Genome mapping identified gain of a segment of the chromosome 1 short arm from 1p12 to 1p11.2 but did not identify the centromere or the pericentromeric heterochromatin on the chromosome 1 long arm.

10 Region-Specific Assays (RSA)

10.1 Introduction

Region-specific assays (**rsa**) are used to quantify the number of copies or structural rearrangement(s) of a chromosome and/or chromosomal region. They are applicable only to diagnostic tests and encompass several diagnostic technologies, *i.e.*,

- Multiplex ligation-dependent probe amplification (MLPA)
- Quantitative fluorescent PCR (QF-PCR)
- Real-time quantitative PCR (qPCR)
- Non-invasive prenatal diagnosis (NIPD). **Note:** rsa nomenclature **must not** be used for screening technologies, *e.g.*, screening by NIPT (non-invasive prenatal testing)
- Bead-based assays
- Targeted microarrays that are limited to a number of regions that can be reasonably listed in the nomenclature
- Masked or targeted genome mapping
- Targeted chromosome analysis (sometimes referred to as scoring) for a chromosome abnormality where a full karyotype is not performed.

10.2 RSA Nomenclature Specific Rules

a. For general cytogenomic rules that are also applicable to this chapter see Chapter 4.
b. **Region-specific assays** (**rsa**) is a generic nomenclature for targeted assays other than FISH and describes the normal and/or abnormal results for the chromosomes/regions tested.
c. It is essential that the written report includes details of the specific targeted RSA cytogenomic technique undertaken as well as the resolution and limitations of the test.
d. The **rsa** nomenclature can be written in the abbreviated, short, detailed or extended systems depending on whether the results are given in a karyotype format or the microarray format (see Section 4.7). The karyotype format uses the short and detailed systems while the microarray format uses the abbreviated, short and extended systems.

- The abbreviated system (karyotype and microarray formats) describes the abnormality/abnormalities with no breakpoints and no nucleotides, *e.g.*, rsa (21)×3 or rsa (X,Y)×1,(13,18)×2,(21)×3 (Section 10.3.2) or rsa (5,7)×2[20] (Section 10.3.1).
- The short system includes the breakpoints (karyotype format) or nucleotides (microarray format) involved in the abnormality, *e.g.*, rsa (21)×1,i(21)(q10)×1 (see Section 10.3.3) and rsa[GRCh38] 22q11.21 (18,891,533_21,111,169)×2

(see Section 10.4.1). In some instances, the use of the short system, and not the abbreviated system, will be essential to give clarity for an unbalanced result.

- The detailed system (karyotype format only) defines each abnormal chromosome in terms of its band composition from pter to qter.
- The extended system (microarray format only) describes the abnormality in detail including the flanking normal nucleotides, without any commas, *e.g.*, rsa[GRCh38] 22q11.21(18889117×2,18891533_21111169×1,21116218×2).

e. With targeted tests, limited chromosomes/regions/loci are analyzed and the normal state for the other chromosomes/regions/loci tested can either be included in the ISCN or the report description. The decision whether to list the normal loci in the assay in the ISCN is at the discretion of the laboratory, although in some instances the inclusion of the normal results adds clarity to the result. If the normal results are not given in the ISCN, then the normal state of the other chromosomes/regions/ loci tested within the assay **MUST** be stated in the report description.

f. Where a manufacturers' kit is used, the kit number and version must be given in either the ISCN (see Sections 10.3.1 and 10.4) or the report text as applicable.

g. The name of the MLPA kit can be used in the ISCN description if the genomic coordinates are not known; however, greater precision is achieved by providing nucleotide numbers. The span of nucleotides is separated by an underscore (see Section 4.4.5). Commas in nucleotide numbers are optional.

h. There is a space after **rsa** or **rsa[GRCh38]** (see Sections 4.4.1 and 4.4.5).

i. The genome build is given when nucleotides are reported (see Section 4.4.5).

j. If the genome build is not given in the nomenclature, *e.g.*, for chromosome aneuploidy, the reference sequence or kit is given in the written description of the report.

k. To indicate a mixed cell population

- For targeted chromosome analysis, the absolute cell numbers for each cell line are given in **square brackets** (**[ ]**).
- For cytogenomic techniques, the proportion of cells within the sample with the abnormality can be estimated and included in **square brackets** (**[ ]**) following the copy number. If the proportion of abnormal cells cannot be estimated, the copy number range may be given (see Section 4.5.3).
- The abbreviation **mos** is NOT used in rsa nomenclature.

l. Results are listed in ascending numerical chromosome order, with the sex chromosomes listed first (see Section 4.3).

m. Chromosomes with the same copy number can be included in the same parentheses but the chromosome order rule must be followed (see Section 4.3 for chromosome order rules).

n. Loci and genes are listed in chromosomal order and, within a chromosome, from **pter** to **qter** (see Section 4.3).

o. Some of the ISCN examples in this chapter do not represent observed data but are provided to demonstrate the nomenclature principles.

10.2.1 Targeted Chromosome Analysis

a. The abbreviated system (karyotype format) describes only the targeted chromosome(s) complement.

b. The number of chromosomes is indicated by a **multiplication** (×) sign followed by the number of copies present.
c. The short system describes the structural abnormality including the breakpoints. The inclusion of the non-rearranged homologues is optional unless there is loss or gain when their inclusion is essential, *i.e.*,

- For *balanced structural chromosome complements* where the homologues are apparently normal the abbreviated or short system can be used. However, if the non-rearranged homologue is lost, then the short system of the nomenclature is used with the number of normal homologues described as zero, *e.g.*, rsa (21)×0,i(21)(q10)×1 and rsa (8)×1,t(8;21)(q22;q22)×1,(21)×0[20] when there is no normal chromosome 21.
- *Unbalanced chromosome complements* are always described in the short system where the normal chromosomes are also listed in the ISCN, *e.g.*, rsa (21)×1,i(21)(q10)×1 (see Section 10.3.3).

d. When a targeted screen is undertaken in combination with a full karyotype, the inclusion of the **rsa** ISCN description is optional if it does not add any additional information, *i.e.*, If the karyotype is 46,XX,t(9;22)(q34;q11.2)[4]/46,XX[18], and it is optional to include rsa t(9;22)(q34;q11.2)×1[30]/(9,22)×2[10].
e. Absolute cell numbers are given in **square brackets** (**[ ]**) in targeted chromosome analysis for neoplastic samples and to indicate mixed cell populations in both constitutional and neoplastic samples.

10.2.2 Fusion Genes

a. Evidence of a fusion or juxtaposition of genes is indicated by a **double colon** (**::**), *e.g.*, *BCR*::*ABL1*.
b. In gene fusions, only the chimeric genes or those that alter the regulation of the gene is given in the ISCN description, *e.g.*, *BCR*::*ABL1* or *IGH*::*CCND1*, respectively. The reciprocal gene fusion is only given if both products are known to be oncogenic/expressed.
c. If two or more different gene fusions are present, they are listed in the chromosomal order of the clinically relevant fusion gene.
d. When it is unknown which is the active oncogenic transcript, then the fusion is described according to the numerical order of the chromosomes, and from **pter** to **qter**.

10.2.3 Methylation Specific Analysis

a. Methylation specific MLPA (MS-MLPA) can detect copy number variation as well as the methylation pattern.
b. Both the copy number and methylation status must be given in the ISCN.
c. The technique abbreviation used is **rsa-ms**.
d. A normal methylation pattern is represented by **met**.
e. If the methylation pattern is abnormal, then **lom** is used to describe the absence of methylation and **gom** for gain of methylation.
f. The methylation nomenclature follows HGVS nomenclature (Monk et al., 2018) unless this contradicts the generic ISCN rules (see notes below under 10.2.3).

g. The copy number is indicated by a **multiplication** (×) sign followed by the number of copies present (×), *e.g.*, ×1 or ×2.
h. The **pipe character** (|) is used to indicate that there is a modification of the sequence not a sequence variant, *i.e.*, indicates a change of methylation status, *e.g.*, rsa-ms 11p15.5p15.4(ME030)×2(KCNQ1OT1:TSS-DMR)|lom,(H19/IGF2:IG-DMR)met
i. If the copy number and methylation specific region are within the same breakpoint, then the breakpoint is not repeated for the methylation part of the ISCN, *e.g.*, rsa-ms[GRCh38] 11p15.5(1,995,605_2,004,583)×3(KCNQ1OT1:TSS-DMR)met,(H19/IGF2:IG-DMR)|gom
j. Different CpG positions within the imprinted differentially methylated regions (DMRs) may be examined and the level of mosaicism may be different for each CpG position. If all the CpG islands show loss of methylation, it is optional whether the level of mosaicism is reported. If the mosaicism is reported, then it is recommended that the methylation status is described as an average percentage of all CpGs analyzed, *i.e.*, [0.25]. **Note:** in HGVS **curled parentheses** (**{}**), *i.e.*, are used for the average percentage, and **square brackets** (**[ ]**) are used for alleles.
k. If only some of the individual CpG islands show loss of methylation, then these may be specified individually (see Monk et al., 2018) at the discretion of the laboratory.
l. If multiple methylation alleles are examined, these are separated by a comma. **Note:** in HGVS a **semicolon** (**;**) is used for different alleles and a **comma** (**,**) is used to separate different transcripts of the same allele (see Monk et al., 2018).

10.3 RSA Nomenclature for Aneuploidy and Targeted Cytogenomic Analysis

10.3.1 Normal Results

i. 46,XX.rsa (X,13,18,21)×2Apparently normal female karyotype and normal copy number of chromosomes X, 13, 18 and 21 using a region-specific assay such as QF-PCR or MLPA.
ii. rsa (X,Y)×1,(13,18,21)×2Normal copy number of chromosomes X, Y, 13, 18 and 21 in a male using a region-specific assay such as QF-PCR or MLPA.
iii. rsa (11,22)×2Targeted microarray or targeted chromosome analysis for chromosomes 11 and 22 to exclude an unbalanced translocation in the offspring where one of the parents carries a t(11;22)(q23.3;q11.2) or alternatively for targeted chromosome analysis to exclude a balanced translocation in a family member.
iv. rsa (5,7)×2[20]Targeted chromosome analysis for chromosomes 5 and 7 in a neoplastic sample in 20 metaphases.
v. rsa (14,21)×2Targeted chromosome analysis for chromosomes 14 and 21 to exclude the presence of a der(14;21)(q10;q10).
vi. rsa (15,17)×2[30]Targeted chromosome analysis in a neoplastic sample for chromosomes 15 and 17 did not detect the presence of a t(15;17)(q22;q21.1) in 30 metaphases.
vii. 46,XX,t(9;22)(q34;q11.2)[2]/46,XX[18].rsa (9,22)×2[30]A low-level t(9;22) neoplastic clone detected in 2 out of 50 metaphases on combined full karyotyping and scoring. The targeted chromosome analysis (scoring) for only chromosomes 9 and 22 did not detect a t(9;22)(q34;q11.2) in 30 metaphases. The text of the report gives the limitations of each analysis.

viii. rsa (X,1-22)(P070-B3)×2Targeted MLPA analysis for all the subtelomere probes using the kit P070 version B3 showed a normal copy number in a female.

ix. rsa (X,Y)(P070-B3)×1,(1-22)(P070-B3)×2Targeted MLPA analysis for all subtelomere probes using the kit P070 version B3 showed a normal copy number in a male.

10.3.2 Aneuploidy

For the abbreviated system (karyotype and microarray formats) of the rsa nomenclature, the abnormal aneuploid nomenclature is the same for MLPA, QF-PCR, targeted microarray, or targeted chromosome analysis.

i. rsa (21)×3*Targeted chromosome* analysis using the karyotype format confirms a non-disjunction trisomy 21 (*i.e.*, excludes a Robertsonian translocation) following a positive trisomy 21 result on QF-PCR.*QF-PCR & MLPA* analysis using the microarray format shows an abnormal copy number result for chromosome 21 indicating a gain for the chromosome (trisomy). The normal disomic state for the other chromosomes tested must be given in the written description of the report. **Note:** for clarity, the apparently normal disomic states for the sex chromosomes (male) and chromosomes 13 and 18, which were also tested, may be included in the abbreviated system nomenclature, *i.e.*, rsa (X,Y)×1,(13,18)×2,(21)×3 or rsa (X,13,18)×2,(21)×3.*Targeted microarray* analysis using the microarray format confirms trisomy 21 following a positive trisomy 21 result on NIPT; no other chromosome profiles were analyzed. **Note:** the abnormal nucleotides may also be included in the short system (microarray format) nomenclature, *i.e.*, rsa[GRCh38] 21q11.2q22.3(13,531,865_46,914,745)×3. If all chromosomes had been analyzed, the nomenclature would be arr (21)×3 (abbreviated system, micorarray format) or arr[GRCh38] 21q11.2q22.3(13,531,865_46,914,745)×3 (short system, microarray format) (see Section 8.2.2).

ii. rsa (13)×3*Targeted chromosome* analysis using the karyotype format confirms a non-disjunction trisomy 13 (*i.e.*, excludes a Robertsonian translocation) following a positive trisomy 13 result on QF-PCR.*QF-PCR & MLPA* analysis using the microarray format shows an abnormal copy number result for chromosome 13 indicating a gain for the chromosome (trisomy). The normal disomic state for the other chromosomes tested must be given in the written description of the report. **Note:** for clarity, the apparently normal disomic states for the sex chromosomes (female) and chromosomes 18 and 21, which were also tested, may be included in the abbreviated system nomenclature, *i.e.*, rsa (X)×2,(13)×3,(18,21)×2.*Targeted microarray* analysis using the microarray format confirms trisomy 13 following a positive trisomy 13 result on NIPT; no other chromosome profiles were analyzed. **Note:** the abnormal nucleotides may also be included using the short system (microarray format) in the nomenclature, *i.e.*, rsa[GRCh38] 13q12.11q34 (19,606,120_114,341,521)×3. If all chromosomes had been analyzed the nomenclature would be arr (13)×3 or using the short system (microarray format) arr[GRCh38] 13q12.11q34 (19,606,120_114,341,521)×3.

iii. rsa (X)×2,(Y)×1,(13)×2,(18)×3,(21)×2
or
rsa (X)×2,(Y)×1,(18)×3Abnormal copy number result for chromosomes X and 18 showing an additional X chromosome in a male and gain of chromosome 18 (trisomy) using a region-specific assay, *e.g.*, QF-PCR or MLPA. **Note:** if the normal disomic state for chromosomes 13 and 21 is not included in the ISCN, then it **must** be stated in the written description of the report.

iv. rsa (X)×2,(Y)×1,(13,18)×2,(21)×3
or
rsa (X)×2,(Y)×1,(21)×3Abnormal copy number result showing an additional X chromosome in a male and gain of chromosome 21 (trisomy) using a region-specific assay, *e.g.*, QF-PCR or MLPA. **Note:** if the normal disomic state for chromosomes 13 and 18 is not included in the ISCN, then it **must** be stated in the written description of the report.

v. rsa (X)×1,(13,18,21)×2
or
rsa (X)×1Abnormal copy number showing a loss of one sex chromosome, consistent with monosomy X using a region-specific assay, *e.g.*, QF-PCR. **Note:** for clarity, the normal disomic states for chromosomes 13, 18, and 21 may be included in the nomenclature. Also in a prenatal sample it is optional whether (Y)×0 is included. **Note:** if the normal disomic state is not included in the ISCN, then it **must** be stated in the written description of the report.

vi. rsa (X)×2,(Y)×1,(13,18,21)×3Abnormal copy number showing an additional X chromosome plus gain of chromosomes 13, 18, and 21 (three copies) in a male using a region-specific assay, *e.g.*, QF-PCR. This result may be indicative of triploidy.

vii. rsa (21)×1[0.5]
or
rsa 21q11.2q22.3(13,531,865_46,914,745)×1[0.5]Targeted microarray analysis for chromosome 21 showing mosaic loss of this chromosome following an inconclusive QF-PCR result for chromosome 21. No other chromosome profiles were analyzed.

viii. rsa (X)×2,(Y)×1,(21)×3Targeted chromosome analysis for the sex complement and chromosome 21 following an abnormal NIPT test that showed an XXY sex complement and trisomy 21. A Robertsonian translocation involving chromosome 21 was excluded. No other chromosomes were analyzed.

ix. rsa (21)×3[25]/(21)×2[5]Targeted chromosome analysis for chromosome 21 showing mosaicism for trisomy 21. No other chromosomes were analyzed. **Note:** if the largest cell line was (21)×2[25], the normal cells are listed last, *i.e.*, rsa (21)×3[5]/(21)×2[25].

x. rsa (X,13,18)×2,(21)×2∼3Abnormal copy number result for chromosome 21 showing two to three copies for the chromosome 21 (mosaic trisomy) in a female using a region-specific assay, *e.g.*, QF-PCR or MLPA. For chromosomes X, 13 and 18 a normal disomic state is evident. **Note:** if the ISCN is written as rsa (21)×2∼3, then the normal disomic results for chromosomes X, 13 and 21 must be stated in the written text of the report.

xi. rsa (X,13)×2,(18)×3[0.6],(21)×2
or
rsa (18)×3[0.6]Abnormal copy number result for chromosome 18 showing

mosaicism for chromosome 18 (mosaic trisomy) in a female. Approximately 60% of the cells have this gain using a region-specific assay, *e.g.*, QF-PCR or MLPA. For chromosomes X, 13 and 21 a normal disomic state is evident. **Note:** if the ISCN is written as rsa (18)×3[0.6] then the normal disomic results for chromosomes X, 13 and 21 must be stated in the written text of the report.

xii. rsa (X,13,18,21)hmzAbnormal copy number for chromosomes X, 13, 18 and 21 using a region-specific assay, *e.g.*, QF-PCR or MLPA, consistent with a diploid mole where all signals are homozygous and copy number cannot be determined. **Note: pat** cannot be added as the region-specific assay does not prove this.

xiii. rsa (X,Y)×1,(13,18,21)×2htzAbnormal result for chromosomes X, Y, 13, 18 and 21 showing heterodisomy using a region-specific assay, *e.g.*, QF-PCR or MLPA, consistent with a male hydatidiform mole (complete mole) resulting from two different sperm.

10.3.3 Abnormal Structural

i. rsa der(14;21)(q10;q10)×1Targeted chromosome analysis for a der(14;21)(q10;q10) showed a balanced der(14;21) carrier result in the parent of a trisomy 21 child. It is optional whether the normal chromosomes 14 and 21 are listed, *i.e.*, rsa (14)×1,der(14;21)(q10;q10)×1,(21)×1.

ii. rsa (14)×1,der(14;21)(q10;q10)×1,(21)×2Targeted chromosome analysis for a der(14;21)(q10;q10) showed trisomy 21 with a der(14;21). The two normal copies of chromosome 21 **must** be listed for full comprehension of the unbalanced result.

iii. rsa (21)×0,i(21)(q10)×1Targeted chromosome analysis for chromosome 21. The lack of a normal chromosome 21 **must** be listed for full comprehension of this balanced result.

iv. rsa (21)×1,i(21)(q10)×1Targeted chromosome analysis for chromosome 21. Trisomy 21 with an isochromosome 21. The normal chromosome 21 **must** be listed for full comprehension of the unbalanced result.

v. rsa inv(8)(p22q12.1)×1Targeted chromosome analysis of parental blood for an inv(8)(p22q12.1) seen in the fetus.

vi. rsa t(9;22)(q34;q11.2)×1[10]/(9,22)×2[20]Targeted chromosome analysis for a t(9;22)(q34;q11.2) in a neoplastic sample. The cell numbers are given for neoplastic samples.

vii. rsa t(6;16)(p22.1;q22.1)×1matTargeted chromosome analysis for a t(6;16)(p22.1;q22.1). As the t(6;16) is known to be inherited from the mother **mat** is included.

10.4 RSA Nomenclature for Investigation of Partial Gain or Loss

10.4.1 Normal Results

i. rsa (kit name with version)×2A normal result for all probes within the MLPA kit. The name of the kit can be inserted within the parentheses when all the probes are apparently normal.

ii. rsa 22q11.2(kit name with version or nucleotides)×2A normal result for a specific probe using a targeted analysis, *e.g.*, MLPA or targeted microarray.

iii. rsa (22q11.2)×2Targeted microarray analysis specifically for 22q11.2.
iv. rsa[GRCh38] 22q11.21(18,891,533_21,111,169)×2Targeted microarray analysis shows normal copy number for the 22q11.2 deletion syndrome critical region.

10.4.2 Abnormal Results

i. rsa 22q11.2(kit name with version)×1Abnormal copy number result showing a loss of 22q11.2 using an MLPA kit. The name of the kit can be inserted in the parentheses.
ii. rsa (22q11.2)×1
or
rsa[GRCh38] 22q11.21(18,891,533_21,111,169)×1
or
rsa[GRCh38] 22q11.21(18889117×2,18891533_21111169×1,21116218×2)Targeted microarray analysis specifically for the 22q11.2 deletion syndrome region showing a loss of one copy. No other regions within chromosome 22 were analyzed. The three alternatives are given for the abbreviated, short, and extended systems (microarray format).
iii. rsa[GRCh38] Xp21.1(32,448,538_32,472,228)×1
or
rsa[GRCh38] Xp21.1(32441314×2,32448538_32472228×1,32484970×2)Abnormal copy number result showing loss within the *DMD* gene by targeted microarray in a female. The extended system (microarray format) nomenclature shows that the next neighboring nucleotides that do not show a loss are 7,224 and 12,742 nucleotides away from the alteration.
iv. rsa[GRCh38] Xp21.2p21.1(31,037,731_33,457,670)×1Relative haplotype dosage using NIPD showed an abnormal copy number result for Xp21.2 to Xp21.1 involving a 2.4 Mb loss within the *DMD* gene.
v. rsa[GRCh38] 1p36.33p36.32(849,466_2,432,509)×1Targeted microarray analysis showed a single copy loss of the short arm of chromosome 1 at 1p36.33 to 1p36.32.or rsa 1p36.33(P070-B3)×1Targeted MLPA (kit P070-B3) showed a single copy loss of the short arm of chromosome 1 at 1p36.33. The kit number is given as the nucleotide coordinates are not known.
vi. rsa 20q13.3(P070-B3)×1,22q13.3(P070-B3)×1Targeted MLPA (kit P070-B3) showed a subtelomeric loss of both 20q13.3 and 22q13.3. The kit number is given as the nucleotide coordinates are not known.
vii. arr[GRCh38] 8p23.1(8,479,797_11,897,580)×1.rsa[GRCh38] 8p23.1(11,676,959_11,760,002)×1
or the ISCN can be listed on separate lines without the **period (.)**arr[GRCh38] 8p23.1(8,479,797_11,897,580)×1
rsa[GRCh38] 8p23.1(11,676,959_11,760,002)×1Microarray analysis shows an interstitial deletion of 8p at subband 8p23.1. A region-specific assay, *e.g.*, PCR, targeting the *GATA4* gene confirmed loss of this region but could not further delineate the extent of the 8p deletion.
viii. rsa[GRCh38] 4q32.2q35.1(163,146,681_183,022,312)×1Abnormal copy number result for 4q32.2 to 4q35.1 showing a single copy loss using a region-specific assay, *e.g.*, targeted microarray.

ix. rsa 13q14.2(RB1,DLEU2)×1,13q34(LAMP1)×3Abnormal result in a neoplastic sample showing a loss of the *RB1* and *DLEU2* genes and gain of the *LAMP1* gene using a region-specific assay such as MLPA (P377-A3). Genes are listed from **pter** to **qter**.

x. rsa 13q14.2(RB1×1,DLEU2×3),13q34(LAMP1)×2Abnormal result in a neoplastic sample showing a loss of the *RB1* gene plus gain of *DLEU2* gene using a region-specific assay such as MLPA kit (P377-A3). The *LAMP1* result is normal. Loci and genes are listed from **pter** to **qter** within the same chromosome.

xi. rsa 13q14.2(D13S319)×1,13q34(LAMP1)×1,17p13.1(TP53)×1Abnormal result in a neoplastic sample showing a loss of the marker D13S319 plus the *LAMP1* gene and loss of the *TP53* gene using a region-specific assay such as MLPA kit (P377-A3). Loci and genes are listed in chromosomal order.

xii. rsa 15q12(GABRB3)×1,16p11.2(LAT)×3Abnormal copy number result showing a loss of the *GABRB3* gene and gain of the *LAT* gene using a region-specific assay such as MLPA kits (P036-E3 and P070-B3).

xiii. rsa 15q11.2(UBE3A)×1,15q12(GABRB3)×3Abnormal copy number result showing a loss of the *UBE3A* gene and a gain of the *GABRB3* gene and using a region-specific assay such as MLPA kit (P336-B1).

xiv. rsa 22q11.2(P250-B2)×1Targeted MLPA kit (P250-B2) showed an interstitial loss of 22q11.2.

xv. rsa 22q11.21(HIRA)×1matAbnormal copy number result showing interstitial loss of 22q11.21, inherited from the mother, using a region-specific assay targeting the *HIRA* gene such as targeted microarray or MLPA kit (P250-B2).

xvi. rsa 22q11.21(MICAL3x1,HIRAx1,MED15×2,HIC2×1),22q13.33(ARSA)×1Abnormal copy number result showing a loss within 22q11.21 and 22q13.33 using a region-specific assay such as an MLPA-HD kit. Genes *MICAL3*, *HIRA*, *HIC2*, and *ARSA* show a loss. *MED15* has a normal copy number. The genes are listed from **pter** to **qter** within the same chromosome region according to the genome build. The normal copy number for *MED15* is given as this clarifies the extent of the abnormality.

xvii. rsa 22q11.21(MICAL3,HIRA,MED15,HIC2)×1,22q13.33(ARSA)×1Abnormal copy number result showing two separate losses within 22q11.21 and 22q13.33 using a region-specific assay such as an MLPA-HD kit. Genes *MICAL3*, *HIRA*, *MED15*, *HIC2* and *ARSA* show a loss. The genes are listed from **pter** to **qter** within the same chromosome region.

xviii. rsa 22q11.21(CLDN5,GP1BB)×1,22q11.21(SNAP29,PPIL2)×2,22q11.22q11.23(RTDR1)×1Abnormal copy number result showing a partial loss within 22q11 using a region-specific assay targeting several loci such as an MLPA-HD kit. The proximal (*CLDN5* and *GP1BB*) and distal (*RTDR1*) regions genes are only deleted. *SNAP29* and *PPIL2* have a normal copy number.

10.5 RSA Nomenclature for Balanced Translocations or Fusion Genes

10.5.1 Normal Results

i. rsa (FIP1L1,CHIC2,PDGFRA,PDGFRB,PCM1,FGFR1,JAK2,ETV6)×2A normal result using genome mapping as a region-specific analysis for a panel of genes that are disrupted in myeloid and lymphoid neoplasia with eosinophilia. There is no *ETV6*::*PDGFRB* fusion.

ii. rsa (ABL1,BCR)×2Normal result using a region-specific assay (*e.g.*, targeted sequencing) that shows no evidence of a *BCR*::*ABL1* fusion or juxtaposition.

10.5.2 Abnormal Results

i. rsa (BCR::ABL1)×1Abnormal result using a region-specific assay (*e.g.*, targeted sequencing) that shows evidence of a *BCR*::*ABL1* fusion or juxtaposition. Only the active oncogenic gene fusion is given in the ISCN (see Section 10.2.2).

ii. rsa (IGH::MMSET)×1[0.45],(IGH::FGFR3)×1[0.45]Abnormal result using a region-specific assay (*e.g.*, targeted sequencing) that shows evidence of a fusion or juxtaposition of *IGH* and *MMSET* in addition to a fusion between *IGH* and *FGFR3* in a myeloma. The *IGH*::*MMSET* rearrangement is present in 45% of the sample. Both rearrangements are given in the nomenclature as both have altered regulation.

iii. rsa (BCR::ABL1)×2[0.9]Abnormal result using a region-specific assay (*e.g.*, targeted sequencing) that shows evidence of a fusion or juxtaposition of *ABL1* and *BCR*. There are two copies of the *BCR*::*ABL1* fusion indicating gain of this region. The *BCR*::*ABL1* rearrangement is present in 90% of the sample. **Note:** the *ABL1*::*BCR* reciprocal chimeric gene is not reported in the nomenclature as it is known to lack clinical significance.

iv. rsa (ETV6::PDGFRB)×1[0.30]An abnormal result using genome mapping as a region-specific analysis (*e.g.*, targeted sequencing) showing an *ETV6*::*PDGFRB* fusion or juxtaposition in 30% of the DNA sample. No other fusions or abnormalities for all other regions analyzed. **Note:** the *PDGFRB*::*ETV6* reciprocal chimeric gene is not reported in the nomenclature as it is known to lack clinical significance.

v. rsa (KMT2A::AFF1)×1[0.75]Abnormal result using a region-specific assay (*e.g.*, targeted sequencing) that shows evidence of a fusion or juxtaposition of *KMT2A* and *AFF1* in a pediatric ALL in 75% of the DNA sample.

vi. arr[GRCh38] (8)×3,9q34.12(130,700,664_130,806,532)×1.rsa (CBFB::MYH11)×1,(BCR::ABL1)×1Abnormal microarray result showing a gain of chromosome 8 and loss within chromosome band 9q34.12 involving nucleotides 130,700,664 to 130,806,532. In addition, evidence of two fusions or juxtapositions were identified (*CBFB*::*MYH11* and *BCR*::*ABL1*) with region-specific assay (*e.g.*, targeted sequencing). **Note:** the ISCN band 9q34.1 is given in more detail in GRCh38, *i.e.*, 9q34.12 (see Section 2.4). The *CBFB*::*MYH11* fusion gene is listed first as the fusion is on chromosome 16 while the active fusion gene for *BCR*::*ABL1* is located on chromosome 22.

10.6 Repeat Expansion and Contraction Disorders

10.6.1 Normal Results

i. rsa (4q35)×2Targeted genome mapping showed no abnormality of the 4q35 region which encompasses the *FSHD1* gene.

10.6.2 Abnormal Results

i. rsa del(4)(q35)(D4Z4)×5,4qATargeted genome mapping of a patient with a family history of FSH Muscular Dystrophy showing a reduced number (<10) of repeats at D4Z4 and the permissive 4qA allele.
ii. rsa del(4)(q35)(D4Z4)×4[?],4qATargeted genome mapping analysis of a patient with a family history of FSH Muscular Dystrophy showing a mosaic deletion, with a reduced number (<10) of D4Z4 repeats on the permissive 4qA allele. The proportion of the sample with this deletion could not be determined as indicated by the **question mark** in **square brackets** (**[?]**)
iii. rsa Xq27.3(FMR1-CGG)×~550Targeted genome mapping of a patient with a family history of Fragile X syndrome, showing an expansion of CGG repeats in the 5′ untranslated region of the *FMR1* gene on the X chromosome, with an estimate of 550 CGG repeats, which is in the full expansion range.
iv. rsa 19q13.32(DMPK-CTG)×~1,000Targeted genome mapping of a patient with a family history of myotonic dystrophy type I, showing an expansion of CTG repeats in the 3′ untranslated region of the *DMPK* gene on chromosome 19, with an estimate of 1,000 CTG repeats, which is in the full expansion range.

10.7 Methylation Disorders

10.7.1 Normal Results

i. rsa-ms (ME034)×2(ME034)metNormal result for the multi locus imprinting kit (ME034) including 6q24.2, 7q32.2, 11p15.5p15.4, 14q32.2, 15q11.2q13.1, 19q13.43 and 20q13.32 imprinted regions.
ii. rsa-ms 7p12.2(ME032)×2(GRB10:alt-TSS-DMR)met,7q32.2(ME032)×2(MEST:alt-TSS-DMR)metNormal copy number and methylation result for 7p12.2 and 7q32.2 using a methylation specific kit (ME032) and a targeted analysis for chromosome 7 imprinting only.
iii. rsa-ms 14q32.2(ME032)×2(MEG3:TSS-DMR)metNormal copy number and methylation result for 14q32.2 using a methylation specific kit (ME032) and a targeted analysis for chromosome 14 imprinting only.
iv. rsa-ms 7p12.2(ME032)×2(GRB10:alt-TSS-DMR)met,7q32.2(ME032)×2(MEST:alt-TSS-DMR)met,14q32.2(ME032)×2(MEG3:TSS-DMR)metNormal copy number and methylation result for 7p12.2, 7q32.2 and 14q32.2 using a methylation specific kit (ME032).
v. rsa-ms 11p15.5p15.4(ME030)×2(KCNQ1OT1:TSS-DMR,H19/IGF2:IG-DMR)metNormal copy number and methylation result for 11p15.5p15.4 using a methylation specific kit (ME030) and a targeted analysis. If the copy number and

methylation specific region are in the same chromosome location, they are not repeated.

vi. rsa-ms 15q11.2q13.1(ME028)×2(MAGEL2:TSS-DMR,SNURF:TSS-DMR)metNormal copy number and methylation result for 15q11.2q13.1 region using a methylation specific kit (ME028) including *MAGEL2* and *SNRPN* differentially methylated regions.

10.7.2 Abnormal Results

i. rsa-ms 11p15.5p15.4(ME030)×2(KCNQ1OT1:TSS-DMR)met,(H19/IGF2:IG-DMR)|gomAbnormal result using a methylation region-specific assay (ME030) that shows two copies of the 11p15.5p15.4 region and gain of methylation in the H19 DMR (differential methylation of imprinting control regions) that is consistent with Beckwith-Wiedemann syndrome. It is optional whether the level of mosaicism is given for *H19* DMR, *e.g.*, rsa-ms 11p15.5p15.4(ME030)×2(KCNQ1OT1:TSS-DMR)met,(H19/IGF2:IG-DMR)|gom[0.5].

ii. rsa-ms 11p15.5p15.4(ME030)×2(KCNQ1OT1:TSS-DMR)|lom,(H19/IGF2:IG-DMR)metAbnormal result using a methylation region-specific assay (ME030) that shows two copies of the 11p15.5p15.4 region and loss of methylation in the *KCNQ1OT1* DMR (differential methylation of imprinting control regions), which is consistent with Beckwith-Wiedemann syndrome. It is optional whether the level of mosaicism is given for *KCNQ1OT1* DMR, *e.g.*, rsa-ms 11p15.5p15.4(ME030)×2(KCNQ1OT1:TSS-DMR)|lom[0.6](H19/IGF2:IG-DMR)met

iii. rsa-ms 11p15.5p15.4(ME030)×2(KCNQ1OT1:TSS-DMR)|lom,(H19/IGF2:IG-DMR)|gomAbnormal result using a methylation region-specific assay (ME030) that shows two copies of the 11p15.5p15.4 region and loss of methylation in the *KCNQ1OT1* DMR and gain of methylation in the *H19* DMR that is consistent with Beckwith-Wiedemann syndrome. It is optional whether the level of mosaicism is given for *H19/IGF2:IG*-DMR and *KCNQ1OT1:TSS*-DMR, *e.g.*, rsa-ms 11p15.5p15.4(ME030)×2(H19/IGF2:IG-DMR)|gom[0.5],(KCNQ1OT1:TSS-DMR)|lom[0.4].

iv. rsa-ms[GRCh38] 11p15.5(1,995,605_2,004,583)×3(KCNQ1OT1:TSS-DMR)met,(H19/IGF2:IG-DMR)|gomAbnormal result using a methylation region-specific assay (ME030) that shows three copies of *H19* in the 11p15.5 region (duplication) between nucleotides 1,995,605 and 2,004,583. The methylation pattern shows a gain of methylation for *H19* DMR that is consistent with Beckwith-Wiedemann syndrome through a possible paternal duplication of 11p15.5.

v. rsa-ms[GRCh38] 15q11.2q13.1(23,566,578_28,032,024)×1(MAGEL2:TSS-DMR,SNURF:TSS-DMR)|lom
or
rsa-ms[GRCh38] 15q11.2q13.1(23,566,578_28,032,024)×1(SNURF:TSS-DMR)|lomAbnormal result using a methylation region-specific assay (ME028) that shows one copy of the *MKRN3*, *MAGEL2*, *NDN*, *SNRPN*, *UBE3A*, *ATP10A*, *GABRB3*, *OCA2* genes in the 15q11.2q13.1 region (between nucleotides 23,566,578 and 28,032,024), with

absence of methylation of *MAGEL2* and *SNRPN* CpG islands, which is consistent with Angelman syndrome.

vi. rsa-ms 15q11.2q13.1(ME028)×2(MAGEL2:TSS-DMR,SNURF:TSS-DMR)|gom or
rsa-ms 15q11.2q13.1(ME028)×2(SNURF:TSS-DMR)|gomAbnormal result using a methylation region-specific assay (ME028) that shows two copies of all targeted genes in the 15q11.2q13.1 region, with both alleles of *MAGEL2* and *SNRPN* methylated. There is no normal paternal methylation pattern for 15q11.2q13.1. This is consistent with Prader-Willi syndrome.

vii. rsa-ms 15q11.2q13.1(ME028)×2(MAGEL2:TSS-DMR,SNURF:TSS-DMR)|lom or
rsa-ms 15q11.2q13.1(ME028)×2(SNURF:TSS-DMR)|lomAbnormal result using a methylation region-specific assay (ME028) that shows two copies for all targeted genes. Both alleles of *MAGEL2* and *SNRPN* are unmethylated, *i.e.*, there is no normal maternal methylation pattern for 15q11.2q13.1. This is consistent with Angelman syndrome.

viii. rsa-ms 7p12.2(ME032)×2(GRB10:alt-TSS-DMR)|gom,7q32.2(ME032)×2(MEST:alt-TSS-DMR)|gomAbnormal result using a methylation region-specific assay (ME032) that shows two methylated copies of the 7p12.2 and 7q32.2 regions (maternal uniparental disomy or an abnormal methylation pattern on the paternal allele), consistent with Silver-Russell syndrome. Targeted analysis of MEG3:TSS-DMR on chromosome 14 was not analyzed with the (ME032) kit and therefore is not included in the ISCN.

ix. rsa-ms 7p12.2(ME032)×2(GRB10:alt-TSS-DMR)|gom,7q32.2(ME032)×2(MEST:alt-TSS-DMR)|gom,14q32.2(ME032)x2(MEG3:TSS-DMR)metAbnormal result using a methylation region-specific assay (ME032) that shows two methylated copies of the 7p12.2 and 7q32.2 regions (maternal uniparental disomy or an abnormal methylation pattern on the paternal allele), consistent with Silver-Russell syndrome. Normal methylation pattern for chromosome 14.

x. rsa-ms 11p15.5(ME034)×2(H19/IGF2:IG-DMR)|lom,14q32.2(ME034)×2(MEG3:TSS-DMR)|lomAbnormal result using a multi-locus methylation region-specific assay (ME034) that shows normal copy number at both loci in 11p15.5 and 14q32.2. There is also an abnormal methylation pattern for *H19* and *MEG3* with loss of methylation that may be indicative of a multi-locus imprinting disorder (MLID).

11 Sequencing

11.1 Introduction

Historically, ISCN has covered the description of numerical and structural chromosome changes detected using a variety of traditional and molecular cytogenetic techniques, while the Human Genome Variation Society (https://hgvs-nomenclature.org/; den Dunnen et al., 2016) covered the description of changes at the nucleotide level. Both ISCN and HGVS have developed methods to describe variants detected by microarrays, PCR, MLPA, and other technologies used to detect copy number variation (CNV). Given the increased use of sequencing technologies to characterize chromosomal abnormalities (Schluth-Bolard et al., 2013; Ordulu et al., 2014; Newman et al., 2015), the method of combining the ISCN description of chromosome rearrangements with HGVS nucleotide variant descriptions, developed jointly between the ISCN and HGVS, was initially introduced in ISCN 2016. Sequencing technologies, including Sanger sequencing, next generation short-read and long-read sequencing, or other sequence-based techniques can use this nomenclature to describe copy number and/or structural variants. These techniques are quite broad in scope and resolution; they can be targeted to one region (*e.g.*, single gene or exon), many regions (*e.g.*, amplicon or capture-based gene panels), or genome wide. Depending on the bioinformatic algorithms used, a structural variant detected from next generation sequence data may have a precise breakpoint and structural location information, such as the insertional location and orientation of a duplication. On the other hand, copy number variants may be detected using read depth-based algorithms, which detect copy number as a relative value to control(s) with neither precise breakpoints nor additional structural information, similar to how copy number is detected from microarray technologies. Regardless of approach, uncertainty may be present, with a known uncertainty range (*e.g.*, between two hybridization baits or within a repeated element such as a LINE) or as an approximate breakpoint without a defined range (*e.g.*, detected using a read depth caller from low coverage genome sequencing).

11.2 General Principles

11.2.1 Sequence-Based Nomenclature Principles

a. The nomenclature should be as precise as possible for the technologies and bioinformatic algorithms used.

b. ISCN and HGVS nomenclature can be used together to describe a structural or copy number variant. When both the ISCN and HGVS nomenclature are described, the ISCN line of the description appears first.
c. When details of the chromosomal structure are derived from sequencing techniques, both the ISCN description of chromosome aberrations and the HGVS nucleotide variant descriptions should be included for clarity and completeness.
d. When only relative copy number state is determined, and neither the precise breakpoints nor structural information is known, either the ISCN microarray format or HGVS nomenclature can be used alone.
e. When only breakpoint information is available without the information sufficient to describe the nature of the structural rearrangements, HGVS standards should be used alone (examples are not detailed in this publication, see den Dunnen et al. (2016) and https://hgvs-nomenclature.org/).

11.2.2 ISCN Principles

a. The ISCN line of the description begins with **seq** to indicate that the aberration is characterized by **sequence**-based technology. It must include the genome build in **square brackets** (**[ ]**) after **seq** if the nomenclature includes nucleotide coordinates. If **shallow sequencing** is performed, **sseq** should be used in the ISCN description of the variation (see Section 8.1.1).
b. For description of structural or copy number variation when both the ISCN and HGVS are used, the ISCN uses the karyotype format nomenclature (see Section 4.7 and Chapter 5). Where several abnormalities are described in the ISCN, a mixture of the short and detailed systems within the karyotype format nomenclature can be used, as different levels of information may be known for each of the described aberrations.
c. For description of copy number variations where structural information and exact breakpoints are not detected (*e.g.*, relative copy number detection from exome sequencing), the ISCN should use the microarray format nomenclature (see Section 4.7 and Chapter 8).
d. When chromosome analysis is performed, this is presented first and a **period** (**.**) precedes the **sequencing** nomenclature (**.seq**). For other techniques the results may be presented in any order, although this is usually the order in which they are performed.
e. Sex chromosomes are not given, with the exceptions of (a) if a variant involving a sex chromosome is reported or (b) if the sex chromosome complement is informative or required for interpretation of the result. Otherwise, the sex chromosome complement may be indicated in the written description without being explicitly stated in the nomenclature.

11.2.3 HGVS Principles

a. The combined nomenclature uses the existing HGVS standards for the HGVS line (see below, den Dunnen et al., 2016 and https://hgvs-nomenclature.org/) along with additional recommendations outlined below for the description of an aberration.

b. HGVS nomenclature was developed to describe variants. Chromosomes or chromosomal segments that do not contain variants are not described using HGVS nomenclature, unless to indicate sex chromosome complement.
c. Each line details the reference sequence(s) used, the genomic coordinates, and the type of variation(s) involved. Variants affecting different chromosomes are described on a separate line.
d. The segment containing the centromere is the reference for the derivative chromosome(s). The orientation of the derivative chromosome is the same as the reference chromosome segment that includes the centromere. A derivative chromosome is described from **pter** to **qter,** regardless of the origin of the sequences. This would mean that the new **pter** of a derivative chromosome could be the original **qter** of another chromosome.
e. Multiple variants within the same homologue are described from **pter** to **qter** of the derivative chromosome, anchored in the positive strand.
f. As in ISCN, aberrations affecting sex chromosomes are listed first (X then Y) followed by those affecting autosomes in ascending numbers.
g. A specific reference for each chromosome is given, rather than the general **genome build** reference (*e.g.*, NC_000023.11 for the NCBI RefSeq version for *Homo sapiens* X chromosome, build **GRCh38**). The chromosome is given before the **period** (**.**), with the X chromosome as 23 and the Y chromosome as 24. The number following the **period** (**.**) indicates the specific version of the chromosome reference sequence.
h. A letter prefix indicates the type of reference sequence used. For **linear genomic** reference sequence **g** is used, followed by a **period** (**.**).
i. The genomic reference sequence contains undefined nucleotides (Ns) at the start and end of the chromosome making the use of specific nucleotide positions for these sites problematic. The beginning and end of a chromosome are therefore represented as **pter** and **qter**.
j. When the chromosome structure associated with a gain is not known (*e.g.*, insertional location), gains can be indicated using the copy number in **square brackets** (**[ ]**) at the end of the nomenclature description, with [2] indicating one additional copy observed of a particular chromosome or chromosome region compared to the reference, [3] indicating two additional copies, *etc*.
k. To describe **variants** (**var**), HGVS uses the following allele format:

- **g.[var1];[var2]** in the two different alleles (*in trans*).
- **g.[var1;var2]** to describe different variants in one allele (*in cis*).
- **g.var1(;)var2** if the phase of the alleles is not known or uncertain.

l. If mosaicism/clonal change is present, the variant(s) are separated by a **single slant line** (/). The normal reference sequence, if present, is always described first and is followed by an **equal symbol** (=).
m. To indicate sex chromosome complement, the HGVS allele format can be used; adding NC_000023.11:g.[pter_qter=] indicates the presence of a normal X chromosome, and NC_000024.10:g.[pter_qter=] the presence of a normal Y chromosome.
n. For variants within the pseudoautosomal regions where there is uncertainty whether the X or Y chromosome is involved, a **caret** (^) should be used between the two possible variants.

11.2.3.1 Breakpoint Description

a. An **underscore** (**_**) indicates a range of nucleotides, *e.g.*, g.123_456del indicates a deletion of nucleotides 123 to 456.
- When the breakpoints have not been determined at the precise nucleotide level, variants are described with the ranges of uncertainty given in **parentheses** (**()**), using the format g.(A_B)_(C_D). In this format A_D represents the maximal and B_C the minimal extent of the rearrangement.
- Unknown nucleotide positions are indicated using a **question mark** (**?**), *e.g.*, g.(?_B)_(C_?)del when the minimal range of a deletion is known, but not the maximal range.
- For **terminal** (**ter**) copy number changes involving an unknown position in the direction of the telomere, the format (pter)_B or C_(qter) is used.

b. To determine the location of the breakpoint, the general HGVS rule of maintaining the longest un-changed sequence applies (HGVS **3′rule**) (see Section 11.2.3.2).
- In runs of identical nucleotides, the most 3′nucleotide in the run is designated as variant, *e.g.*, g.4del (not g.2del nor g.3del) describes the change CTTTA to CTTA (see also Section 11.2.3.2).

c. A **double colon** (**::**) is used to designate breakpoint junctions in HGVS, *e.g.*, a ring chromosome. It is also used in the detailed system (karyotype format) (see Sections 5.4.2.2, 9.3 and 10.2.2).

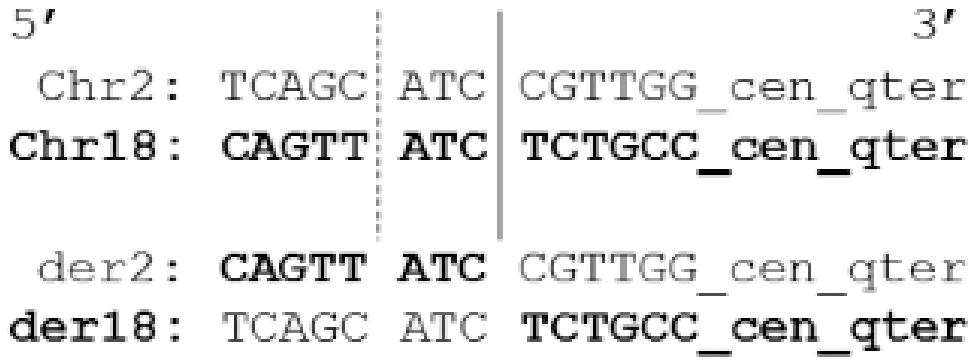
11.2.3.2 Structural Variant Description

The type of structural variation is indicated following the nucleotide breakpoint positions except for insertions where it precedes the nucleotides:

a. **del** – indicates a **deletion**. If the deletion is homozygous (*e.g.*, found on both chromosomes), both chromosomes should be described using the HGVS allele format (*e.g.*, g.[123_456del];[123_456del]).
b. **dup** – exclusively indicates a **tandem, direct duplication**. If the duplicated sequence is not directly in tandem, *e.g.*, separated by one or more nucleotides, inverted, and/or inserted elsewhere in the genome, **ins** (for **insertion**) is used instead.
c. **inv** – indicates an **inverted** sequence (*e.g.*, g.123_456inv).
d. **ins** – indicates an **insertion** of a sequence (*e.g.*, insAAGTAC) that is not a tandem duplication. When the inserted sequence is long, the sequence can be replaced by referring to a reference sequence and specifying the inserted nucleotides (*e.g.*, ins[NG_012232.1:g.4566_8781]). This insertion can be balanced or involve duplicated material from elsewhere in the genome. A balanced insertion (transposition) would have a corresponding **del** nomenclature, indicating the genomic sequences are no longer present *in situ*.
e. **delins** – indicates **deletion** and **insertion**, *i.e.*, a sequence change where nucleotides are replaced by other nucleotides (*e.g.*, balanced or unbalanced translocations where genomic material is being replaced by sequence from a different chromosomal location).

f. **sup** – indicates a **supernumerary** sequence, *i.e.*, the presence of an additional sequence that is not attached to other chromosomal material (*i.e.*, trisomy, supernumerary marker or ring chromosome).

g. Application of the **3′ rule** to chromosome rearrangements:



A translocation joins chromosome 2 and chromosome 18 (**seq[GRCh38]** nomenclature line above in bold). According to the chromosome 2 and chromosome 18 reference sequences, there are two options to align the breakpoints (dashed and solid vertical lines). The 3′ rule determines that, starting with the lowest chromosome number involved (here chromosome 2), the sequence should be aligned as far 3′ as possible, aligning with the solid vertical line. The correct description of the rearrangement is therefore:

seq[GRCh38] t(2;18)(p25.3;p11.32)

NC_000002.12:g.pter_8delins[NC_000018.10:g.pter_8]

NC_000018.10:g.pter_8delins[NC_000002.12:g.pter_8]

Note: a 5′ alignment would give an incorrect result:
NC_000002.12:g.pter_5delins[NC_000018.10:g.pter_5] and
NC_000018.10:g.pter_5delins[NC_000002.12:g.pter_5]

11.3 Normal Results

i. seq (X,1–22)×2Sequencing reveals two copies of the X chromosome and all autosomes with no apparent abnormality detected in a female. As with the microarray nomenclature, the specific genome build is not necessary when describing a normal copy number profile. HGVS nomenclature describes variants in relation to the reference sequence and is not used in this context.

ii. seq (X,Y)×1,(1–22)×2Sequencing reveals one copy of the X and Y chromosomes, and two copies of the autosomes with no apparent abnormality detected in a male. HGVS nomenclature describes variants in relation to the reference sequence and is not used in this context.

iii. seq (1–22)×2Sequencing reveals two copies of all autosomes with no apparent abnormality detected, and the sex chromosome complement is normal but undisclosed.

HGVS nomenclature describes variants in relation to the reference sequence and is not used in this context.

11.4 Abnormal Results

11.4.1 Aneuploidy

i. seq (X)×1
or
NC_000023.11:g.pter_qterdel^NC_000024.10:g.pter_qterdelSequencing reveals a single X chromosome, and no other sex chromosomes are present in this individual. The result is given using the abbreviated system (microarray format) nomenclature, the specific genome build is not necessary when describing an aneuploidy. The HGVS nomenclature describes the deletion of an X or Y chromosome, as the missing chromosome is unknown (in HGVS 'or' is represented by a **caret** (^)).

ii. seq (13)×3
or
NC_000013.11:g.(pter)_(qter)[2]Sequencing shows a gain of chromosome 13 sequences. The result is given using the abbreviated system (microarray format) nomenclature. No structural information is detected regarding whether the trisomy is associated with a Robertsonian translocation or any other type of structural rearrangement. The HGVS nomenclature indicates that, compared to the reference sequence, there is one additional copy [2] of chromosome 13 sequences detected. **Note**: **dup** or **sup** are not used in the nomenclature because the nature of the abnormality is not known. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

iii. 47,XY,+13.seq (13)×3
or
NC_000013.11:g.(pter)_(qter)supChromosome analysis and sequencing shows gain of chromosome 13. The HGVS nomenclature indicates there is one additional copy of chromosome 13 (**sup**) compared to the reference sequence. ISCN description and HGVS nomenclature lines both indicate that the additional copy number is associated with a supernumerary chromosome 13, confirmed by the karyotype. **Note:** ISCN describes the chromosome abnormality and excludes a Robertsonian translocation while HGVS implies it is a gain of a supernumerary chromosome 13 but does not provide any additional information.

iv. seq[GRCh38] 18p11.32p11.21(158,684_14,853,925)×4
or
seq (18p)×4
or
NC_000018.10:g.(pter_158684)_(14853925_?)[3]Sequencing shows four copies of the short arm of chromosome 18. No structural information is determined, and it is unknown if the additional copies of 18p are associated with an abnormal chromosome (*e.g.,* supernumerary isochromosome 18p) or present in tandem. The ISCN microarray format is applied and either the short system or abbreviated system can be used to describe the variant. The HGVS describes this finding as the detection of two additional copies [3] of chromosome 18 sequence located between positions

158,684 and 14,853,925. **Note**: **dup** or **sup** are not used in this circumstance because the nature of the abnormality is not known. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

v. seq (X)×3
or
NC_000023.11:g.[pter_qter[2]];[pter_qter=]Sequencing shows three copies of the X chromosome using the abbreviated system (microarray format). There are no copies of the Y chromosome, suggesting that this individual's sex chromosome complement is XXX. The HGVS nomenclature indicates that, compared to the reference sequence, there is one additional copy [2] of all X chromosome sequences detected. The HGVS allele format used indicates that one normal copy of an X chromosome is also detected, giving a total of three X chromosomes. **Note**: **sup** is not used in this circumstance because the nature of the abnormality is not known. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

vi. 47,XXX.seq (X)×3
or
NC_000023.11:g.[pter_qter=];[pter_qter=];[pter_qtersup]Chromosome analysis and sequencing data show three copies of the X chromosome, associated with a 47,XXX karyotype. HGVS nomenclature indicates that compared to the reference sequence, three X chromosome sequences are detected, two normal (=) and one additional copy (**sup)**. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

vii. seq (X)×2,(Y)×1
or
[NC_000023.11:g.pter_qter[2]];[NC_000024.10:g.pter_qter=]Sequencing shows two copies of all X chromosome sequences, and one copy of all Y chromosome sequences. The copy number status of both the X and Y are explicitly given using the abbreviated system (microarray format) to clarify the sex chromosome complement of this individual. HGVS nomenclature indicates that, compared to the reference sequence, one additional copy [2] of all X chromosome sequences is detected with one copy of all Y chromosome sequences (NC_000024.10:g.pter_qter=). Since ISCN and HGVS nomenclature indicate similar information, either can be used.

viii. seq (X)×1,(Y)×2
or
[NC_000023.11:g.pter_qter=];[NC_000024.11:g.pter_qter[2]]Sequencing shows one copy of all X chromosome sequences, and two copies of all Y chromosome sequences. The copy number state of both X and Y are given using the abbreviated system (microarray format) to clarify the sex chromosome complement of this individual. HGVS nomenclature indicates that, compared to a reference sequence, a normal copy of the X chromosome sequences is detected (NC_000023.11:g.pter_qter=) and an additional copy [2] of all Y chromosome sequences is detected. **Note: sup** is not used in this circumstance because the nature of the Y chromosome abnormality is not known. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

ix. seq (X)×1[0.6]
or

NC_000023.11:g.[pter_qter=];[pter_qter=/del]Sequencing shows mosaicism for single copy loss of the X chromosome in 60% of the DNA sample, described using the abbreviated system (microarray format). The normal state is implied to be XX in this individual. HGVS nomenclature indicates there is one X chromosome (=) present in the sample, with a mosaic loss of the second X chromosome (**=/del**) in a proportion of the sample. The mosaicism percentage is not indicated in the HGVS nomenclature. Since the ISCN line is more informative this can be used in isolation without the HGVS nomenclature. **Note:** the limitation of sequencing is that it cannot always differentiate between X/XX or X/XXX.

11.4.2 Large Structural and Copy Number Variation

11.4.2.1 Deletion

i. seq[GRCh38] del(10)(p15.3)dn
NC_000010.11:g.(pter)_2944337delSequencing shows an apparently terminal deletion of the short arm of chromosome 10. The ISCN short system (karyotype format) describes a *de novo* terminal deletion with a breakpoint in 10p15.3. The short system (karyotype format) is used to indicate that no additional structural variation is associated with this terminal deletion. The breakpoints for the deletion are indicated in the HGVS line of the nomenclature. The deletion involves 10pter to nucleotide 2,944,337. In this case, since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

ii. seq[GRCh38] 10p15.3(46,696_1,737,263)×1dn
or
NC_000010.11:g.(pter_46696)_(1737263_?)delSequencing shows an apparently terminal deletion of the short arm of chromosome 10. The ISCN short system (microarray format) describes a *de novo* terminal deletion with a breakpoint in 10p15.3 using a relative copy number detection methodology (*e.g.*, exome sequencing) where neither the precise breakpoint nor structural information are determined. The deletion involves the region 46,696 to 1,737,263 and the uncertainty range is not specified. **Note:** this deletion is likely terminal, but the nomenclature describes only the region of the chromosome that is assayed for copy number, similar to microarray format nomenclature. The HGVS nomenclature indicates that the deletion is likely terminal, with the use of **pter** for the 5′ breakpoint, and the use of a **question mark** (**?**) for the undefined 3′ breakpoint. While ISCN and HGVS nomenclature indicate similar genomic information, only ISCN conveys the inheritance information and is therefore recommended.

iii. seq[GRCh38] 10p15.3(46696_1737263×1,3067438×2)dn
or
NC_000010.11:g.(pter_46696)_(1737263_3067438)delSequencing shows an apparently terminal deletion of the short arm of chromosome 10. The ISCN extended system (microarray format) describes a *de novo* terminal deletion with a breakpoint in 10p15.3 using a relative copy number detection methodology from a targeted capture assay (*e.g.*, exome sequencing), where neither the precise breakpoint nor structural information is detected. The apparently terminal deletion involves the most distal targeted region assayed (46,696). The uncertainty region

for the proximal breakpoint corresponds to the region between the end of the deleted region (1,737,263) and the next neighboring region assayed that shows a normal copy number (30,067,438). **Note:** delimiting commas are not used in the extended system (microarray format). While ISCN and HGVS nomenclature indicate similar genomic information, only ISCN conveys the inheritance information and is therefore recommended.

iv. seq[GRCh38] 22q11.21(18,891,533_21,111,169)×1pat
or
NC_000022.10:g.(?_18891533)_(21111169_?)delSequencing shows an interstitial deletion within the long arm of chromosome 22. The ISCN short system (microarray format) describes a paternally inherited deletion within 22q11.2, consistent with the recurrent 22q11.2 deletion syndrome (low copy number repeats LCR-A to LCR-D). Neither the precise deletion breakpoint nor structural information is detected and the uncertainty region is not determined due to limitations of the assay. While ISCN and HGVS nomenclature indicate similar genomic information, only ISCN conveys the inheritance information and is therefore recommended.

v. seq[GRCh38] 22q11.21(18164049×2,18891533_21111169×1,21443266×2)pat
or
NC_000022.10:g.(18164049_18891533)_(21111169_21443266)delSequencing shows an interstitial deletion within the long arm of chromosome 22. The ISCN extended system (microarray format) describes a paternally inherited deletion within 22q11.2, consistent with the recurrent 22q11.2 deletion syndrome (low copy number repeats LCR-A to LCR-D). The precise breakpoint is not detected as the breakpoints appear to fall within repetitive regions of the genome. The uncertainty region for the proximal breakpoint corresponds to segmental duplication regions between 18,164,049 and 18,891,533, with the distal breakpoint between 21,111,169 and 21,443,266. **Note:** delimiting commas are not used in the extended system. While ISCN and HGVS nomenclature indicate similar genomic information, only ISCN conveys the inheritance information and is therefore recommended.

vi. seq[GRCh38] X,del(X)(q21.31q22.1)
NC_000023.11:g.89555676_100352080delSequencing shows an interstitial deletion within the long arm of the X chromosome in an XX individual. The ISCN short system (karyotype format) describes a heterozygous deletion within the long arm of the X chromosome from band Xq21.31 to Xq22.1. The normal X is indicated in the ISCN line to clarify the sex chromosome complement. The use of the short system indicates that the deletion is interstitial and is not associated with any other structural rearrangements. The HGVS line indicates that the deletion includes the segment from nucleotide 89,555,676 to nucleotide 100,352,080, with nucleotides 89,555,675 to 100,352,081 now joined. Since the breakpoint and structural information are known for this deletion, both the ISCN and HGVS nomenclature are required.

vii. seq[GRCh38] Xq21.31q22.1(91,435,563_100,342,090)×1
or
NC_000023.11:g.[pter_qter=];[(?_91435563)_(100342090_?)del]Sequencing shows an interstitial deletion within the long arm of the X chromosome. The ISCN

short system (microarray format) describes a heterozygous interstitial deletion within the long arm of the X chromosome from band Xq21.31 to Xq22.1 where neither the precise breakpoint nor related structural information is determined. The minimal deletion includes the segment from nucleotide 91,435,563 to nucleotide 100,342,090, and the uncertainty region is not defined. This deletion is inferred to be present in an XX individual. The HGVS description indicates that the extent of the deleted region is not known with the use of **question marks** (**?**). To indicate that a deletion is seen in the heterozygous state in an XX individual, the normal sex chromosome is given using the HGVS allele format (see Section 11.2.3). Since ISCN and HGVS nomenclature indicate similar information, either can be used.

viii. seq[GRCh38] Xq21.31q22.1(88754300×2,91435563_100342090×1,100402866×2)
or
NC_000023.11:g.[pter_qter=];[(88754300_91435563)_(100342090_100402866)del
]Sequencing shows an interstitial deletion within the long arm of the X chromosome in an XX individual. The ISCN extended system (microarray format) describes a heterozygous interstitial deletion within the long arm of the X chromosome from band Xq21.31 to Xq22.1 where neither the precise breakpoint nor related structural information is determined. The minimal deletion includes the segment from nucleotide 91,435,563 to nucleotide 100,342,090. The extended system indicates the neighboring proximal and distal regions that show normal copy number (two copies). As the extended system indicates that the normal copy is two for the X chromosome, and the Y chromosome is not present, this individual can be inferred to have two X chromosomes, one with a deletion. The HGVS nomenclature indicates that there is an interstitial deletion of the X chromosome with the 5′ breakpoints between 88,754,300 and 91,435,563 and the 3′ breakpoints between 100,342,090 and 100,402,866. To indicate that a deletion is seen in the heterozygous state in an XX individual, the normal sex chromosome is indicated by using the HGVS allele format. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

ix. seq[GRCh38] Y,del(X)(q21.31q22.1)
NC_000023.11:g.89555676_100352080delSequencing shows an interstitial deletion within the long arm of the X chromosome in an XY individual. The ISCN short system (karyotype format) describes a hemizygous interstitial deletion within the long arm of the X chromosome from band Xq21.31 to Xq22.1. The normal Y is indicated in the ISCN line to clarify the sex chromosome complement. The use of the short system indicates that the deletion is interstitial and is not associated with other structural rearrangements. The HGVS line of the nomenclature indicates that the deletion includes the segment from nucleotide 89,555,676 to nucleotide 100,352,080, with nucleotides 89,555,675 to 100,352,081 now joined. Since the breakpoint and structural information are known for this deletion, both the ISCN and HGVS nomenclature lines are required.

x. seq[GRCh38] (Y)×1,Xq21.31q22.1(91,435,563_100,342,090)×0
or
[NC_000023.11:g.(?_91435563)_(100342090_?)del];[NC_000024.10:g.pter_qter=]
Sequencing shows an interstitial deletion within the long arm of the X chromosome in an XY individual. The ISCN uses the abbreviated system (microarray format) for

the Y chromosome and the short system (microarray format) for the hemizygous deletion from band Xq21.31 to Xq22.1 where neither the precise breakpoint nor related structural information is detected. The minimal deletion includes the segment from nucleotide 91,435,563 to nucleotide 100,342,090, and the uncertainty region is not defined. The normal Y chromosome is indicated to clarify the sex chromosome complement to show that this deletion is not found in the homozygous state in an XX individual, nor is found to be present on the single X chromosome in an individual with 45,X. The HGVS nomenclature uses a **question mark** (**?**) to indicate that the extent of the X chromosome deletion is unknown. The presence of one copy of a normal Y chromosome using the HGVS allele format is given to indicate X chromosome deletion is hemizygous. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

xi. seq[GRCh38] (Y)×1,Xq21.31q22.1(88754300×1,91435563_100342090×0,100402866×1) or [NC_000023.11:g.(88754300_91435563)_(100342090_100402866)del];[NC_000024.10:g.pter_qter=]Sequencing shows an interstitial deletion within the long arm of the X chromosome in an XY individual. The ISCN extended system (microarray format) describes a hemizygous deletion from band Xq21.31 to Xq22.1 where neither the precise breakpoint nor related structural information is determined. The deletion includes the segment from nucleotide 91,435,563 to nucleotide 100,342,090. The extended system (microarray format) indicates the neighboring proximal (88,754,300) and distal (100,402,866) targeted regions that show normal copy number (one copy). The normal Y is indicated to clarify the sex chromosome complement. The HGVS nomenclature indicates that there is an interstitial deletion of the X chromosome with the 5′ breakpoint between 88,754,300 and 91,435,563 and the 3′ breakpoint between 100,342,090 and 100,402,866. To indicate the zygosity of the deletion, the HGVS allele format is used. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

xii. seq[GRCh38] del(X)(q21.31q22.1),del(X)(q21.31q22.1) NC_000023.11:g.[89555676_100352080del];[89555676_100352080del]Sequencing shows identical interstitial deletions within the long arms of both X chromosomes in an XX individual. The ISCN short system (karyotype format) description indicates that no additional structural rearrangements are associated with the interstitial deletions. Alternatively, the ISCN description could be written: seq[GRCh38] del(X) (q21.31q22.1)×2. The HGVS line of the nomenclature indicates identical interstitial deletions within the long arms of both X chromosomes from band Xq21.31 to band Xq22.1 involving the region from nucleotide 89,555,676 to nucleotide 100,352,080. In the HGVS description each allele is described between square brackets ([89555676_100352080del]), separated by a **semicolon** (**;**) to indicate the variants are *in trans* (different chromosomes). Since both the breakpoint and structural information are known for these deletions, both the ISCN and HGVS nomenclature lines are required.

xiii. seq[GRCh38] Xq21.31q22.1(88754300×2,91435563_100342090×0,100402866×2) or NC_000023.11:g.[(88754300_91435563)_(100342090_100402866)del];[(8875430

0_91435563)_(100342090_100402866)del]Sequencing shows identical interstitial deletions within the long arms of both X chromosomes. The ISCN extended system (microarray format) describes the homozygous deletion from band Xq21.31 to Xq22.1, where neither the precise breakpoint nor structural information is determined. The homozygous deletion includes the segment from nucleotide 91,435,563 to nucleotide 100,342,090. The extended system (microarray format) shows the neighboring proximal and distal targeted regions with normal copy number (two copies), indicating this homozygous deletion ′ 3 is observed in an XX individual. HGVS nomenclature describes each allele between **square brackets** (**[ ]**), separated by a **semicolon** (**;**) to indicate the variants are *in trans*. Since ISCN and HGVS nomenclature indicate similar information, either can be used.

xiv. seq[GRCh38] del(X)(q21.31q22.1),del(X)(q21.31q22.1)
NC_000023.11:g.[89555674_100352088del];[90111276_99878726del]Sequencing shows different interstitial deletions within the long arms of both X chromosomes. The ISCN short system (karyotype format) indicates that an XX individual has both X chromosomes deleted from band Xq21.31 to band Xq22.1; however, the HGVS nomenclature shows that these deletions are not identical and are associated with compound heterozygous interstitial deletions (*in trans*) within the long arms of both X chromosomes. The deletions include the segment from nucleotide 89,555,674 to 100,352,088 on one homologue, and from nucleotide 90,111,276 to 99,878,726 on the other homologue. In the HGVS nomenclature each allele is described between **square brackets** (**[ ]**), separated by a **semicolon** (**;**) to indicate the variants are *in trans*. Since the breakpoint and structural information are known for these deletions, both the ISCN and HGVS nomenclature lines are required.

xv. seq[GRCh38] del(X)(p22.3p22.3) or del(Y)(p11.31p11.2)
NC_000023.11:g.320651_666265del^NC_000024.10:g.320651_666265delSequencing shows a deletion within the pseudoautosomal region 1 (PAR1) of chromosomes X or Y in an XY individual. The ISCN short system (karyotype format) describes an interstitial deletion as either a hemizygous interstitial deletion within the short arm of the X chromosome within band Xp22.3, or with a hemizygous interstitial deletion within the short arm of the Y chromosome within band Yp11.31 to Yp11.2. The HGVS nomenclature describes the deletion in either the X or (^) Y chromosome and includes the segment from nucleotide 320,651 to nucleotide 666,265. Since the breakpoint and structural information are known for these deletions, both the ISCN and HGVS nomenclature lines are required.

xvi. seq[GRCh38] 12q21.32(88,534,851_88,545,966)×0mat pat
or
NC_000012.12:g.[(?_88534851)_(88545966_?)del];[(?_88534851)_(88545966_?)del]Sequencing shows an intragenic homozygous deletion within the long arm of chromosome 12. The ISCN short system (microarray format) indicates an intragenic, homozygous loss is located in the *KITLG* gene within band 12q21.32. Neither the precise breakpoint nor structural information are detected. The homozygous deletion includes the segment between nucleotides 88,534,851, and 88,545,966, and the uncertainty range is not specified. Both parents are known heterozygous carriers of this deletion. The HGVS nomenclature describes each allele between **square brackets** (**[ ]**), separated by a **semicolon** (**;**) to indicate the

variants are *in trans*. While ISCN and HGVS nomenclature indicate similar genomic information, only ISCN conveys the inheritance information and is therefore recommended.

xvii. seq[GRCh38] 12q21.32(88530089×2,88534851_88545966×0,88580216×2)mat pat
or
NC_000012.12:g.[(88530089_88534851)_(88545966_88580216)del];[(88530089_88534851)_(88545966_88580216)del]Sequencing shows a homozygous deletion within the long arm of chromosome 12. The ISCN extended system (microarray format) indicates that an intragenic, homozygous loss is located in the *KITLG* gene within band 12q21.31. Neither the precise breakpoint nor structural information is detected, and the breakpoint uncertainty range is specified. The homozygous deletion includes the segment between nucleotides 88,530,089 to 88,534,851 and 88,545,966 to 88,580,216. The extended system indicates that the neighboring proximal and distal targeted regions show normal copy number (two copies). Both parents are known heterozygous carriers of this deletion. The HGVS nomenclature describes each allele between **square brackets** (**[ ]**) separated by a **semicolon** (**;**) to indicate that the variants are *in trans*. While ISCN and HGVS nomenclature indicate similar genomic information, only ISCN conveys the inheritance information and is therefore recommended.

xviii. seq[GRCh38]
1p22.3(86092388×2,86112508_86915211×1,86993002×2)dn,1q31.3q32.1(193249904×2,196228171_200650737×1,200658989×2)dn,2q33.1q34(201145490×2,201148901_208572138×1,209653108×2)dn
or
NC_000001.11:g.[(86092388_86112508)_(86915211_86993002)del](;)[(193249904_196228171)_(200650737_200658989)del]
NC_000002.12:g.(201145490_201148901)_(208572138_209653108)delSequencing shows multiple deletions involving the short and long arm of chromosome 1 and the long arm of chromosome 2. The ISCN extended system (microarray format) describes three *de novo* interstitial losses where the precise breakpoint nor structural information is determined. These three heterozygous deletions include a loss of approximately 800 kb in 1p22.3, a loss of approximately 4.4 Mb in 1q31.3 to 1q32.1, and a loss of approximately 7.4 Mb in 2q33.1 to 2q34. As no precise breakpoints or structural information is obtained from this analysis, it cannot be determined if these findings are associated with a larger structural rearrangement, such as a translocation or pericentric inversion. The HGVS nomenclature describes the deletions involving chromosome 1 on a single line, with the use of **semicolon** (**;**) to indicate that is it not known if the two deletions are *in cis* (same chromosome) or *in trans* (different chromosomes). The deletion involving chromosome 2 is described on a separate line. While ISCN and HGVS nomenclature indicate similar genomic information, only ISCN conveys the inheritance information and is therefore recommended.

11.4.2.2 Duplication and Triplication

i. seq[GRCh38] dup(18)(q23q23)
NC_000018.10:g.79670244_79724961dupSequencing shows an interstitial duplication within the long arm of chromosome 18. The ISCN short system (karyotype format) nomenclature describes a tandem duplication of sequences within chromosome 18q23. As the duplication is within a single chromosome band, the ISCN cannot distinguish the orientation of the duplicated material. The HGVS line indicates the 54.7 kb tandem duplication within chromosome 18 involves nucleotides 79,670,244 to 79,724,961. **Note:** in HGVS **dup** can only be used when the duplicated sequence is in the same orientation as the reference sequence. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

ii. seq[GRCh38] dup(18)(q23q23)
NC_000018.10:g.79670243_79670244ins79670244_79724961invSequencing shows an interstitial duplication within the long arm of chromosome 18. As above, there is a 54.7 kb duplication within chromosome band 18q23, and the ISCN short system (karyotype format) cannot distinguish the orientation of the duplicated sequences. The HGVS nomenclature indicates that, compared to the reference sequence, the genomic region 79,670,244 to 79,724,961 is inserted in an inverted orientation between nucleotides 79,670,243 and 79,670,244 (*i.e.*, proximal to the reference copy). Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

iii. seq[GRCh38] dup(18)(q23q23)
NC_000018.10:g.79724961_79724962ins79670244_79724961invSequencing shows an interstitial duplication within the long arm of chromosome 18. As above, there is a 54.7 kb duplication within chromosome band 18q23, and the ISCN short system (karyotype format) cannot distinguish the orientation of the duplicated sequences. The HGVS description indicates the genomic region 79,670,244 to 79,724,961 is inserted in an inverted orientation between nucleotides 79,724,961 and 79,724,962 (*i.e.*, distal to the reference copy). Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

iv. seq[GRCh38] 18q23(79,679,933_79,718,031)×3
or
NC_000018.10:g.(?_79679933)_(79718031_?)[2]Sequencing shows a single copy gain of an interstitial segment of the long arm of chromosome 18. The ISCN short system (microarray format) indicates a gain (three copies) of a part of chromosome band 18q23; however, the methodology could not determine the insertion location or orientation of the gain. The gain includes the segment from nucleotide 79,679,933 to nucleotide 79,718,031, and the uncertainty region is not specified. The HGVS line describes an additional copy **[**2**]** of the reference sequence of chromosome 18 between 79,679,933 to nucleotide 79,718,031. **Note: dup**, **sup**, and **delins** can neither be used nor assumed, as the insertional location and orientation of the duplicated sequences has implications on classification, interpretation, and recurrence risk. Since ISCN and HGVS nomenclature indicate similar information regarding the variants, either can be used.

v. seq[GRCh38] 18q23(79527592×2,79679933_79718031×3,79728892×2)
or
NC_000018.10:g.(79527592_79679933)_(79718031_79728892)[2]Sequencing shows an interstitial single copy gain within the long arm of chromosome 18. The ISCN extended system (microarray format) indicates a gain (three copies) within chromosome band 18q23; however, the methodology could not determine the insertion location or orientation of the gain. The gain includes the segment from nucleotide 79,679,933 to nucleotide 79,718,031. The extended system indicates the neighboring proximal and distal targeted regions that show normal copy number (two copies). The HGVS nomenclature indicates that, compared to the reference sequence, there is an additional copy **[**2**]** of the chromosome 18 sequence between nucleotides 79,527,592 to 79,679,933 and 79,718,031 to 79,728,892. **Note:**
dup, **sup** and **delins** can neither be used nor assumed, as the insertional location and orientation of the duplicated sequences has implications on classification, interpretation, and recurrence risk. Since ISCN and HGVS nomenclature indicate similar information regarding the variants, either can be used.

vi. seq[GRCh38] 16p11.2(29,604,826_30,188,489)×3
or
NC_000016.10:g.(?_29604826)_(30188489_?)[2]Sequencing shows an interstitial gain within the short arm of chromosome 16. The ISCN short system (microarray format) indicates a gain (three copies) of material from chromosome band 16p11.2 that is consistent with the proximal recurrent duplication of 16p11.2 (breakpoints BP4-BP5); however, the insertion location or orientation of the gain could not be determined as the breakpoints fall within segmental duplications. The gain duplication includes the segment from nucleotides 29,604,826 to 30,188,489 and the uncertainty region is not specified. The HGVS nomenclature describes that, compared to the reference sequence, there is an extra copy **[**2**]** of the chromosome 16 sequence. **Note: dup**, **sup** and **delins** can neither be used nor assumed since the insertional location and orientation of the duplicated sequences has implications on classification, interpretation, and recurrence risk. Since ISCN and HGVS nomenclature indicate similar information regarding the variants, either can be used.

vii. seq[GRCh38] 16p11.2(29410365×2,29604826_30188489×3,30335398×2)
or
NC_000016.10:g.(29410365_29604826)_(30188489_30335398)[2]Sequencing shows an interstitial gain within the short arm of chromosome 16. The ISCN extended system (microarray format) indicates a gain of 16p11.2 that is consistent with the proximal recurrent duplication of 16p11.2 (breakpoint BP4-BP5); however, the insertion location or orientation of the gain could not be determined as the breakpoints fall within segmental duplications. The gain includes the segment from nucleotide between 29,410,365 to 29,604,826 and 30,188,489 to 30,335,398. The HGVS nomenclature describes that, compared to the reference sequence, there is an additional copy **[**2**]** of the chromosome 16 sequence. **Note: dup**, **sup** and **delins** can neither be used nor assumed since the insertional location and orientation of the duplicated sequences has implications on classification, interpretation, and recurrence risk. Since ISCN and HGVS nomenclature indicate similar information regarding the variants, either can be used.

viii. 47,XY,+dic(15;15)(q13;q13).seq[GRCh38] 15q11.2q13.1(22572598_28318712×4,28724458×2)
or
NC_000015.10:g.[(pter_22572598)_(28318712_28724458);(pter_22572598)_(28318712_28724458)inv]supSequencing data and chromosome analysis show two additional copies of the proximal long arm of chromosome 15 associated with a supernumerary dicentric chromosome as indicated by both ISCN short system (karyotype format) and extended system (microarray format). The precise breakpoint and structural information are not determined by the sequencing data; however, the karyotype data show the nature of the extra copies of this region are associated with a dicentric supernumerary chromosome, composed of inverted copies of 15pter to 15q13.1. The region of four copies detected by sequencing includes the segment from nucleotide 22,572,598 to 28,318,712 in bands 15q11.2 to 15q13.1; however, the proximal breakpoint is not known as it involves the most proximal region assayed for copy number, while the distal breakpoint occurs in the segmental duplication region between 28,318,712 and 28,724,458. The HGVS nomenclature line describes a supernumerary chromosome composed of two copies of the short arm of chromosome 15 ((pter_22572598)_(28318712_28724458)) where, compared to the reference sequence, one is in a normal orientation, and one is in an inverted orientation. The use of **sup** indicates that this finding is associated with a supernumerary chromosome, as confirmed by the karyotype. Since ISCN gives more information on the structure of the abnormality, the inclusion of the HGVS line is optional.

ix. seq[GRCh38] der(11)(pter→q22.3::q22.3→q14.3::q14.3→qter)
NC_000011.10:g.106009182_106009183ins[91466078_106007033inv;91448961_106009182]Sequencing shows a complex gain within the long arm of chromosome 11. The ISCN detailed system (karyotype format) indicates a complex finding, with two additional copies of 11q14.3 to 11q22.3 on the same chromosome 11 homologue, with the middle copy in an inverted orientation. The HGVS line indicates that the derivative chromosome involves additional copies of 11q material with two different sizes: one additional copy of a 14.541 Mb region involving nucleotides 91,466,078 to 106,007,033 which is inserted in an inverted orientation after position 106,009,182, followed by an additional copy of a 14.56 Mb region involving nucleotides 91,448,961 to 106,009,182. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

x. seq[GRCh38] 11q14.3(91,448,700_91,465,000)×3,11q14.3q22.3(91,465,500_106,007,000)×4,11q22.3(106,008,600_106,019,700)×3
or
NC_000011.10:g.(?_91448700)_(91465000_91465500)[2](;)(91465500_106007000)[3](;)(106007000_106008600)_(106019700_?)[2]Sequencing shows multiple copy number gains within the long arm of chromosome 11. The ISCN short system (microarray format) indicates a 14.5 Mb region of four copies of sequence from chromosome bands 11q14.3 to 11q22.3, with two smaller regions of three copies of adjacent sequence involving a 16.3 kb gain in 11q14.3, and an 11.1 kb gain in 11q22.3. The methodology used could not determine the exact breakpoints, nor the

insertion location or orientation of the regions of copy number gain. The HGVS line describes, compared to the reference sequence, the detection of one additional copy **[**2**]** of the sequence from 91,448,700 to 91,465,000, two additional copies **[**3**]** of the sequence from 91,465,500 to 106,007,000, and one additional copy **[**2**]** of the sequence from 106,008,600 to 106,019,700. The insertional locations and orientations are not known for these gains, as indicated by the **semicolon** (**;**) to indicate that it is not known whether the gains are *in cis* (same chromosome) or *in trans* (different chromosomes). Since ISCN and HGVS nomenclature indicate similar information regarding the variants, either can be used.

11.4.2.3 Derivative Chromosome

The following examples describe copy number alterations that are associated with structural rearrangements. If multiple copy number alterations are detected without any structural information, the nomenclature can be written similar to the microarray format nomenclature, with the copy number alterations listed in chromosomal numerical order. For complex findings, including chromothripsis, chromoanasynthesis, or other complexities that would result in a prohibitive number of abnormalities to describe in one nomenclature line, the microarray format for complex findings may be used (see Section 8.2.7 for examples).

i. seq[GRCh38] der(2)t(2;11)(p25.1;p15.2)
NC_000002.12:g.pter_8247756delins[NC_000011.10:g.pter_15825272]Sequencing shows an apparently terminal deletion of the short arm of chromosome 2 and an apparently terminal gain of the short arm of chromosome 11 associated with an unbalanced translocation. The ISCN short system (karyotype format) describes the derivative chromosome 2 with breakpoints in 2p25.1 and 11p15.2. The breakpoints of the translocation are described in the HGVS line of the nomenclature and occur at 2p25.1 (between nucleotides 8,247,756 and 8,247,757) and 11p15.2 (between nucleotides 15,825,272 and 15,825,273). The **delins** after the chromosome 2 breakpoints indicates that, compared to the reference sequence, the terminal region from chromosome 2 (2pter to 2p25.1) is deleted and is replaced by the terminal segment of chromosome 11 (11pter to 11p15.2). The HGVS line of the nomenclature does not explicitly state that this sequence from chromosome 11 is a gain, but the gain is implied since there is no derivative 11 described. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

ii. seq[GRCh38]
2p25.3p25.1(45,440_7,044,179)×1,11p15.5p15.2(197,297_15,247,208)×3
or
NC_000002.12:g.(pter_45440)_(7044179_?)del
NC_000011.10:g.(pter_197297)_(158247208_?)[2]Sequencing shows an apparently terminal deletion of the short arm of chromosome 2 and an apparently terminal gain of the short arm of chromosome 11. The ISCN short system (microarray format) describes an apparently terminal deletion of the short arm of chromosome 2 with a breakpoint in 2p25.1 using a relative copy-number detection methodology

(*e.g.*, exome sequencing), where the precise breakpoints nor structural information is determined. The deletion involves the first assayed region on the short arm of chromosome 2 (45,440) to 7,044,179. The copy number gain involves the first assayed region of the short arm of chromosome 11 (197,297) to 15,247,208. The uncertainty region of both copy number changes are not indicated. **Note:** the deletion and gain are likely terminal, but the nomenclature describes only the region of the chromosome that is assayed for copy number, similar to array nomenclature. The HGVS line describes two variants: an apparently terminal deletion of chromosome 2 sequences, and an additional copy of chromosome 11 sequences. Since no structural information is obtained from the sequencing data, the insertional location of the 11p sequences is unknown, and each copy number variant is described on a different line as it is not confirmed if they are structurally related. **Note:**
dup, **sup** and **delins** cannot be used in this circumstance, and it should not be assumed since the insertional location and orientation of the duplicated sequences have implications on classification, interpretation, and recurrence risk. Since ISCN and HGVS nomenclature indicate similar information regarding the variants, either can be used.

iii. seq[GRCh38] der(5)t(5;10)(p13.3;q21.3)
NC_000005.10:g.pter_29658442delins[NC_000010.11:g.67539995_qterinv]Sequencing shows an apparently terminal deletion of the short arm of chromosome 5 and an apparently terminal gain of the long arm of 10 associated with an unbalanced translocation. The ISCN short system (karyotype format) nomenclature describes a derivative chromosome 5 from an unbalanced translocation between 5p13.3 and 10q21.3. The HGVS line of the nomenclature describes the deletion of chromosome 5 sequences from pter to nucleotide 29,658,442, which are replaced by chromosome 10 sequences from nucleotides 67,539,995 to qter. Compared to the reference sequence, the orientation of chromosome 10 sequence is inverted; **inv** is used to indicate the change in orientation. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

iv. seq[GRCh38] der(2)t(2;13)(q37.2;q31.1)
NC_000002.12:g.235100310_qterdelins[NC_000013.11:g.85862019_qter]Sequencing shows an apparently terminal deletion of the long arm of chromosome 2 and an apparently terminal gain of the long arm of chromosome 13. The ISCN short system (karyotype format) describes a derivative chromosome 2 from an unbalanced translocation between 2q37.2 and 13q31.1. The HGVS line describes the terminal deletion of chromosome 2 sequence from nucleotide 235,100,310 to qter, which is replaced by terminal chromosome 13 sequence from nucleotides 85,862,019 to qter. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

v. seq[GRCh38] der(9)t(9;10)(q34.3;p15.3)
NC_000009.12:g.137175878_qterdelins[NC_000010.11:g.pter_2944334inv]Sequencing shows an apparently terminal deletion of the long arm of chromosome 9 and an apparently terminal gain of the short arm of chromosome 10 associated with an unbalanced chromosome. The ISCN short system (karyotype format) describes a derivative chromosome 9 from an unbalanced translocation between 9q34.3 and 10p15.3. The HGVS line describes the absence of the sequences from nucleotide

137,175,878 to the qter of chromosome 9, which is replaced by nucleotides from pter to 2,944,334 from chromosome 10. The **inv** is used since, compared to the reference sequence, the orientation of the chromosome 10 sequences is inverted. Since the ISCN and HGVS lines give different information, both should be used to describe the variant.

vi. seq[GRCh38] der(3)(3pter→3q25.32::8q24.21→8qter)
NC_000003.12:g.158573187_qterdelins[NC_000008.11:g.(128534000_128546000)_qter]Sequencing shows an apparently terminal deletion of the long arm of chromosome 3 and an apparently terminal gain of the long arm of chromosome 8 associated with an unbalanced translocation. The ISCN detailed system (karyotype format) describes a derivative chromosome 3 from a translocation between 3q25.32 and 8q24.21. The breakpoint in chromosome 3 is between nucleotides 158,573,186 and 158,573,187, while the breakpoint in chromosome 8 is uncertain (as shown by the parentheses) and between nucleotides 128,534,000 and 128,546,000. Since the ISCN and HGVS lines give different information, both should be used to describe the variant.

vii. seq[GRCh38] XX,der(4)ins(4;X)(q28.3;q22.1q21.31)
NC_000004.12:g.134850793_134850794ins[NC_000023.11:g.(89555676_89556012)_(100351998_100352080)inv]Sequencing shows gain of an interstitial region of the long arm of the X chromosome, which is inserted into the long arm of chromosome 4. The ISCN short system (karyotype format) describes a derivative chromosome 4, with an additional inverted copy of Xq21.31 to Xq22.1 inserted into 4q28.3. Sequence data indicates the site of the insertion in chromosome 4 is between 134,850,793 to 134,850,794. The duplicated X chromosome sequences have uncertain breakpoints, between 89,555,676 to 89,556,012 and 100,351,998 to 100,352,080. This duplicated region of the X chromosome is inserted in an inverted orientation relative to the X chromosome reference sequence. In the ISCN description the sex chromosome complement is indicated, as it may help to interpret the clinical significance and clarify the copy number involving the duplicated region of the X chromosome. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

viii. seq[GRCh38]
der(6)(6pter→6q14.1::21q22.12→21qter),der(12)(6qter→6q23.2::12p13.2→12qter),der(21)(21pter→21q22.12::12p13.2→12pter)
NC_000006.11:g.78952474_qterdelins[NC_000021.8:g.35039585_qter]
NC_000012.11:g.pter_11878386delins[NC_000006.11:g.132514527_qterinv]
NC_000021.8:g.35042090_qterdelins[NC_000012.11:g.pter_11878495inv]Sequencing shows a complex rearrangement between chromosomes 6, 12, and 21 resulting in three derivative chromosomes. The ISCN detailed system (karyotype format) describes each derivative chromosome from **pter** to **qter**, with multiple breakpoints in 6q14.1, 6q23.2, 12p13.2, and 21q22.12. Sequencing reveals deletions at the breakpoints of each derivative chromosome, thus the use of the short system (karyotype format) is inappropriate. The HGVS description indicates that, compared to the reference sequence, there are deletions of 53 Mb on chromosome 6 (nucleotides 78,952,474 to 132,514,526), 109 bp on chromosome 12 (nucleotides 11,878,386 to 11,878,494), and a copy number of 2.5 kb on chromosome 21

(nucleotides 35,039,585 to 35,042,089). The copy number alterations are indicated by the differences between the corresponding deleted regions (*e.g.,* 78,952,474 to qter for the deleted region of chromosome 6) and inserted regions (*e.g.,* 132,514,527 to qter for the inserted region of chromosome 6). Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

ix. seq[GRCh38] der(6)t(6;13)(q14.3;q31.1),der(13)t(6;13)(q14.3;q31.1)inv(6)(q14.3q14.3)del(6)(q14.3q14.3)del(6)(q14.3q16.1) NC_000006.12:g.85897871_qterdelins[A;NC_000013.11:g.80659609_qter] NC_000013.11:g.80659607_qterdelins[NC_000006.12:g.[85897899_85900540inv;85900541_86488291;93909933_qter]]Sequencing shows a complex rearrangement between chromosomes 6 and 13. The ISCN short system (karyotype format) describes two derivative chromosomes. The derivative 6 involves a translocation between 6q14.3 and 13q31.1. A single base pair (A) inserted at the breakpoint between nucleotide position 85,897,871 at 6q14.3 and position 80,659,609 at 13q31.1. The derivative 13 is more complicated with a translocation at 6q14.3, and with an inversion and deletion within the chromosome 6 sequence that are translocated to the derivative chromosome 13. The chromosome 6 sequences now located on the derivative 13 involve a 2.6 kb inversion within 6q14.3 (85,897,899 to 85,900,540) and a 7.4 Mb deletion (86,488,292 to 93,909,932) of chromosome 6q14.3 to 6q16.1. In addition to the large chromosome 6 deletion, there is a 2 bp deletion of chromosome 13 sequences (80,659,607 to 80,659,608) and a 28 bp deletion (85,897,871 to 85,897,898) of chromosome 6 sequences at the breakpoints. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

x. seq[GRCh38] der(5)ins(5;?)(q22.1;?) NC_00005.10:g.112173754_112173755insN[696]Sequencing shows an insertion of sequence with unknown origin into the long arm of chromosome 5. The ISCN short system (karyotype format) describes the insertion of unknown sequences indicated by a **question mark** (**?**) into the long arm of chromosome 5 at band 5q22.1. The HGVS line describes the insertion of 696 nucleotides that are not specified (insN[696]) into chromosome 5 between nucleotides 112,173,754 and 112,173,755. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

xi. seq[GRCh38] Xp22.33p22.31(276,356_6,383,977)×1,Xp22.31q28(7,050,341_156,010,409)×2,Yp11.32p11.2(276,356_9,547,294)×1,Yp11.2q12(10,266,944_56,961,317)×0 or NC_000023.11:g.(pter_276356)_(6383977_7050341)=(;)(6383977_7050341)_(156010409_qter)[2] NC_000024.10:g.(9547294_10266944)_(56961317_qter)delg.?_?ins[NC_000024.10:g.(pter_276356)_(9547294_10266944)]Sequencing data from a targeted assay (*e.g.* exome sequencing) show the presence of two copies of the X chromosome and a non-centromeric fragment of the Y chromosome in a male. One of the X chromosomes has an apparently terminal deletion of the short arm involving the

pseudoautosomal region and additional material from the X-specific region of Xp22.33 to Xp22.31. The insertional location of the fragment of the Y chromosome is not known and should not be assumed in the nomenclature. The ISCN short system (microarray format) describes copy number findings involving the X and Y chromosomes. One copy of the distal end of the short arm of the X chromosome from 276,356 to 6,383,977 is present, with two copies for the remainder of the X chromosome (7,050,341 to 156,010,409). There is also one copy of the distal end of the short arm of the Y chromosome that includes the *SRY* gene (276,356 to 9,547,294); the rest of the Y chromosome, including the centromere, is absent (10,266,944 to 56,961,317). The HGVS nomenclature describes the presence of an additional copy of the X chromosome sequences and loss of the Y chromosome sequences compared to the male reference. The nature of this additional copy of X sequences, involving the region between 6,383,977 to 7,050,341 and 156,010,409 to the qter is not known as indicated by the use of the allele format for **unknown phase** (**(;)**). The Y chromosome is described as a deletion of the majority of the Y, from between 9,547,294 to 10,266,944 to between 56,961,317 and the qter. Since the fragment of the Y chromosome is lacking a centromere, it is described as an insertion into the genome at an unknown location indicated by **g.?_?ins**. Follow-up testing using routine chromosome analysis, FISH, genome mapping, or sequencing across the breakpoints is essential to confirm any structural alterations associated with these copy number findings, such as 46,X,der(X)t(X;Y)(p22.31;p11.2). Since ISCN and HGVS nomenclature indicate similar information regarding the variants, either can be used.

xii. seq[GRCh38]
14q31.3q32.33(82692819×2,85528649_104180813×3,104244199×2),14q32.33(105771415×2,105837032_106881350×1)
or
NC_000014.9:g.(82692819_85528649)_(104180813_104244199)[3](;)(105771415_105837032)_(106881350_pter)delSequencing shows an interstitial gain and an apparently terminal deletion within the long arm of chromosome 14. The ISCN extended system (microarray format) describes two imbalances in chromosome 14: an interstitial gain of approximately 18.7 Mb of 14q31.3q32.33 from 85,528,649 to 104,180,813 and an apparently terminal loss of approximately 1.0 Mb of 14q32.33 from 105,837,032 to 106,881,350. A normal copy number (two copies) is found for the region of approximately 1.5 Mb between these two imbalances (104,244,199 to 105,771,415). The insertional location and orientation of the gain is not known, nor if the deletion and gain involve the same homologue. Follow-up testing such as routine chromosome analysis or FISH is essential to confirm the structural nature of the imbalance. The HGVS nomenclature describes the gain of the chromosome 14 sequences and the terminal deletion with **unknown phase** using a **semicolon** in **parenthesis** (**(;)**). Since ISCN and HGVS nomenclature indicate similar information regarding the variants, either can be used.

11.4.2.4 Ring Chromosome

i. seq[GRCh38] r(8)(p23.2q24.3) NC_000008.11:g.(pter)_3300105del::139535561_(qter)delSequencing shows terminal deletions of the short and long arm of chromosome 8 associated with a ring chromosome. The combination of the ISCN short system (karyotype format) and of the HGVS nomenclature describes a ring chromosome derived from chromosome 8 with breakpoints at band 8p23.2 and 8q24.3 joining nucleotide 3,300,106 to nucleotide 139,535,560. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant. If the structural information is not known, this finding should be described as two terminal deletions with unknown phase using either the ISCN array format (see Section 11.4.2.1) or the HGVS allele format, NC_000008.11:g.(pter)_3300105del(;)139535561_(qter)del (see Section 11.4.2.1).

ii. 47,XY,+mar.seq[GRCh38] +r(8)(p23.2q24.3) NC_000008.11:g.3300106::139535560supSequencing shows a gain of the centromeric region of chromosome 8, clarifying the identity of a supernumerary marker chromosome identified by G-banding. The ISCN short system (karyotype format) indicates the copy number gain involves chromosome 8 from 8p23.2 to 8q24.3. HGVS nomenclature indicates the breakpoints at nucleotide 3,300,106 is now joined to nucleotide 139,535,560 using a **double colon** (**::**). If the structural information is not known from the karyotype, this supernumerary ring chromosome should be described as a duplication NC_000008.11:g.(?_3300106)_(139535560_?)[2] (see Section 11.4.2.2). Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

The following sections describe balanced chromosomal alterations, with no associated copy number changes (see Sections 11.4.2.5, 11.4.2.6 and 11.4.2.7). All examples use a combination of both ISCN and HGVS. The ISCN karyotype format nomenclature, either short or detailed system, is used to describe the structural finding, with the HGVS nomenclature line indicating the breakpoint details.

11.4.2.5 Insertion

i. seq[GRCh38] X,ins(4;X)(q28.3;q21.31q22.1) NC_000023.11:g.89555676_100352080del NC_000004.12:g.134850793_134850794ins[NC_000023.11:g.89555676_100352080]Sequencing shows a balanced insertion of an interstitial region of the long arm of the X chromosome into the long arm of chromosome 4. The combination of the ISCN short system (karyotype format) and of the HGVS nomenclature describe a balanced interchromosomal insertion of X chromosome long arm sequences (nucleotides 89,555,676 to 100,352,080) into the long arm of chromosome 4 (between nucleotides 134,850,793 and 134,850,794) in an XX individual. The inserted sequence from the X chromosome is in the same orientation as the reference sequence. The sex chromosome complement is indicated as the sex chromosome

complement can help to interpret the clinical significance and clarify the zygosity of the X chromosome abnormality. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

ii. seq[GRCh38] X,ins(4;X)(q28.3;q22.1q21.31)
NC_000023.11:g.89555676_100352080del
NC_000004.12:g.134850793_134850794ins[NC_000023.11:g.89555676_100352080inv]Sequencing shows a balanced insertion of an interstitial region of the long arm of X chromosome into the long arm of chromosome 4. The combination of the ISCN short system (karyotype format) and of the HGVS nomenclature describes a balanced interchromosomal insertion of the X chromosome long arm sequences (nucleotides 89,555,676 to 100,352,080) into the long arm of chromosome 4 (between nucleotides 134,850,793 and 134,850,794) in an XX individual. The inserted sequence from the X chromosome is inverted in orientation relative to the reference sequence. The sex chromosome complement is indicated in the ISCN line, as the sex chromosome complement can help to interpret the clinical significance and clarify the zygosity of the X chromosome abnormality. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

iii. seq[GRCh38] ins(3)(pter→q23::q24→q26.32::q24→q23::q26.32→qter)
NC_000003.10:g.[139122717_146206645del;177128243_177128245delins[139122717_146206645inv;AA]]Sequencing shows a balanced intrachromosomal insertion within the long arm of chromosome 3. The combination of the ISCN detailed system (karyotype format) and HGVS nomenclature describe an intrachromosomal balanced insertion involving a 7.1 Mb region within 3q23q24 (139,122,717 to 146,206,645) inserted into 3q26.32 (between positions 177,128,243 and 177,128,245) in an inverted orientation. There is a single base deletion (177,128,244), and an insertion of two bases (AA) at the insertion breakpoint. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

11.4.2.6 Inversion

i. seq[GRCh38] inv(6)(pter→p25.3::q16.1→p25.3::q16.1→qter)
NC_000006.12:g.[776788_93191545inv;93191546T>C]Sequencing shows a pericentric inversion of chromosome 6. The combination of the ISCN detailed system (karyotype format) and of the HGVS nomenclature indicates the inversion involves 776,788 to 93,191,545 with a T to C nucleotide substitution at the breakpoint (nucleotide 93,191,546). Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

ii. seq[GRCh38] inv(2)(pter→p22.3::q31.1→p22.3::q31.1→qter)dn
NC_000002.12:g.[32310435_32310710del;32310711_171827243inv;171827243_171827244insG]Sequencing shows a pericentric inversion of chromosome 2. The combination of the ISCN detailed system (karyotype format) and of the HGVS nomenclature describe a *de novo* pericentric inversion in chromosome 2 (nucleotides 32,310,711 to 171,827,243) with a 276 bp deletion (nucleotides 32,310,435 to 32,310,710) at the short arm breakpoint and a single base pair insertion (G) at the

long arm breakpoint. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

iii. seq[GRCh38] inv(2)(p22.3q31.1)mat NC_000002.12:g.[32310435_32310710delinsG;32310711_171827243inv]Sequencing shows a pericentric inversion of chromosome 2. The combination of the ISCN short system (karyotype format) and of the HGVS nomenclature describe a maternally inherited pericentric inversion in chromosome 2 (nucleotides 32,310,711 to 171,827,243) with a 276 bp deletion (nucleotides 32,310,435 to 32,310,710) and a single base pair insertion (G) at the short arm breakpoint. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

iv. seq[GRCh38] inv(6)(p22.3p21.2) NC_000006.12:g.[20271801_39524349inv;39524350A>C]Sequencing shows a paracentric inversion within the short arm of chromosome 6. The combination of the ISCN short system (karyotype format) and of the HGVS nomenclature describe a paracentric inversion in the short arm of chromosome 6 (nucleotides 20,271,801 to 39,524,349) with a single nucleotide substitution at the breakpoint (39,524,350 A to C). Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

11.4.2.7 Translocation

Translocations that appear balanced karyotypically may show imbalances at the breakpoint(s) by sequencing. The following examples show a combination of the ISCN karyotype format (short system or detailed system) and of the HGVS nomenclature to describe the gross structural change to chromosomes as the result of a translocation that is identified by sequencing.

i. 46,XX,t(2;11)(p24;p15).seq[GRCh38] t(2;11)(p25.1;p15.2) NC_000002.12:g.pter_8247756delins[NC_000011.10:g.pter_15825272] NC_000011.10:g.pter_15825272delins[NC_000002.12:g.pter_8247756]Chromosome analysis and sequencing data show a translocation between the short arms of chromosomes 2 and 11. The karyotype breakpoints, at bands 2p24 and 11p15, are further defined by sequencing to be bands 2p25.1 and 11p15.2. The translocation involves the joining of the chromosome 11 nucleotide 15,825,272 to the chromosome 2 nucleotide 8,247,757 on the derivative chromosome 2, and the joining of the chromosome 2 nucleotide 8,247,756 to the chromosome 11 nucleotide 15,825,273 on the derivative chromosome 11. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

ii. seq[GRCh38] t(2;11)(q31.1;q22.3) NC_000002.12:g.174500009_qterdelins[NC_000011.10:g.108111987_qter] NC_000011.10:g.108111982_qterdelins[NC_000002.12:g.174500009_qter]Sequencing shows a translocation between the long arms of chromosomes 2 and 11. The translocation involves the joining of chromosome 11 nucleotide 108,111,987 to the chromosome 2 nucleotide 174,500,008 on the derivative chromosome 2, and the joining of the chromosome 2 nucleotide 174,500,009 to the chromosome 11

nucleotide 108,111,981 on the derivative chromosome 11. There is a 5 bp deletion of chromosome 11 sequence as evident from the nucleotide numbers given for the two chromosome 11 breakpoints (from 108,111,982 to 108,111,986). Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

iii. seq[GRCh38] t(12;21)(p13.2;q22.12) NC_000012.12:g.pter_11874853delins[NC_000021.9:g.34953708_qterinv] NC_000021.9:g.34953108_qterdelins[NC_000012.12:g.pter_11873172inv]Sequencing shows a translocation between the short arm of chromosome 12 and the long arm of chromosome 21. There is a 1.68 kb deletion of chromosome 12 sequence evident from the nucleotide numbers given for the two chromosome 12 breakpoints (from 11,873,173 to 11,874,853), and a 600 bp deletion of chromosome 21 sequence evident from the nucleotide numbers given for the two chromosome 21 breakpoints (from 34,953,108 to 34,953,707). Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

iv. seq[GRCh38] t(3;14)(14qter→14q12::3p22.2→3qter;14pter→14q12::3p22.2→3pter) NC_000003.12:g.pter_36969141delins[NC_000014.9:g.29745314_qterinv;CATTTGTTCAAATTTAGTTCAAATGA] [NC_000003.12:g.pter_36969141inv]Sequencing shows a translocation between the short arm of chromosome 3 at 36,969,141 and the long arm of chromosome 14 at 29,745,314 with insertion of non-templated sequence (CATTTGTTCAAATTTAGTTCAAATGA) at the breakpoint on the derivative chromosome 3. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

v. seq[GRCh38] t(9;9)(9qter→9q31.1::9p21.2→9qter;9pter→9q31.1::9p21.2→9qter) NC_000009.12:g.[pter_26393001delins102425452_qterinv];[102425452_qterdelinspter_26393001inv]Sequencing shows a translocation between homologous chromosomes with breakpoints at 9p21.2 and 9q31.1. The different chromosome 9 homologues are indicated by the underline of the second chromosome 9 in the ISCN line. The translocation involves the joining of the short arm of the first chromosome 9 at 26,393,002 to the second chromosome 9 long arm at 102,425,452 and the long arm of the second chromosome 9 at nucleotide 102,425,451 to the short arm of the first chromosome 9 at nucleotide 26,393,001. The HGVS nomenclature uses the allele format to indicate that these findings are found *in trans*, indicating that both chromosome 9s are abnormal. Since the ISCN and HGVS nomenclature lines give different information, both should be used to describe the variant.

12 Chromosome Breakage and Instability

This chapter provides a nomenclature for the chromatid and chromosome aberrations that may be observed in, for example, constitutional chromosome breakage syndromes or following clastogenic exposure.

Since many aberrations of this kind are scored on unbanded material, recommendations are given first for non-banded preparations and then for banded preparations.

12.1 Chromatid Aberrations

12.1.1 Non-Banded Preparations

a. A **chromatid** (**cht**) aberration involves only one chromatid in a chromosome at a given locus.
b. A **chromatid gap** (**chtg**) is a non-staining region (achromatic lesion) of a single chromatid in which there is minimal misalignment of the chromatid.
c. A **chromatid break** (**chtb**) is a discontinuity of a single chromatid in which there is a clear misalignment of one of the chromatids.
d. A **chromatid exchange** (**chte**) is the result of two or more chromatid lesions and the subsequent rearrangement of chromatid material. Exchanges may be between chromatids of different chromosomes (*interchanges*) or between or within chromatids of one chromosome (*intrachanges*).
e. In the case of interchanges, it will generally be sufficient to indicate the configuration as:

- **triradial** (**tr**) when there are three arms to the pattern,
- **quadriradial** (**qr**) when there are four, or
- **multiradial** (**mr**) when there are more than four arms to the pattern.

f. The number of centromeres may be indicated within parentheses (1 cen, 2 cen, *etc.*).
g. When necessary, exchanges may be classified in more detail:

- *Asymmetrical* exchanges inevitably result in the formation of an acentric fragment, whereas *symmetrical exchanges* do not. In asymmetrical exchanges, the incompleteness may be proximal when the broken ends nearest the centromere are not rejoined or distal when the ends farthest from the centromere are not rejoined.
- In *complete exchanges*, all broken ends are rejoined, but this does not occur in *incomplete exchanges*.
- Intra-arm events include duplications, deletions, paracentric inversions, and isochromatid breaks showing sister reunion.
- It should be noted that these terms are descriptive only and do not imply knowledge of the origin of the aberrations.

h. **Sister chromatid exchange**, detectable only by special staining methods, results from the interchange of homologous segments between two chromatids of one chromosome. The abbreviation **sce** can be used to describe this event.

12.1.2 Banded Preparations

Some chromatid aberrations can be defined more precisely or can be recognized with certainty only in banded preparations.

a. There is a space between two abbreviations, but there is no space between the last abbreviation and the parentheses.
b. A **chromatid deletion** (**cht del**) is the absence of a banded sequence from only one of the two chromatids of a single chromosome.
c. A **chromatid inversion** (**cht inv**) is the reversal of a banded sequence of only one of the two chromatids of a single chromosome.
d. Both **cht del** and **cht inv** are subclasses of **chromatid exchanges** (**chte**).
e. Where it is desired to specify the location of a chromatid aberration, the appropriate abbreviation can be followed by the band designation.

chtg(4)(q25)	Chromatid gap in chromosome 4 at band 4q25.
chtb(4)(q25)	Chromatid break in chromosome 4 at band 4q25.
chte(4;10)(q25;q22)	Chromatid exchange involving chromosomes 4 and 10 at bands 4q25 and 10q22.
cht del(1)(q12q25)	Chromatid deletion in chromosome 1 with loss of the segment between bands 1q12 and 1q25.
cht inv(1)(q12q25)	Chromatid inversion in chromosome 1 with reversal of the segment between bands 1q12 and 1q25.
sce(4)(q25q33)	Sister chromatid exchanges in chromosome 4 at bands 4q25 and 4q33.

12.2 Chromosome Aberrations

12.2.1 Non-Banded Preparations

a. A **chromosome** (**chr**) aberration involves both chromatids of a single chromosome at the same locus.
b. A **chromosome gap** (**chrg**) is a non-staining region (achromatic lesion) at the same locus in both chromatids of a single chromosome in which there is minimal misalignment of the chromatids. The term *chromosome gap* is synonymous with *isolocus gap* and *isochromatid gap*.
c. A **chromosome break** (**chrb**) is a discontinuity at the same locus in both chromatids of a single chromosome, giving rise to an acentric fragment and an abnormal monocentric chromosome. This fragment is therefore a particular type of acentric fragment (**ace**), and **chrb** should be used only when the morphology indicates that the fragment is the result of a single event. The term *chromosome break* is synonymous with *isolocus break* and *isochromatid break*.

d. A **chromosome exchange** (**chre**) is the result of two or more chromosome lesions and the subsequent relocation of both chromatids of a single chromosome to a new position on the same or on another chromosome. It may be symmetrical (*e.g.*, reciprocal translocation) or asymmetrical (*e.g.*, dicentric formation).
e. A **minute** (**min**) is an acentric fragment smaller than the width of a single chromatid. It may be single or double. In the special situation, when *double minutes* are present clonally in tumor cells, the abbreviation **dmin** is used; see Sections 5.5.3 and 5.5.12.
f. **Pulverization** (**pvz**) indicates a situation where a cell contains both chromatid and/or chromosome gaps and breaks that are not normally associated with exchanges and are present in such numbers that they cannot be enumerated. Occasionally, one or more chromosomes in a cell are pulverized while the remaining chromosomes are of normal morphology; *e.g.*, pvz(1) is a pulverized chromosome 1.
g. **Premature chromosome condensation** (**pcc**) occurs when an interphase nucleus is induced to enter mitosis prematurely. A **pcc** may involve a G1 or a G2 nucleus. The chromatin of S-phase nuclei undergoing **pcc** often appears to be pulverized.
h. The term **premature centromere division** (**pcd**) may be used to describe premature separation of centromeres in metaphase. The **pcd** may affect one or more chromosomes in a fraction of the cells.

12.2.2 Banded Preparations

a. When banded preparations allow adequate identification of chromosome segments or chromosome aberrations, the nomenclature described in ISCN 2024 can be used. When not, the observations can be described in words.
b. A **marker chromosome** (**mar**) is a structurally rearranged chromosome in which no part can be identified by chromosome banding methods (see Section 5.5.12).

12.3 Scoring of Aberrations

a. The main types of aberrations scored are **chtg**, **chtb**, **chte**, **chrg**, **chrb**, **ace**, **min**, **r**, **dic**, **tr**, **qr**, **der**, and **mar**, and reports should, where possible, give the data under these headings. It is recognized, however, that aberrations are frequently grouped to give adequate numbers, *e.g.*, for statistical analysis. When this is done, it should be indicated how the groupings relate to the aberrations listed above, *e.g.*:

- Chromatid aberrations: chtg, chtb, chte
- Fragments (= deletions): chrb, ace, min
- Asymmetric aberrations: ace, dic, r

b. The data should not be presented as deduced breakages per cell but in such a manner that it is possible to calculate the number of aberrations per cell.

13 References

Al-Aish MS: Human chromosome morphology. I. Studies on normal chromosome characterization, classification and karyotyping. Can J Genet Cytol 11:370–381 (1969).

Baliakas P, Jeromin S, Iskas M, Puiggros A, Plevova K, Nguyen-Khac F, Davis Z, Rigolin GM, Visentin A, Xochelli A, et al: Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. Blood 133:1205–1216 (2019).

Behrend C, Karimzad Hagh J, Mehdipour P, Schott H, Schwanitz G: Human Chromosome Atlas: Introduction to Diagnostics of Structural Aberrations (2nd ed., Springer International Publishing, Cham 2023).

Bruford EA, Antonescu CR, Carroll AJ, Chinnaiyan A, Cree IA, Cross NCP, Dalgleish R, Gale RP, Harrison CJ, Hastings RJ, Huret J-L, Johansson B, Le Beau M, Mecucci C, Mertens F, Verhaak R, Mitelman F: HUGO Gene Nomenclature Committee (HGNC) recommendations for the designation of gene fusions. Leukemia 35:3040–3043 (2021).

Caspersson T, Farber S, Foley GE, Kudynoski J, Modest EJ, Simonsson E, Wagh U, Zech L: Chemical differentiation along metaphase chromosomes. Exp Cell Res 49:219–222 (1968).

Caspersson T, Lomakka G, Zech L: The 24 fluorescence patterns of human metaphase chromosomes – distinguishing characters and variability. Hereditas 67:89–102 (1971).

Cheng C, Zhou Y, Li H, Xiong T, Li S, Bi Y, Kong P, Wang F, Cui H, Li Y, et al: Whole-genome sequencing reveals diverse models of structural variations in esophageal squamous cell carcinoma. Am J Hum Genet 98:256–274 (2016).

Chia NL: A comprehensive set of idiograms representing all interpretive levels of resolution: ISCN (2009). Cytogenet Genome Res 125:162–164 (2009).

Chicago Conference (1966): Standardization in Human Cytogenetics. Birth Defects: Original Article Series, Vol 2, No 2 (The National Foundation, New York 1966).

Chun K, Hagemeijer A, Iqbal A, Slovak ML: Implementation of standardized international karyotype scoring practices is needed to provide uniform and systematic evaluation for patients with myelodysplastic syndrome using IPSS criteria: An

International Working Group on MDS Cytogenetics Study. Leukemia Res 34:160–165 (2010).

Cremer T, Landegent J, Bruckner A, Scholl HP, Schardin M, Hager HD, Devilee P, Pearson P, van der Ploeg M: Detection of chromosome aberrations in the human interphase nucleus by visualization of specific target DNAs with radioactive and non-radioactive *in situ* hybridization techniques: diagnosis of trisomy 18 with probe L1.84. Hum Genet 74:346–352 (1986).

den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, Roux AF, Smith T, Antonarakis SE, Taschner PE: HGVS recommendations for the description of sequence variants: 2016 update. Hum Mutat 37:564–569 (2016).

Denver Conference (1960): A proposed standard system of nomenclature of human mitotic chromosomes. Lancet i:1063–1065 (1960).

Dutrillaux B: Obtention simultanée de plusieurs marquages chromosomiques sur les mêmes préparations, après traitement par le BrdU. Humangenetik 30:297–306 (1975).

Dutrillaux J, Lejeune CR: A new technic of analysis of the human karyotype. Acad Sci Hebd Seances Acad Sci D 272:2638–2640 (1971).

Ford CE, Hamerton JL: The chromosomes of man. Nature 178:1020–1023 (1956).

Francke U: High-resolution ideograms of trypsin-Giemsa banded human chromosomes. Cytogenet Cell Genet 31:24–32 (1981).

Francke U: Digitized and differentially shaded human chromosome ideograms for genomic applications. Cytogenet Cell Genet 65:206–218 (1994).

Francke U, Oliver N: Quantitative analysis of high-resolution trypsin-Giemsa bands on human prometaphase chromosomes. Hum Genet 45:137–165 (1978).

Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, Wheatley K, Harrison CJ, Burnett AK, National Cancer Research Institute Adult Leukaemia Working Group: Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood 116:345–365 (2010).

Guan XY, Meltzer PS, Trent JM: Rapid generation of whole chromosome painting probes (WCPs) by chromosome microdissection. Genomics 22:101–107 (1994).

Haase D, Stevenson KE, Neuberg D, Maciejewski JP, Nazha A, Sekeres MA, Ebert BL, Garcia-Manero G, Haferlach C, Haferlach T, et al: *TP53* mutation status divides

myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. Leukemia 33:1747–1758 (2019).

ISCN (1978): An International System for Human Cytogenetic Nomenclature. Birth Defects: Original Article Series, Vol 14, No 8 (The National Foundation, New York 1978); also in Cytogenet Cell Genet 21:309–404 (1978).

ISCN (1981): An International System for Human Cytogenetic Nomenclature – High Resolution Banding. Birth Defects: Original Article Series, Vol 17, No 5 (March of Dimes Birth Defects Foundation, New York 1981); also in Cytogenet Cell Genet 31:1–23 (1981).

ISCN (1985): An International System for Human Cytogenetic Nomenclature, Harnden DG, Klinger HP (eds), Birth Defects: Original Article Series, Vol 21, No 1 (March of Dimes Birth Defects Foundation, New York 1985).

ISCN (1991): Guidelines for Cancer Cytogenetics, Supplement to An International System for Human Cytogenetic Nomenclature, Mitelman F (ed), (S Karger, Basel 1991).

ISCN (1995): An International System for Human Cytogenetic Nomenclature, Mitelman F (ed), (S Karger, Basel 1995).

ISCN (2005): An International System for Human Cytogenetic Nomenclature, Shaffer LG, Tommerup N (eds), (S Karger, Basel 2005).

ISCN (2009): An International System for Human Cytogenetic Nomenclature, Shaffer LG, Slovak ML, Campbell LJ (eds), (S Karger, Basel 2009).

ISCN (2013): An International System for Human Cytogenetic Nomenclature, Shaffer LG, McGowan-Jordan J, Schmid M (eds), (S Karger, Basel 2012).

ISCN (2016): An International System for Human Cytogenomic Nomenclature, McGowan-Jordan J, Simons A, Schmid M (eds), (Karger, Basel 2016); also in Cytogenet Genome Res 149:1–140 (2016).

ISCN (2020): An International System for Human Cytogenomic Nomenclature, McGowan-Jordan J, Moore S, Hastings RJ (eds), (S Karger, Basel 2020).

Iqbal MA, Broeckel U, Levy B, Skinner S, Sahajpal NS, Rodriguez V, Stence A, Awayda K, Scharer G, Skinner C, et al: Multisite Assessment of Optical Genome Mapping for Analysis of Structural Variants in Constitutional Postnatal Cases. J Mol Diagn 25:175–188 (2023).

Landegent JE, Jansen in de Wal N, Dirks RW, Baao F, van der Ploeg M: Use of whole cosmid cloned genomic sequences for chromosomal localization by non-radioactive *in situ* hybridization. Hum Genet 77:366–370 (1987).

Levan A, Frega K, Sandberg AA: Nomenclature for centromeric position on chromosomes. Hereditas 52:201–220 (1964).

Levy B, Baughn LB, Akkari Y, Chartrand S, LaBarge B, Claxton D, Lennon AP, Cujar C, Kolhe R, Kroeger K, et al: Optical Genome Mapping in Acute Myeloid Leukemia: A Multicenter Evaluation. Blood Adv 7:1297–1307 (2022).

Lichter P, Cremer T, Borden J, Manuelidis L, Ward DC: Delineation of individual human chromosomes in metaphase and interphase cells by *in situ* suppression hybridization using recombinant DNA libraries. Hum Genet 80:224–234 (1988).

Lichter P, Tang CJ, Call K, Hermanson G, Evans GA, Housman D, Ward DC: High-resolution mapping of human chromosome 11 by *in situ* hybridization with cosmid clones. Science 247:64–69 (1990).

Liehr T, Claussen U, Starke H: Small supernumerary marker chromosomes (sSMC) in humans. Cytogenet Genome Res 107:55–67 (2004).

Liehr T, Starke H, Heller A, Kosyakova N, Mrasek K, Gross M, Karst C, Steinhaeuser U, Hunstig F, Fickelscher I, et al: Multicolor fluorescence *in situ* hybridization (FISH) applied to FISH-banding. Cytogenet Genome Res 114:240–244 (2006).

Lin YF, Hu Q, Mazzagatti A, Valle-Inclán JE, Maurais EG, Dahiya R, Guyer A, Sanders JT, Engel JL, Nguyen G, et al: Mitotic clustering of pulverized chromosomes from micronuclei. Nature 618:1041–1048 (2023).

Liu P, Erez A, Nagamani SC, Dhar SU, Kolodziejska KE, Dharmadhikari AV, Cooper ML, Wiszniewska J, Zhang F, Withers MA, et al: Chromosome catastrophes involve replication mechanisms generating complex genomic rearrangements. Cell 146:889–903 (2011).

London Conference on the Normal Human Karyotype. Cytogenetics 2:264–268 (1963).

Magenis RE, Barton SJ: Delineation of human prometaphase paracentromeric regions using sequential GTG- and C-banding. Cytogenet Cell Genet 45:132–140 (1987).

Monk D, Morales J, den Dunnen JT, Russo S, Court F, Prawitt D, Eggermann T, Beygo J, Buiting K, Tümer Z, the Nomenclature Group of the European Network for Human Congenital Imprinting Disorders: Recommendations for a nomenclature system for reporting methylation aberrations in imprinted domains. Epigenetics 13:117–121 (2018).

Moore S, McGowan-Jordan J, Smith AC, Rack K, Koehler U, Stevens-Kroef M, Barseghyan H, Kanagal-Shamanna R, Hastings R: Genome Mapping Nomenclature. Cytogenet Genome Res 163(5–6):236–246 (2023).

Newman S, Hermetz KE, Weckselblatt B, Rudd K: Next-generation sequencing of duplication CNVs reveals that most are tandem and some create fusion genes at breakpoints. Am J Hum Genet 96:208–220 (2015).

Ordulu Z, Wong KE, Currall BB, Ivanov AR, Pereira SA, Gusella JF, Talkowski ME, Morton CC: Describing sequencing results of structural chromosome rearrangements with a suggested next-generation cytogenetic nomenclature. Am J Hum Genet 94:1–15 (2014).

Paris Conference (1971): Standardization in Human Cytogenetics. Birth Defects: Original Article Series, Vol 8, No 7 (The National Foundation, New York 1972); also in Cytogenetics 11:313–362 (1972).

Paris Conference (1971), Supplement (1975): Standardization in Human Cytogenetics. Birth Defects: Original Article Series, Vol 11, No 9 (The National Foundation, New York 1975); also in Cytogenet Cell Genet 15:201–238 (1975).

Parra I, Windle B: High resolution visual mapping of stretched DNA by fluorescent hybridization. Nat Genet 5:17–21 (1993).

Patau K: The identification of individual chromosomes, especially in man. Am J Hum Genet 12:250–276 (1960).

Pinkel D, Landegent J, Collins C, Fuscoe J, Segraves R, Lucas J, Gray JW: Fluorescence *in situ* hybridization with human chromosome-specific libraries: detection of trisomy 21 and translocations of chromosome 4. Proc Natl Acad Sci USA 85:9138–9142 (1988).

Rausch T, Jones DT, Zapatka M, Stütz AM, Zichner T, Weischenfeldt J, Jäger N, Remke M, Shih D, Northcott PA, et al: Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with TP53 mutations. Cell 148:59–71 (2012).

Sahajpal NS, Mondal AK, Fee T, Hilton B, Layman L, Hastie AR, Chaubey K, DuPont BR, Kolhe R: Clinical Validation and Diagnostic Utility of Optical Genome Mapping in Prenatal Diagnostic Testing. J Mol Diagn 25:234–246 (2023).

Schluth-Bolard C, Labalme A, Cordier M-P, Till M, Nadeau G, Tevissen H, Lesda G, Boutry-Kryza N, Rossignol S, Rocas D, et al: Breakpoint mapping by next generation sequencing reveals causative gene disruption in patients carrying apparently balanced chromosome rearrangements with intellectual deficiency and/or congenital malformations. J Med Genet 50:144–150 (2013).

Seabright M: A rapid banding technique for human chromosomes. Lancet 298:971–972 (1971).

Smith AC, Neveling K, Kanagal-Shamanna R: Optical genome mapping for structural variation analysis in hematologic malignancies. Am J Hematol 97:975–982 (2022).

Stephens PJ, Greenman CD, Fu B, Yang F, Bignell GR, Mudie LJ, Pleasance ED, Lau KW, Beare D, Stebbings LA, et al: Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 144:27–40 (2011).

Tjio JH, Levan A: The chromosome number of man. Hereditas 42:1–16 (1956).

Trask BJ: Fluorescence *in situ* hybridization: applications in cytogenetics and gene mapping. Trends Genet 7:149–154 (1991).

Viegas-Pequignot E, Dutrillaux B: Une méthode simple pour obtenir des prophases et des prometaphases. Ann Genet 21:122–125 (1978).

Wiegant J, Kalle W, Mullenders L, Brookes S, Hoovers JM, Dauwerse JG, van Ommen GJ, Raap AK: High-resolution *in situ* hybridization using DNA halo preparations. Hum Mol Genet 1:587–591 (1992).

Wiegant J, Wiesmeijer CC, Hoovers JM, Schuuring E, d'Azzo A, Vrolijk J, Tanke HJ, Raap AK: Multiple and sensitive fluorescence *in situ* hybridization with rhodamine-, fluorescein-, and coumarin-labeled DNAs. Cytogenet Cell Genet 63:73–76 (1993).

Wyandt HE, Tonk VS (eds): Atlas of Human Chromosome Heteromorphisms (Springer, New York 2008).

Xue Y, Durocher D: A mitotic glue for shattered chromosomes. Nature 618:909–910 (2023).

Yunis JJ: High resolution of human chromosomes. Science 191:1268–1270 (1976).

Yunis JJ, Sawyer JR, Ball DW: The characterization of high-resolution G-banded chromosomes of man. Chromosoma 67:293–307 (1978).

Zepeda-Mendoza CJ, Morton CC: The iceberg under water: Unexplored complexity of chromoanagenesis in congenital disorders. Am J Hum Genet 104(4):565–577 (2019).

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Acknowledgements

The Committee gratefully acknowledges Dorathe Schindelholz, Karger, for her copy editing. David Betts, Dublin, Ireland, Dr. Berna Beverloo, Rotterdam, The Netherlands, and Melody Tabiner, Oxford, UK for proofreading the document. Finally, the ISCN committee thanks members of the cytogenomics community and OGM user group for their suggestions, examples and images.

Statement of Ethics

As a set of recommendations this publication is exempt from ethical committee approval.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The 2023 Committee meeting and ISCN (2024) publication were made possible by generous contributions from Karger Publishers.

Author Contributions

Dr. Rosalind Hastings collected suggestions from the cytogenomics community, collated all the recommendations of the Standing Committee and edited all chapters. Dr. Rosalind Hastings reorganized Chapters 1, 2, 3, 10, and the Appendix, plus amended Chapters 12, 13, and 14. Dr. Rosalind Hastings, Sarah Moore and Dr. Nicole Chia provided critical review of and contributed ideas and content for all the other chapters. Prof. Jean-Michel Dupont reorganized Chapters 4 and 5 and provided critical review of Chapters 2 and 10. Prof. Jean McGowen-Jordan critically reviewed Chapters 4 and 5. Profs. Myungshin Kim and Jin-Yeong Han provided critical review of, and additional examples for Chapter 6. Prof. Myungshin Kim also reviewed Chapter 10. Sarah Moore and Dr. Nicole Chia provided critical review of, and additional examples for Chapter 7. Dr. Nicole Chia and Prof. Cynthia Morton provided critical review of, and additional examples for Chapter 8. Sarah Moore, Dr. Ros Hastings, Prof. Jean McGowan-Jordan also developed the Genomic mapping nomenclature (Chapter 9) with input from the OGM user group. Dr. Laura Conlin provided critical review of, and additional examples for Chapter 11, as well as contributing additional examples to Chapters 7 and 8. As an ISCN Standing Committee member and Chair of HUGO HGVS Variant Nomenclature Committee (HVNC), Prof. Johan den Dunnen contributed to the revision of the HGVS within Chapter 11.

15 Appendix

15.1 Molecular Basis of Banding

Chromosome bands reflect the functional organization of the genome that regulates DNA replication, repair, transcription, and genetic recombination. The molecular basis of banding methods is known to involve nucleotide base composition, associated proteins, and genome functional organization. In general, Giemsa-positive bands (G-dark bands, R-light bands) are AT-rich, late replicating, and gene poor; whereas, Giemsa-negative bands (G-light bands, R-dark bands) are CG-rich, early replicating, and relatively gene rich. **Note:** if fluorescent R- or G-banding is used, then the dark and light bands may be different.

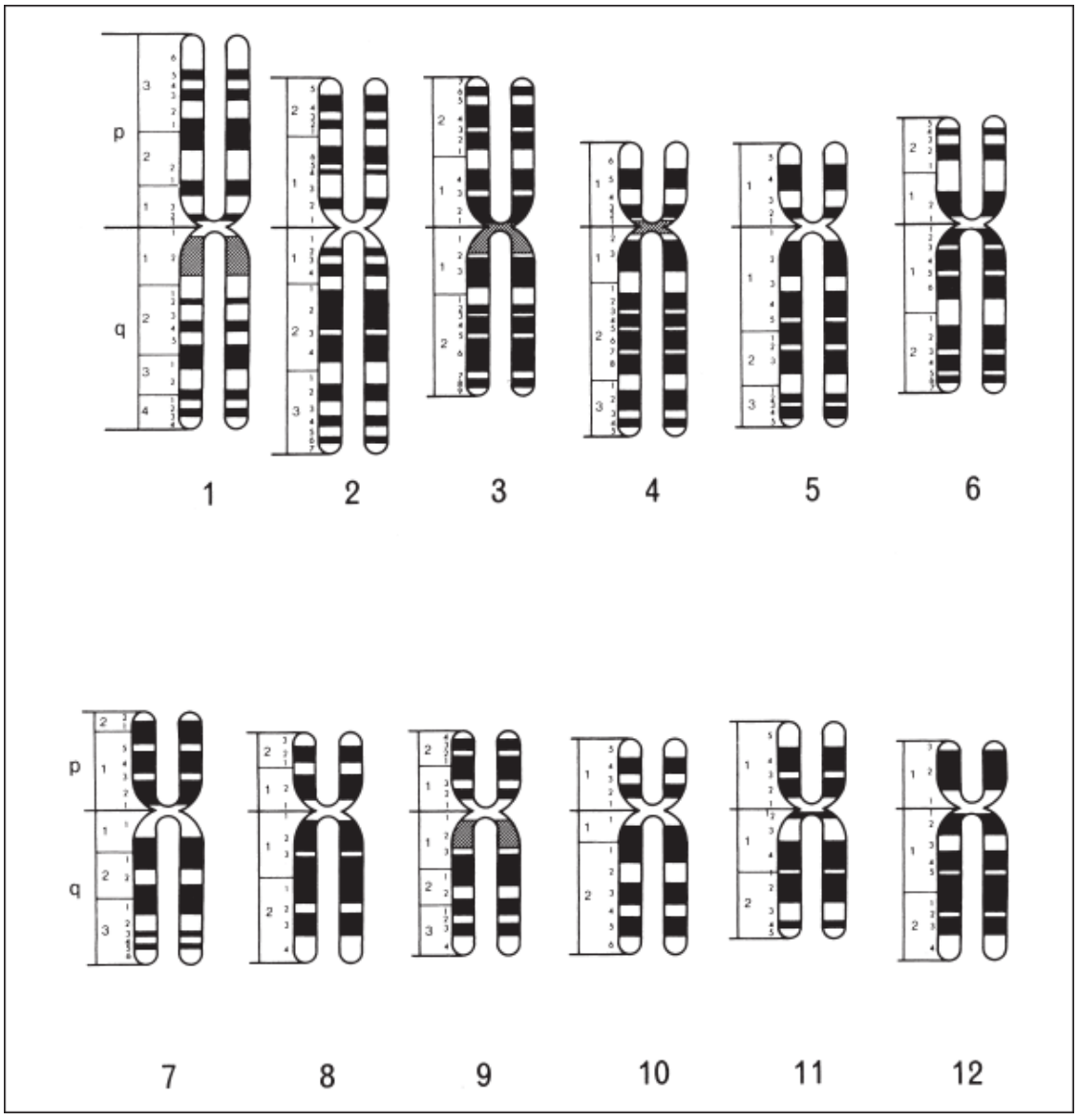
Centromeric DNA and pericentromeric heterochromatin, composed of α-repetitive DNA and various families of repetitive satellite DNA, are easily detected by C-banding. The telomere is composed of 5 to 20kb of tandem hexanucleotide minisatellite repeat units, TTAGGG, and stains darkly by T-banding. The 18S and 28S ribosomal RNA genes are clustered together in large arrays containing about 40 copies of each gene. These are located on the acrocentric short arms, at the nucleolar organizer regions or NORs, and are detected by silver staining.

15.2 Chromosome Banding

The original banding pattern was described in the Paris Conference (1971) report and was based on the patterns observed in different metaphase cells stained with either the Q-, G-, or R-banding technique (Fig. 14). The banding patterns obtained with these staining methods agreed sufficiently to allow the construction of a single idiogram representative of all three techniques. The bands were designated on the basis of their midpoints and not by their margins. Intensity was taken into consideration in determining which bands should serve as landmarks on each chromosome in order to divide the chromosome into natural, easily recognizable morphologic regions. A list of bands serving as landmarks that were used in constructing this diagram is provided in Table 12.

The idiograms showing the G-banding patterns for normal human chromosomes at five different levels of resolution are shown in Figure 15. The corresponding G- and R-banded chromosomes are for approximately the same resolution in Figures 16a and 16b.

15.3 Idiograms



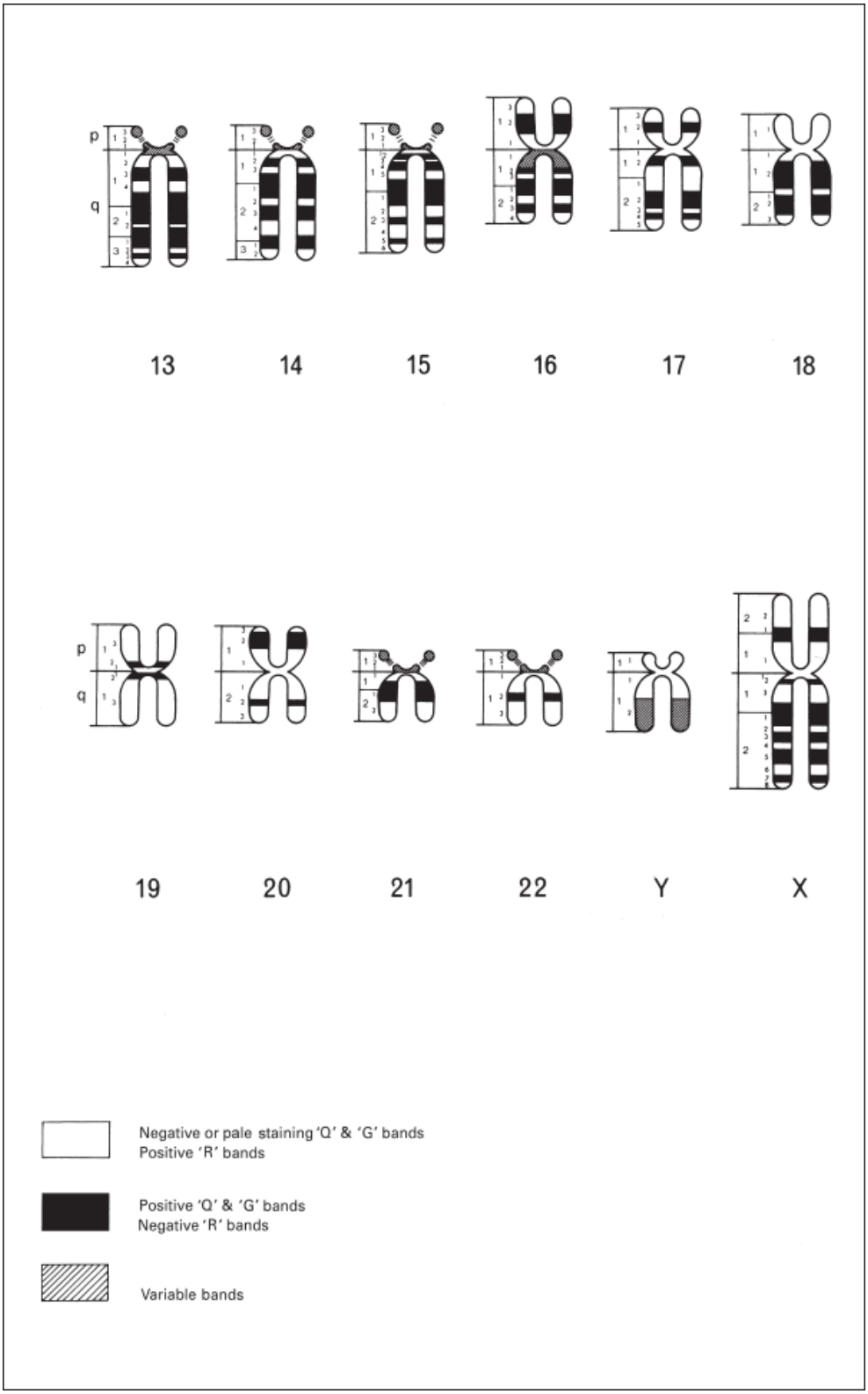
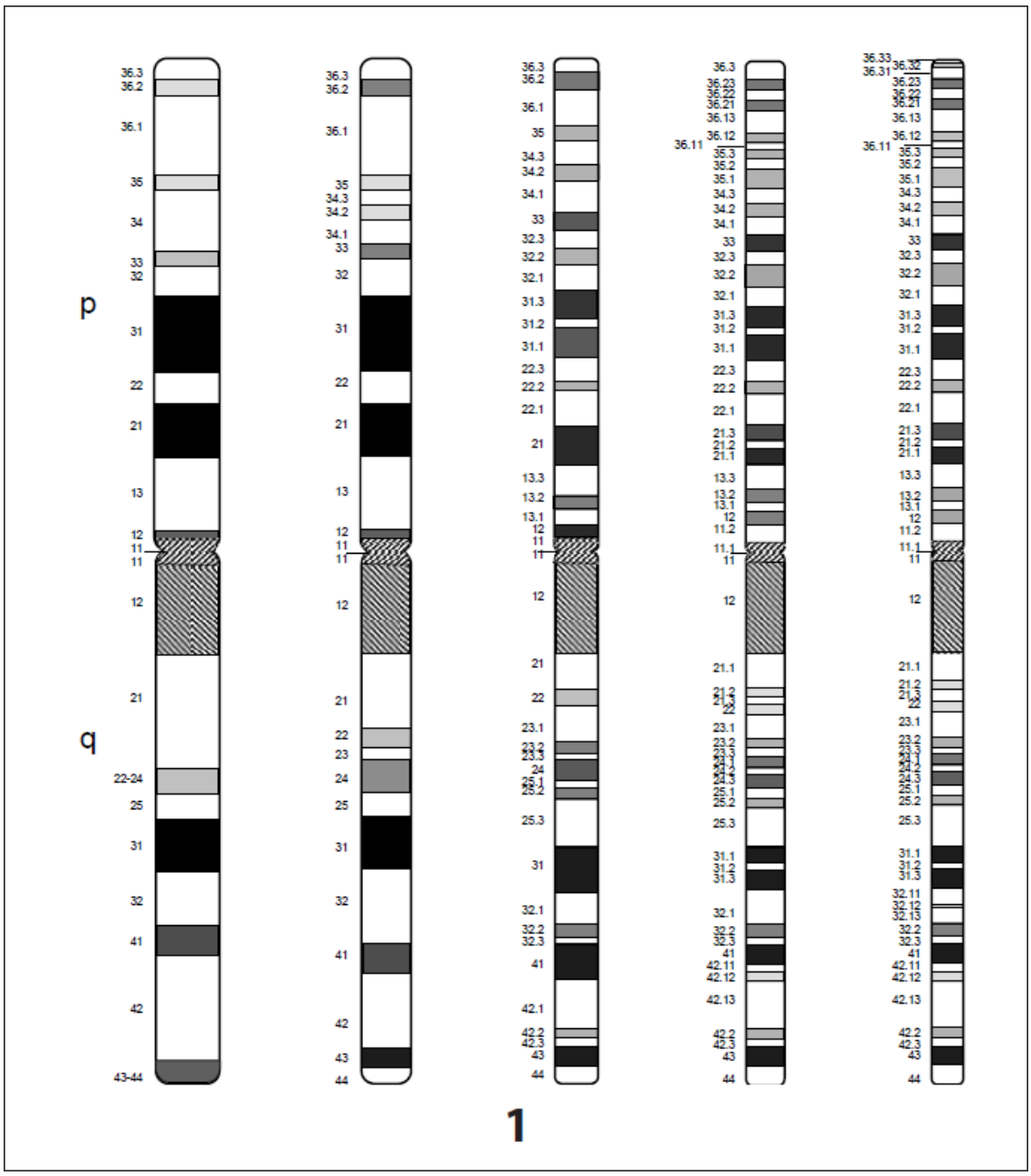


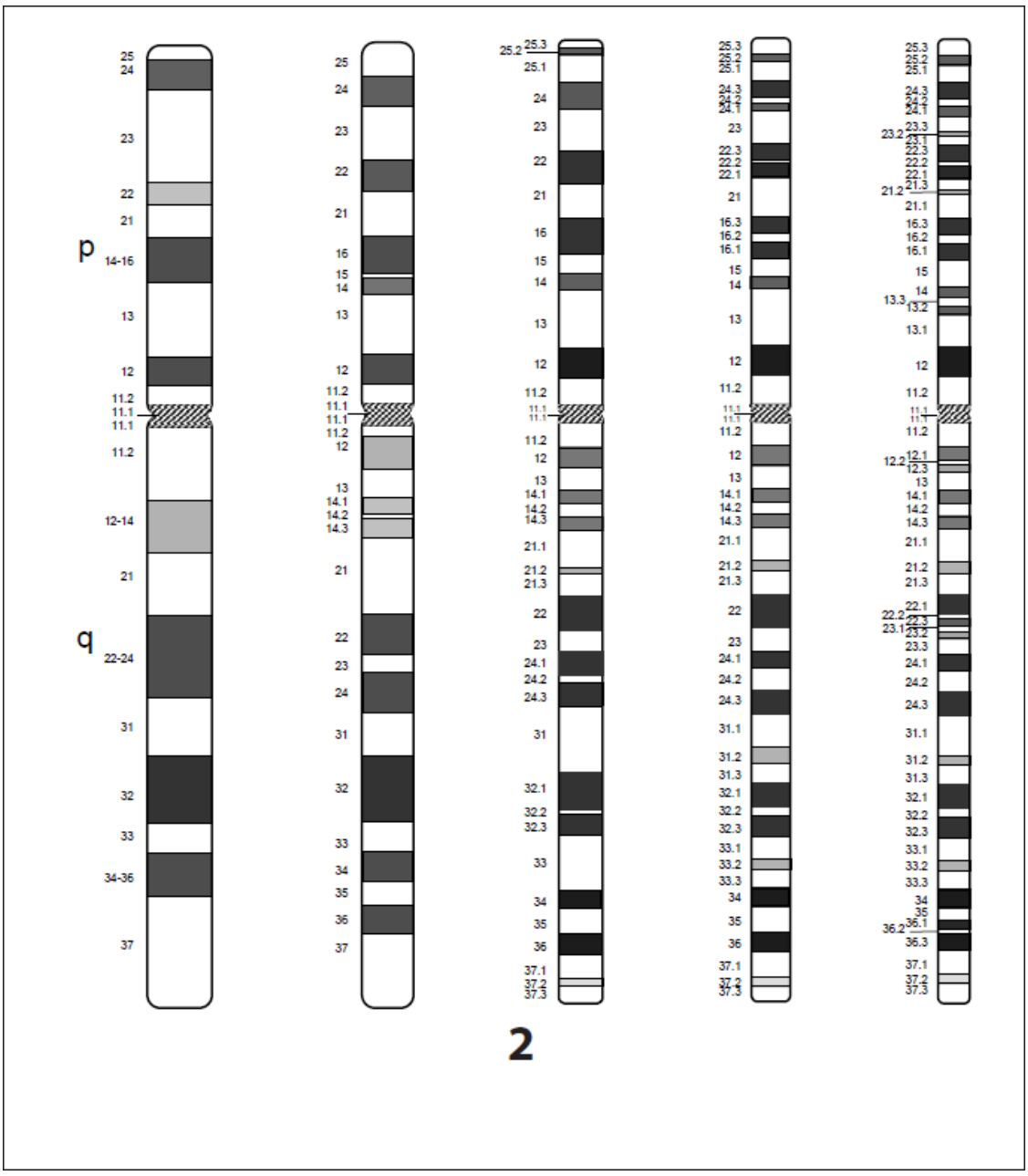
Fig 14. *Diagrammatic representation of human chromosome bands as observed with the Q-, G-, and R- banding methods; centromeric regions are representative of Q-staining method only (Paris Conference, 1971).*

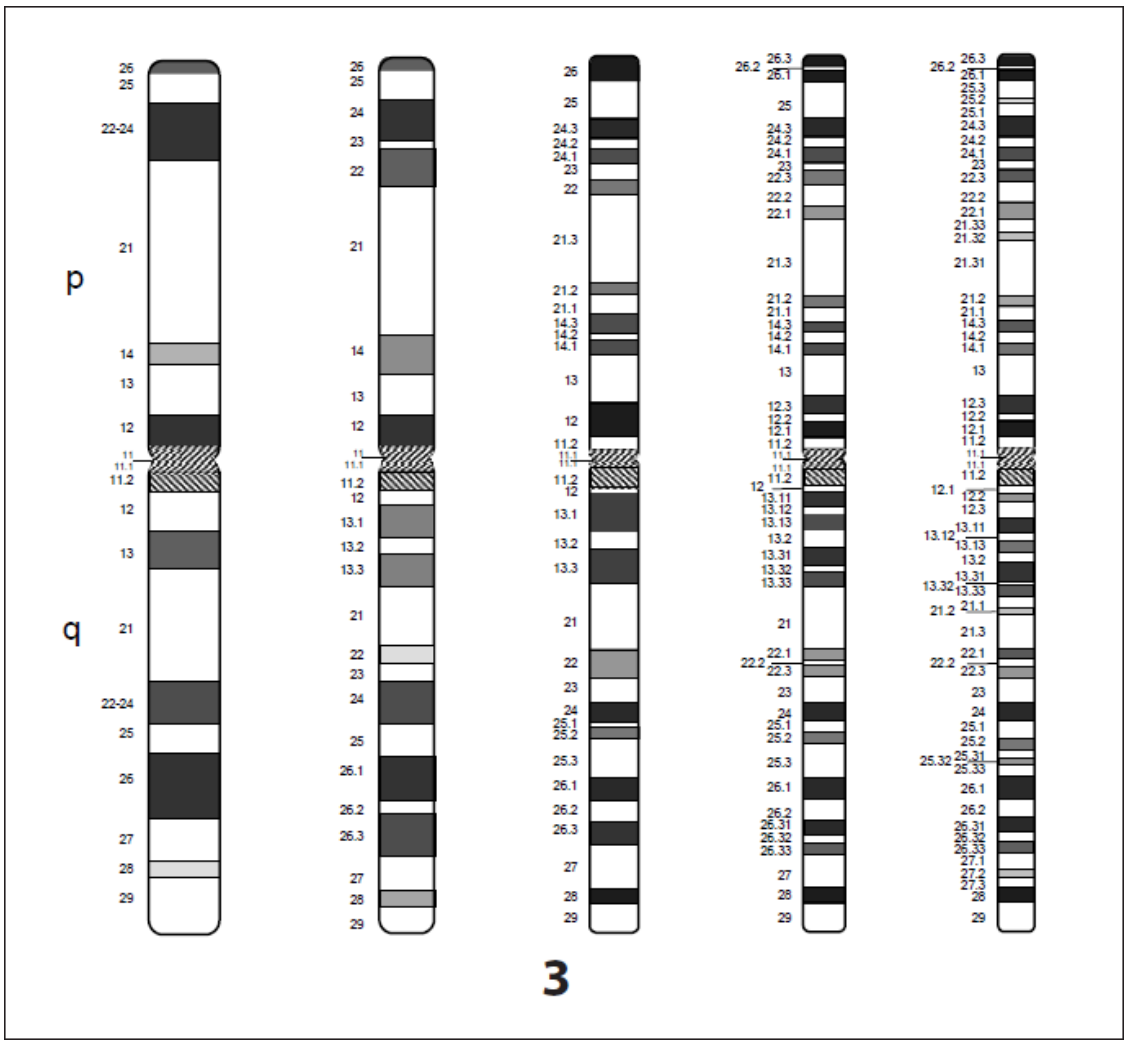
Table 12. Bands identified as landmarks that divide the chromosomes into cytogenetically defined regions. The omission of an entire chromosome or chromosome arm indicates that either both arms or the arm in question consists of only one region, delimited by the centromere and the end of the chromosome arm.

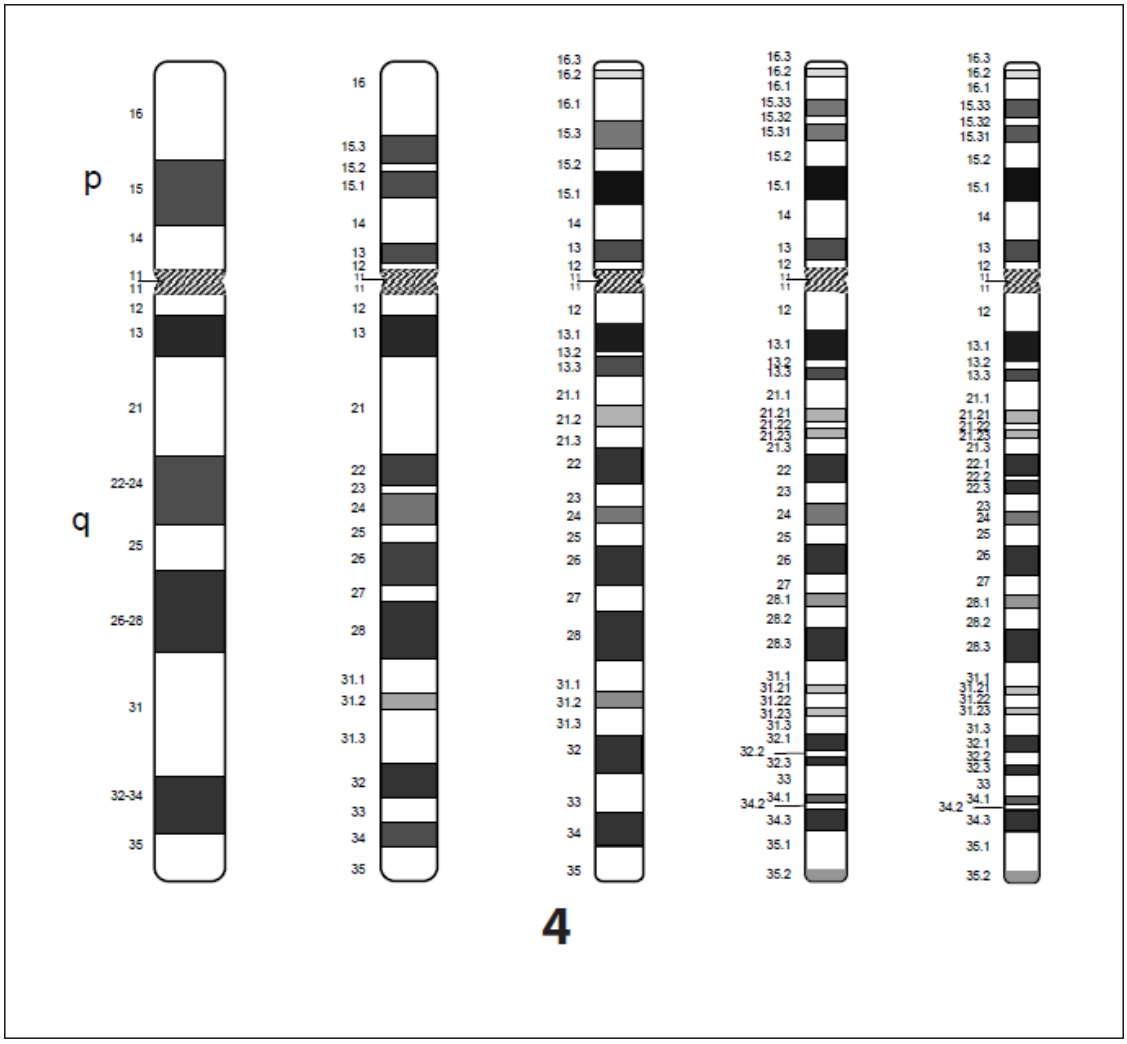
Chromosome		Number of regions	Landmarks[a]
number	arm		
1	p	3	Proximal band of medium intensity (21), median band of medium intensity (31)
	q	4	Proximal negative band (21) distal to variable region, median intense band (31), distal band of medium intensity (41)
2	p	2	Median negative band (21)
	q	3	Proximal negative band (21), distal negative band (31)
3	p	2	Median negative band (21)
	q	2	Median negative band (21)
4	q	3	Proximal negative band (21), distal negative band (31)
5	q	3	Median band of medium intensity (21), distal negative band (31)
6	p	2	Median negative band (21)
	q	2	Median negative band (21)
7	p	2	Distal band of medium intensity (21)
	q	3	Proximal band of medium intensity (21), median band of medium intensity (31)
8	p	2	Median negative band (21)
	q	2	Median band of medium intensity (21)
9	p	2	Median intense band (21)
	q	3	Median band of medium intensity (21), distal band of medium intensity (31)
10	q	2	Proximal intense band (21)
11	q	2	Median negative band (21)
12	q	2	Median band of medium intensity (21)
13	q	3	Median intense band (21), distal intense band (31)
14	q	3	Proximal intense band (21), distal band of medium intensity (31)
15	q	2	Median intense band (21)
16	q	2	Median band of medium intensity (21)
17	q	2	Proximal negative band (21)
18	q	2	Median negative band (21)
21	q	2	Median intense band (21)
X	p	2	Proximal band of medium intensity (21)
	q	2	Proximal band of medium intensity (21)

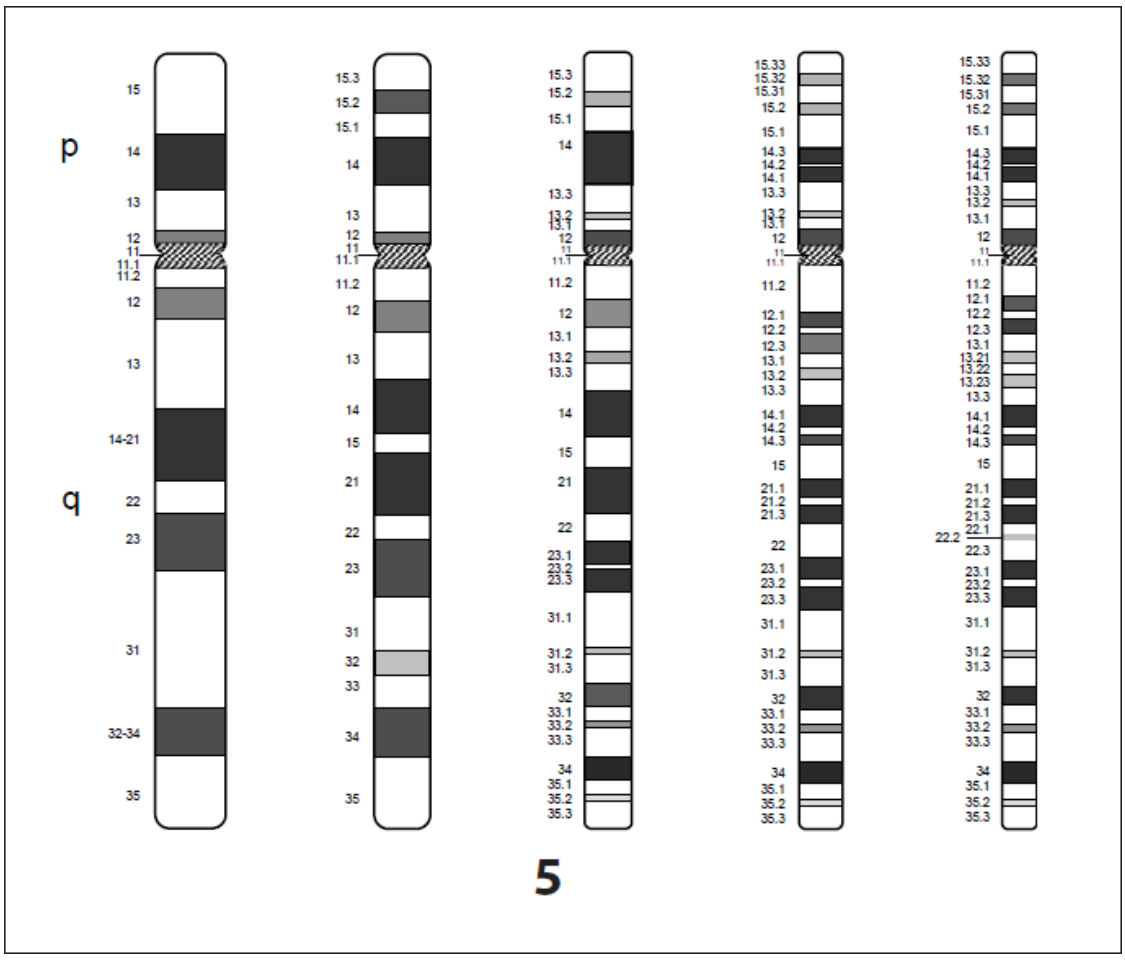
[a] The numbers in parentheses are the region and band numbers as shown in Figure 15.


p
q
1


p
q
2


p
q
3


p
q
4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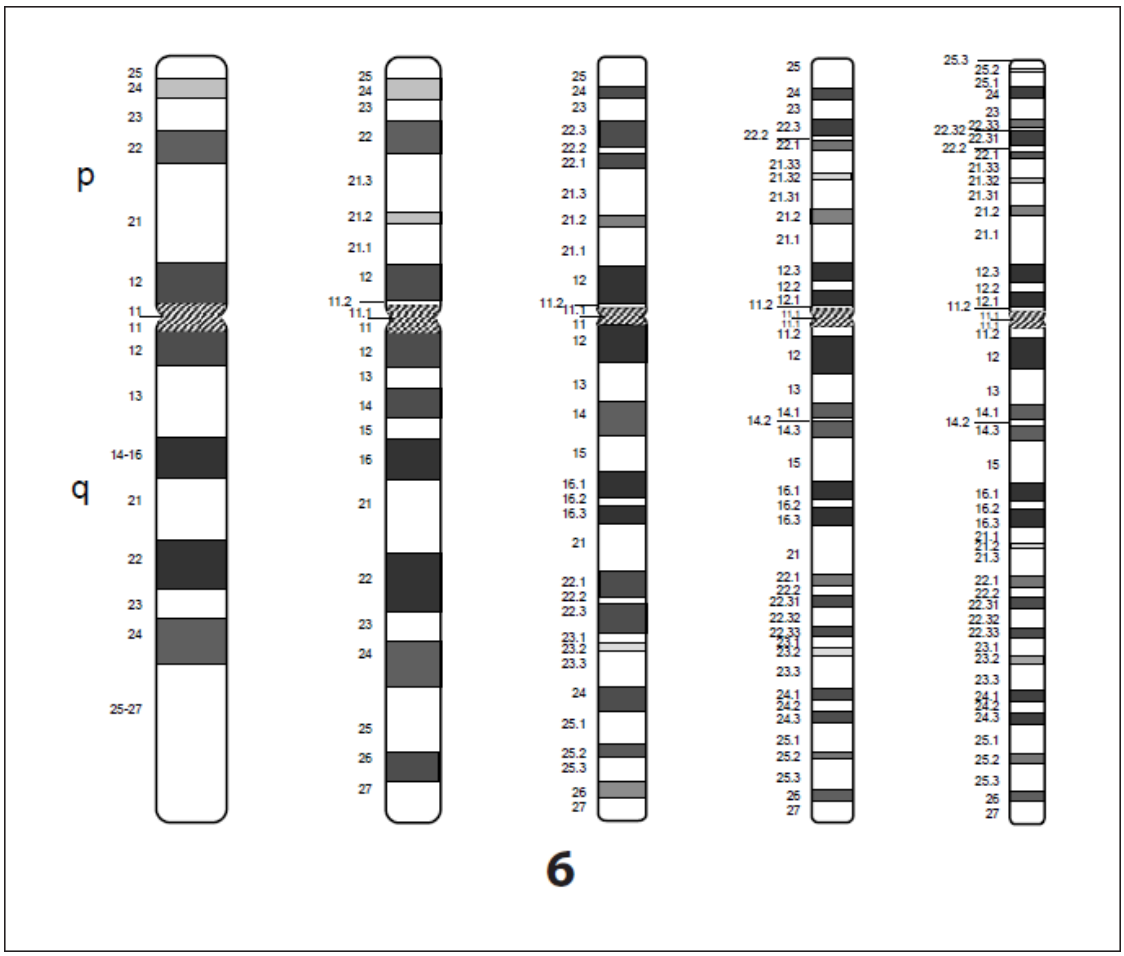
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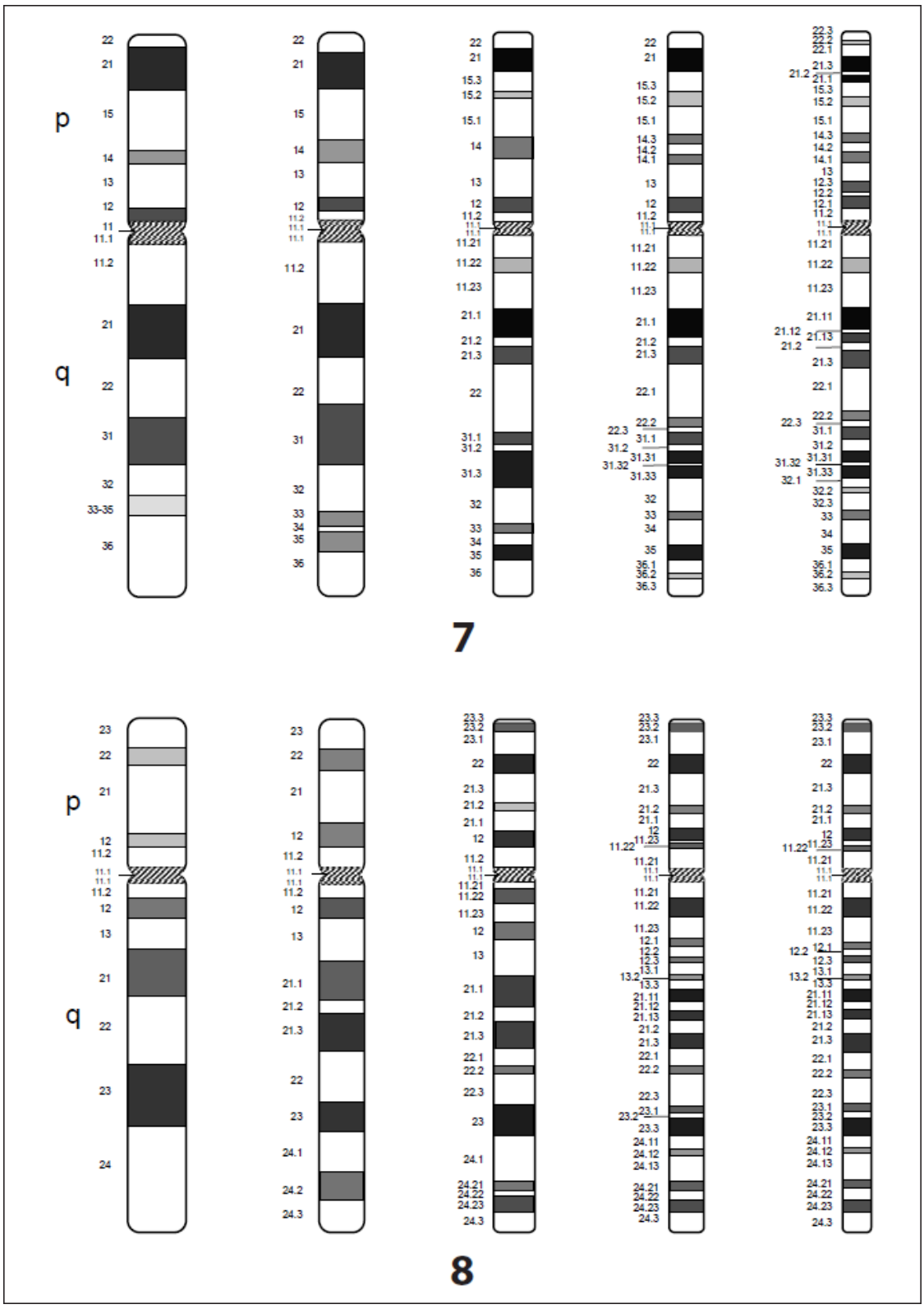
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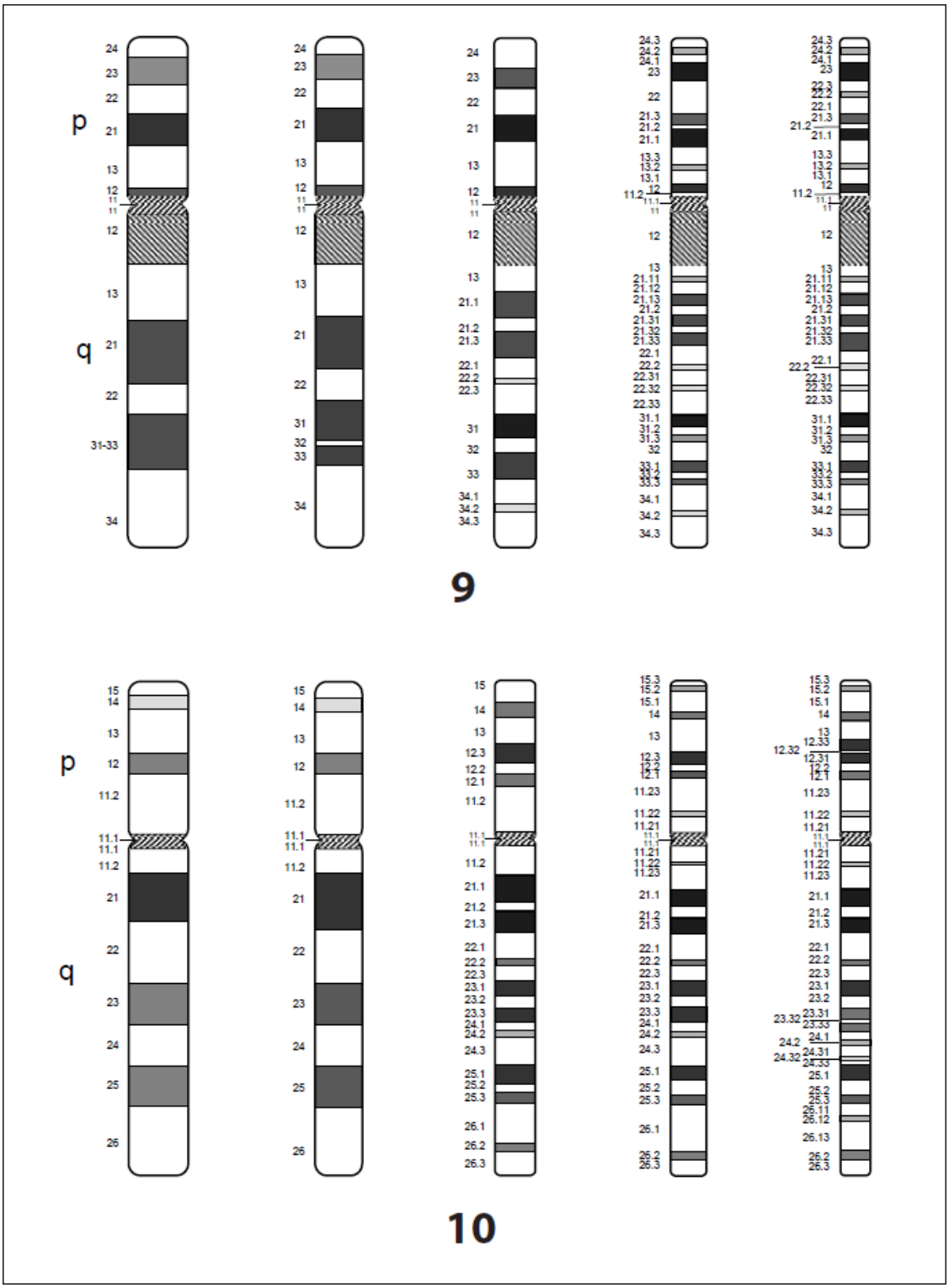
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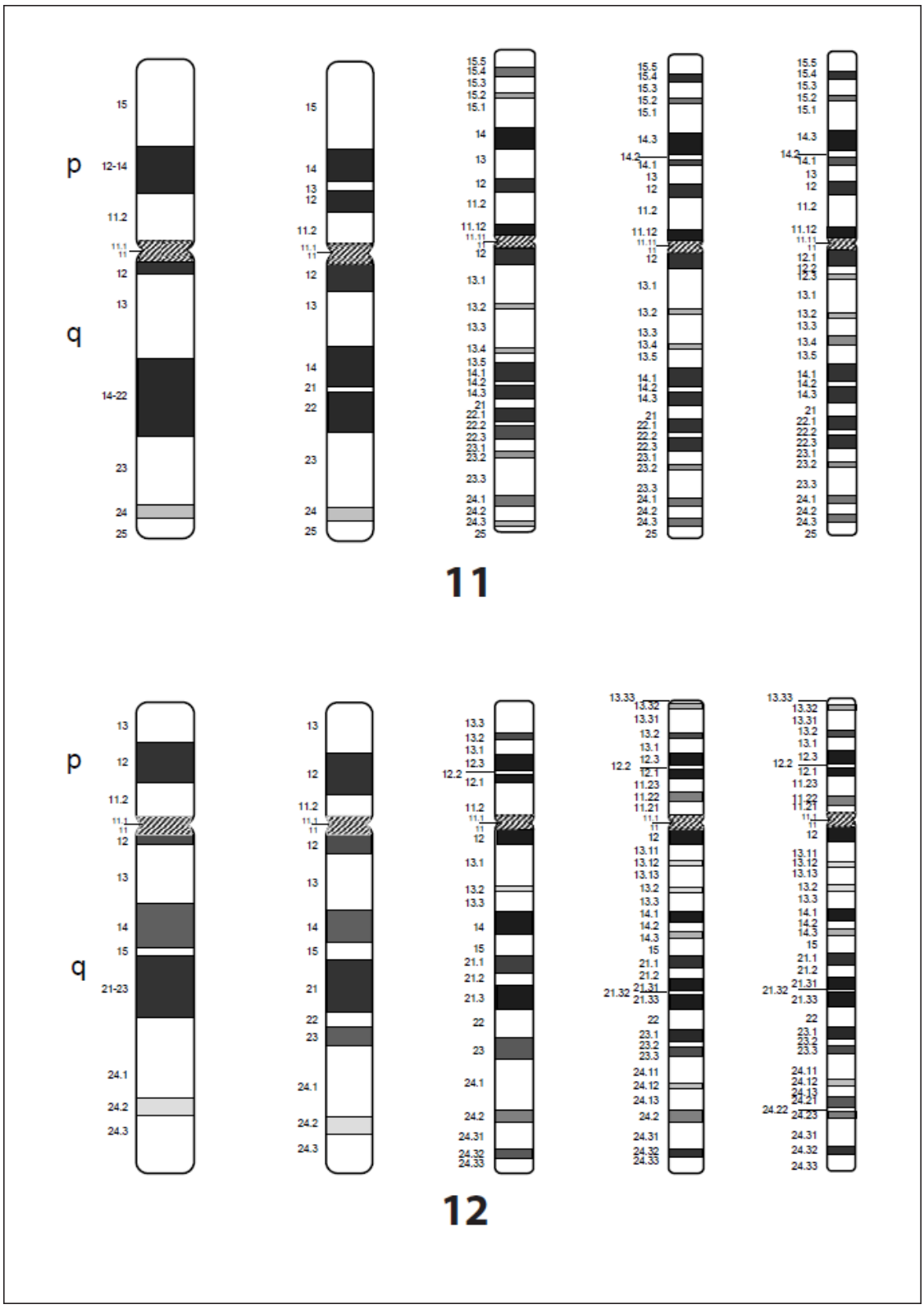
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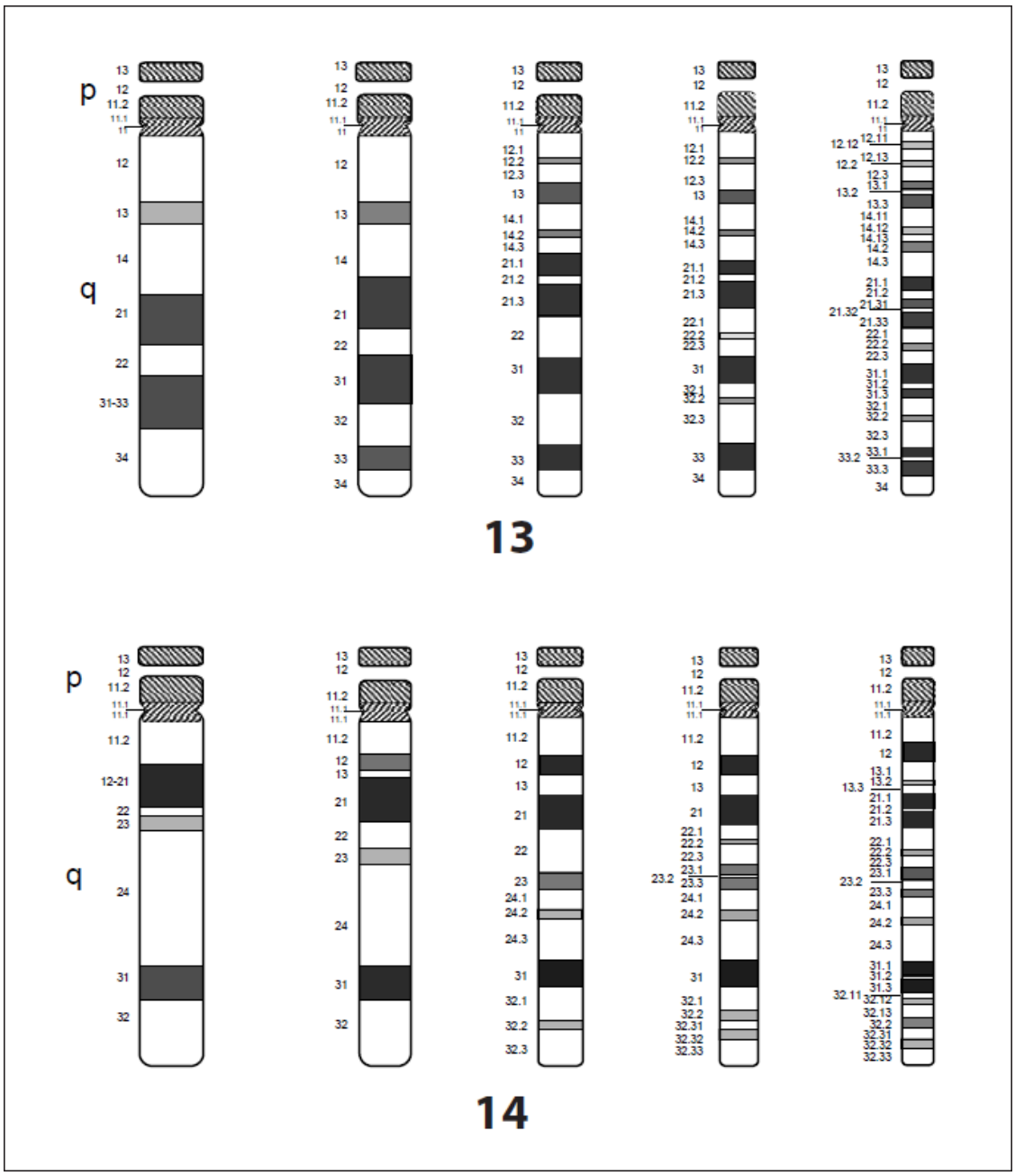
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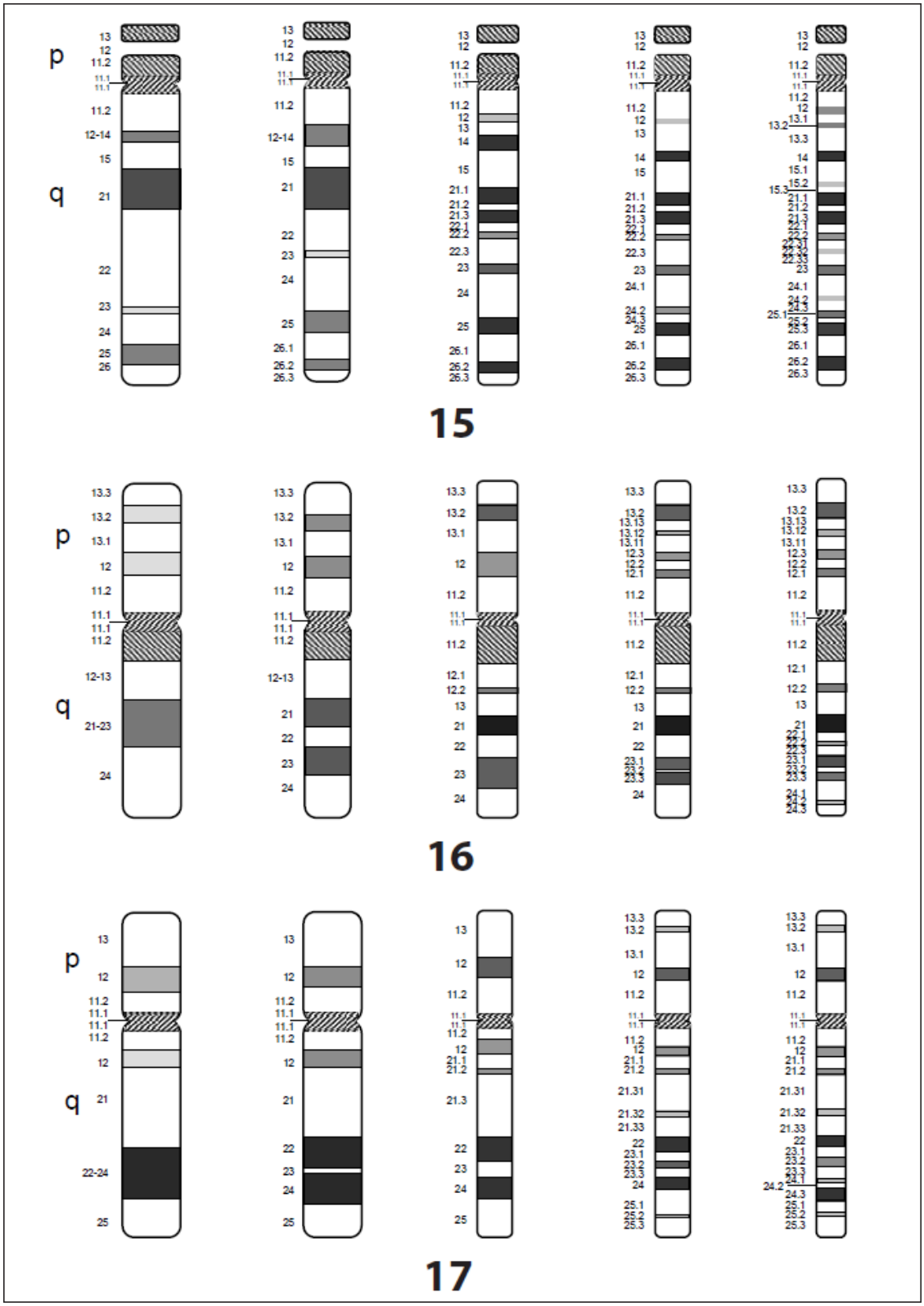
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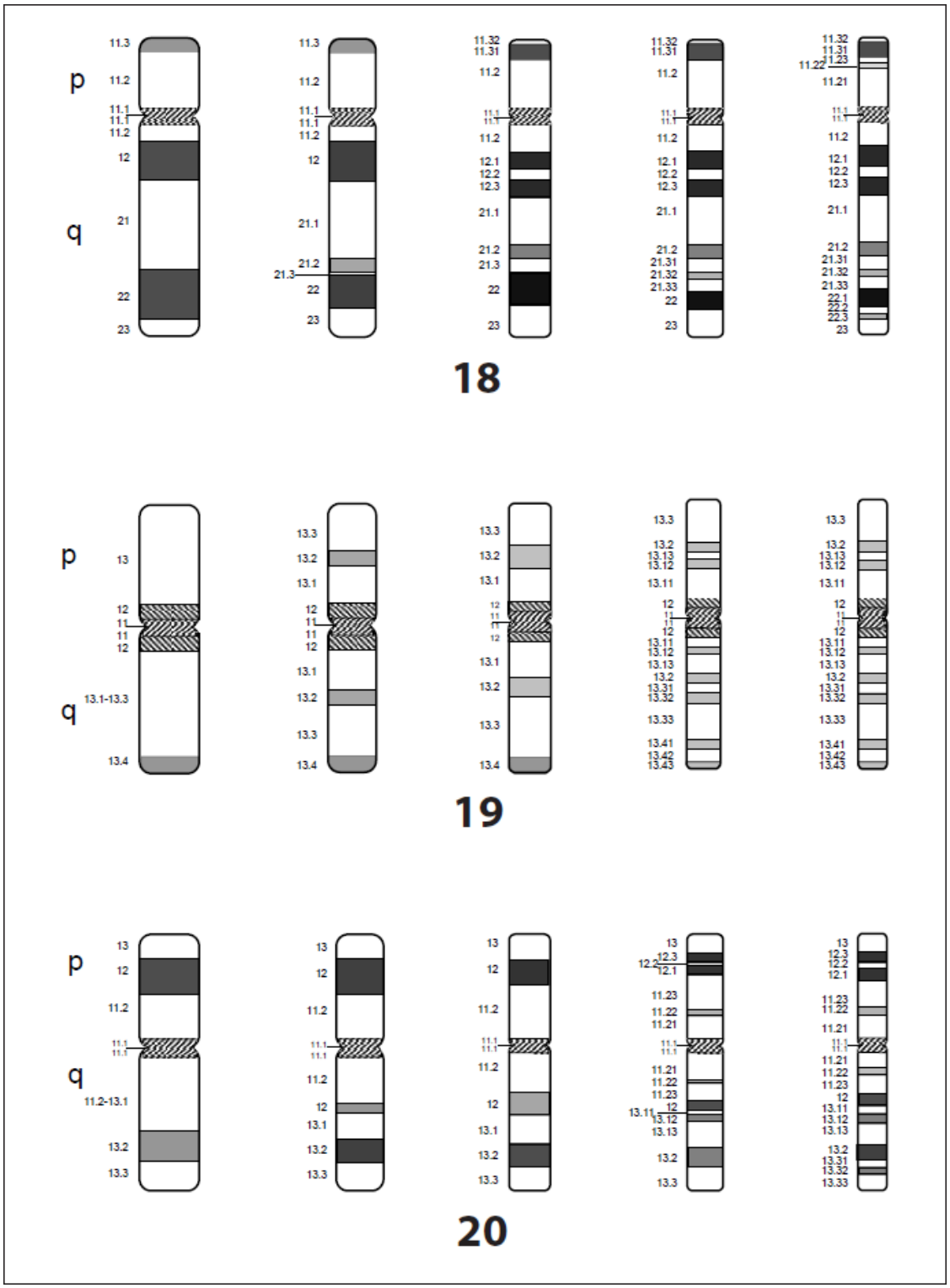
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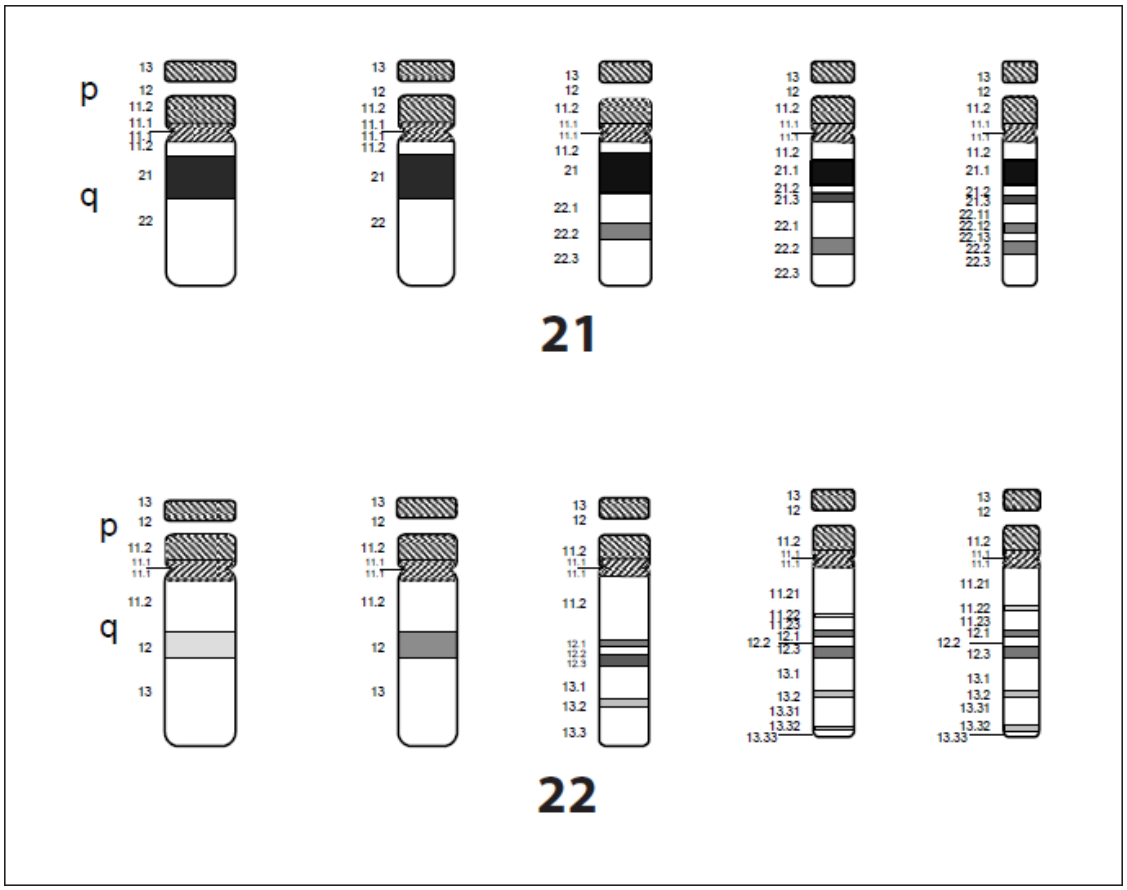
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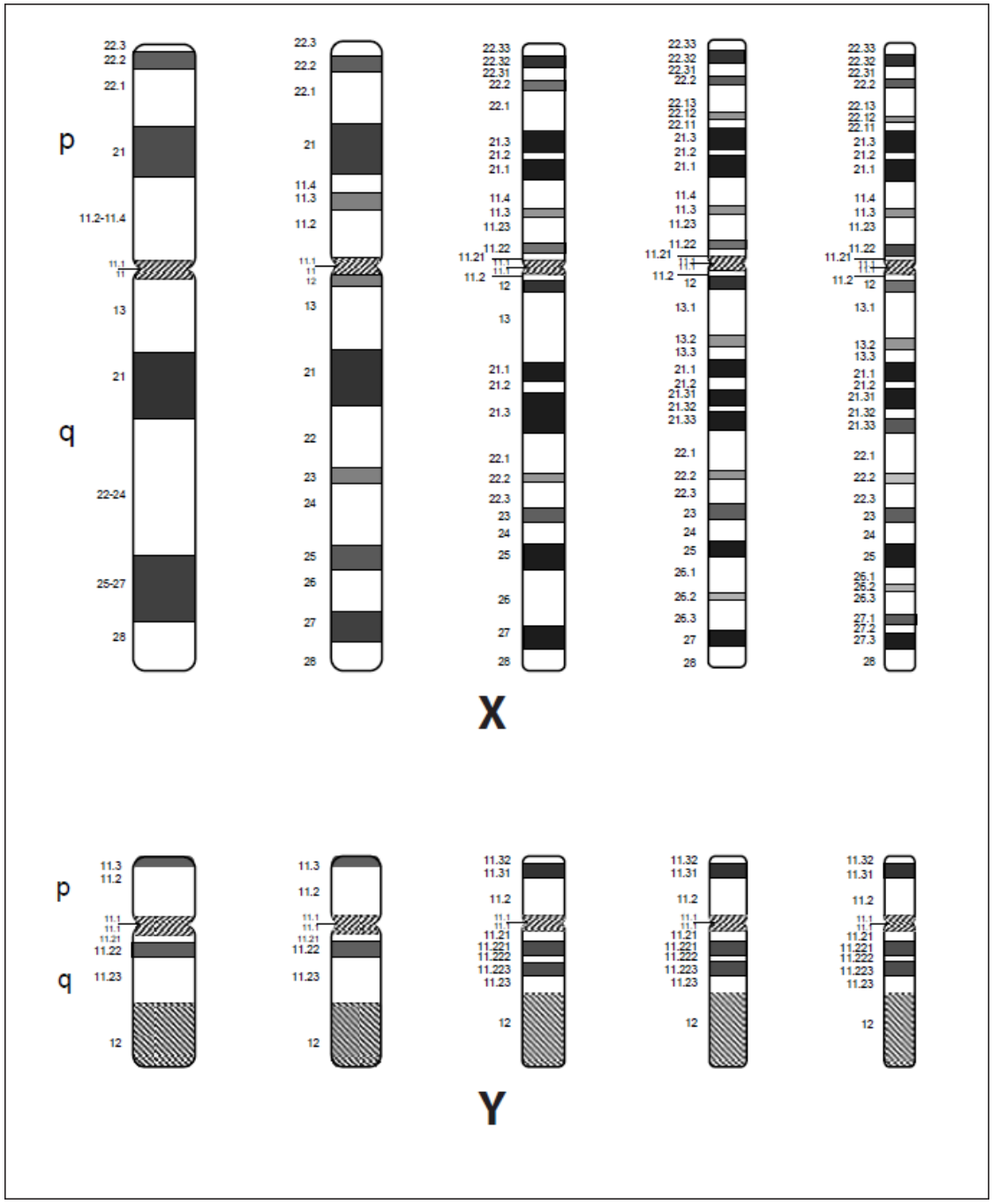
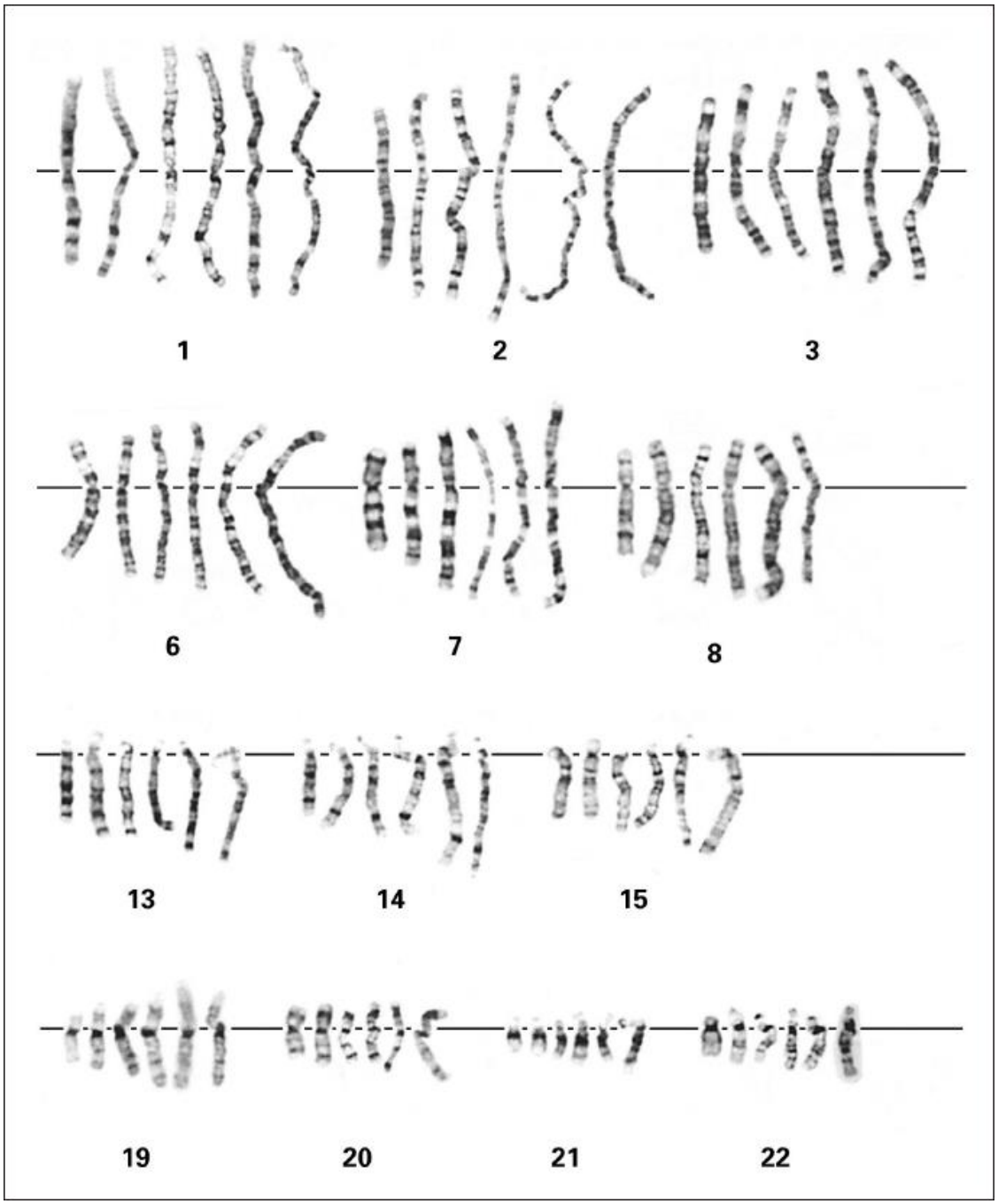


Fig 15. *Idiograms of G-banding patterns for normal human chromosomes at five different levels of resolution. From the left, chromosomes in each group represent a haploid karyotype of approximately 300-, 400-, 550-, 700-, and 850-band levels. The dark G-bands correspond to bright Q-bands, with the exception of the variable regions. The numbering of R-banded chromosomes is exactly the same, with a reversal of light and dark bands. While the band numbers reflect GTG bands, the relative widths and staining intensities of euchromatic bands may vary with resolution and banding method (Francke, 1981, 1994; Chia, 2009). The original idiograms of the Y chromosome are according to observations of Magenis and Barton (1987). The 400-, 550-, and 850-band idiograms correspond to the ISCN (1995) nomenclature. The 300- and 700-band idiograms were provided by N.L. Chia (Chia, 2009). Two types of non-euchromatic regions are indicated by different cross-hatching patterns, one involving the pericentromeric heterochromatin regions on all chromosomes and the other involving the variable regions 1q12, 3q11.2, 9q12, 16q11.2, 19p12, 19q12, Yq12, and the short arms of all acrocentric chromosomes. Bands can be seen within the variable regions, in particular in 1q12, 9q12 and Yq12, but since they are variable they have not been detailed in the idiograms.*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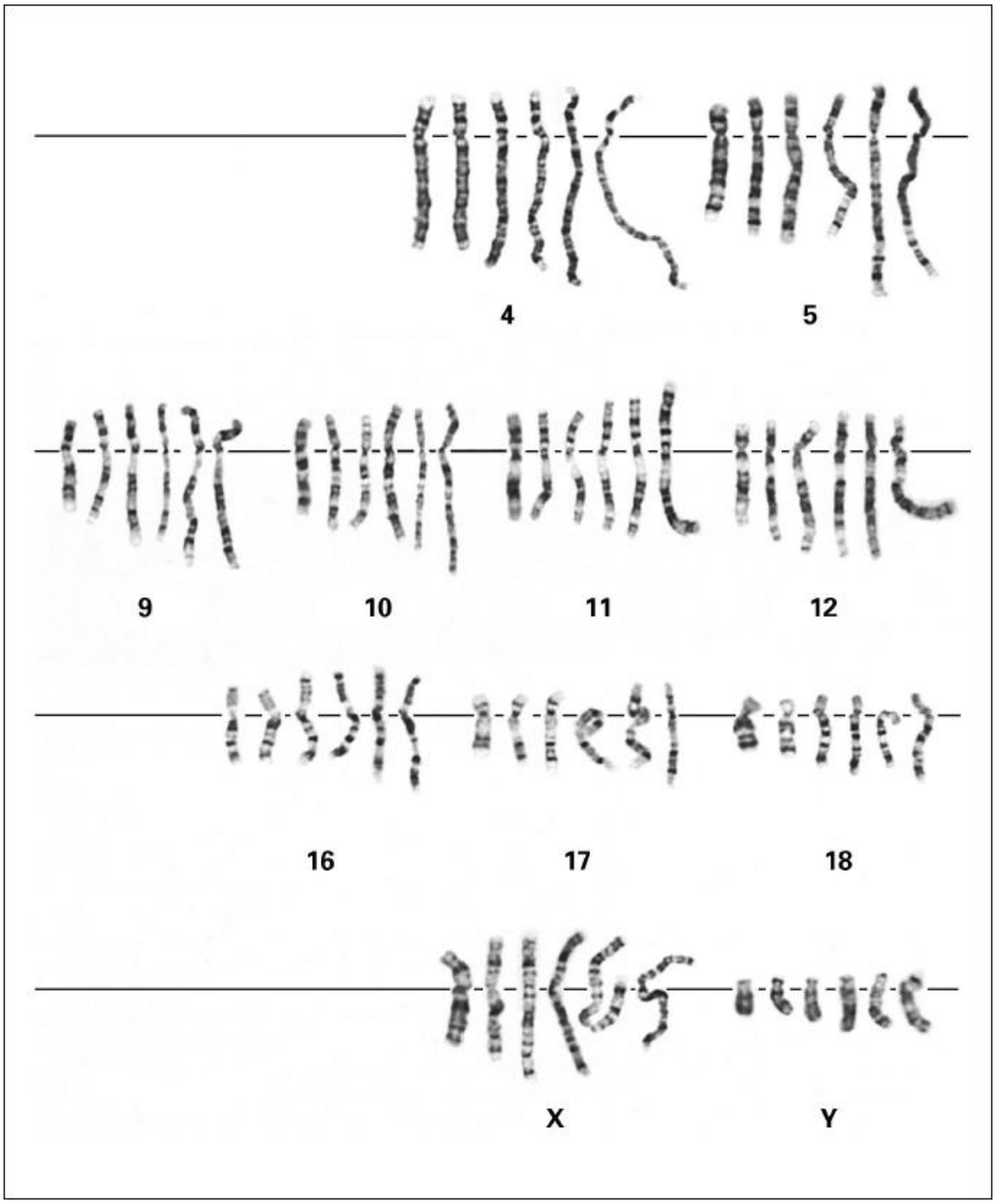
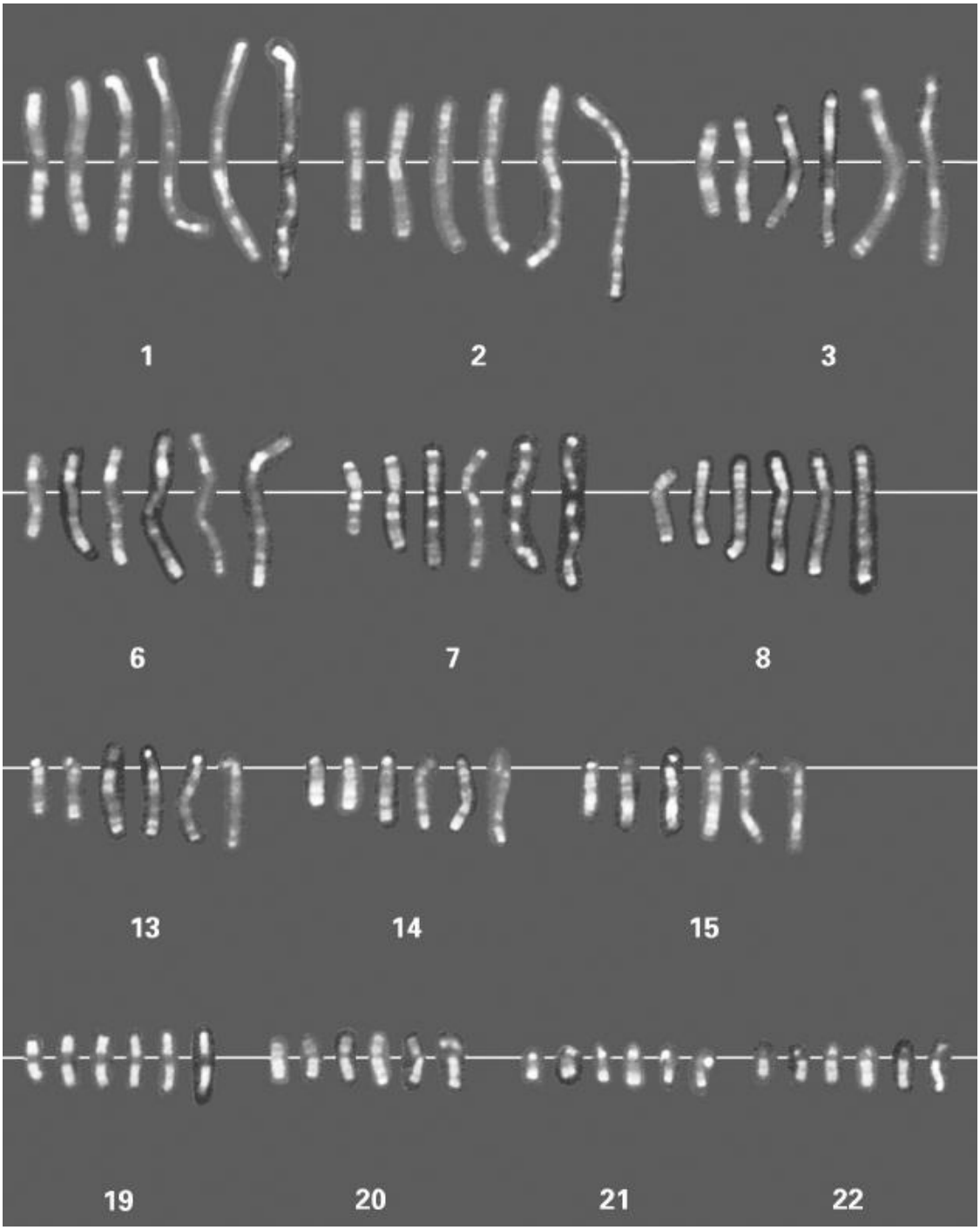


Fig 16. a *G-banded chromosomes arranged in increasing order of resolution from approximately the 500- to the 900-band levels. (Courtesy of Dr. E. Magenis.)*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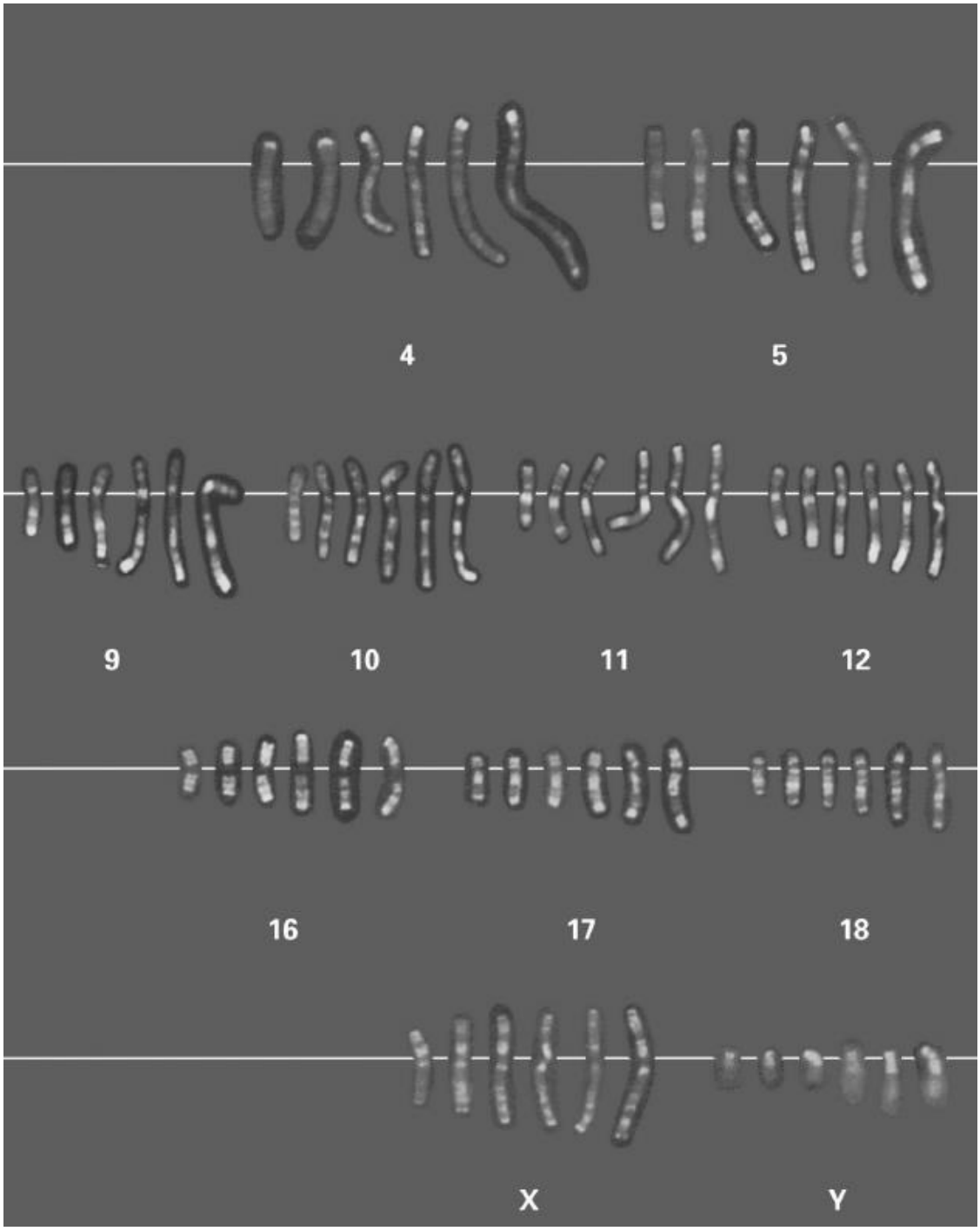

Fig 16. b *R-banded chromosomes arranged in increasing order of resolution from approximately the 400- to the 850-band levels. (Courtesy of Dr. E. Magenis.)*