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Human Chromosome Nomenclature

An Overview and Definition of Terms

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INTRODUCTION

Advancements in methodology and discovery of the diploid human chromosome number invigorated further research in human cytogenetics *(1,2)*. The eventful years that followed witnessed the birth of a new specialty—human cytogenetics—which provided answers to many intriguing phenomena in medicine. Little was known at the time that human cytogenetics would form the backbone of present-day "human genetics," providing answers to questions regarding human reproduction, behavior, aging, and disease while generating knowledge that could be applied to the treatment and prevention of many disorders.

The discovery of the chromosomal etiology of Down syndrome, Turner syndrome, Klinefelter syndrome, Edwards syndrome, and Patau syndrome further added to the knowledge that variations from the normal diploid chromosome number and structure can cause severe phenotypic malformations and mental impairment. The investigators responsible for these early discoveries came from both sides of the Atlantic. Working independently, they devised their own terminology and nomenclature to describe chromosome abnormalities. Confusion in the scientific literature was the result. The need for guidelines and standardization of terminology thus became imperative. At a conference held in Denver, CO, 14 attendees from different countries argued for 3 days. In the end, they agreed upon guidelines for describing human chromosomes and chromosome abnormalities. This historic document is called the *Denver Conference (1960): A Proposed Standard System of Nomenclature of Human Mitotic Chromosomes (3)*.

Although the basic principles adopted in Denver have prevailed to date, new technologies and ever-increasing knowledge in human cytogenetics necessitated periodic revision and update of the nomenclature document (see **Table 1**). The Chicago Conference nomenclature *(4)* was widely used from 1966 to 1971 during the prebanding era (see **Fig. 1**). At the Paris Conference *(5, 6)* the document was expanded so that banded chromosomes (see **Fig. 2**) could be described. With the Stockholm Conference in 1977, the proceedings came to be known as the International System for Human Cytogenetic Nomenclature or ISCN *(7)*. Each ISCN is identified by the year of its publication *(8–10)*. The document currently in use is *An International System for Human Cytogenetic Nomenclature (1995)*, abbreviated as ISCN 1995 as agreed upon by the conferees in Memphis, TN, in October, 1994 *(11)*. ISCN 1995 established a uniform code for designating both constitutional (congenital) and acquired chromosome abnormalities as well as one for describing and reporting results obtained from *in situ* hybridization methodologies.

ISCN 1995 has a certain uniqueness. It has provided a new 850-band-level ideogram based on actual measurements of bands. For comparative purposes, it includes G- and R-banded composite photographs of chromosomes at band resolutions ranging from about 400 to 850 bands. It has introduced

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Table 1
International Conferences on Human Chromosome Nomenclature

Conference/Document		*Year of Publication*
Denver Conference		1960
London Conference		1963
Chicago Conference		1966
Paris Conference		1971
Paris Conference (Supplement)		1975
Stockholm—1977	ISCN	1978
Paris—1980	ISCN	1981
ISCN		1985
Cancer Supplement	ISCN	1991
Memphis—1994	ISCN	1995

specific ways to accurately describe Robertsonian translocations, whole-arm translocations, and uniparental disomy. Keeping up with technical developments, this document for the first time has established nomenclature guidelines for the description of fluorescence *in situ* hybridization (FISH). In the following pages, I have attempted to simplify the use and point out the highlights of ISCN 1995. The examples that appear in this chapter are based on the dictates of this nomenclature document. However, for a detailed understanding of ISCN 1995, the reader is requested to refer to the original document *(11)*.

HUMAN CHROMOSOMES

Of the 46 chromosomes in a normal human somatic cell, 44 are autosomes and 2 are sex chromosomes. The autosomes are designated as pairs 1–22. The numbers are assigned in descending order of the length, size, and centromere position of each chromosome pair. In a normal female the sex chromosomes are XX, and in a normal male, they are XY.

Until the advent of certain specialized staining techniques, arbitrary identification of individual chromosome pairs was based on the size and position of the centromere *(4)*. Variability in the centromere position of different chromosomes allowed them to be classified into three basic categories. A chromosome with its centromere in the middle is *metacentric*, one with the centromere closer to one end is *sub-metacentric*, and one with the centromere almost at one end is *acrocentric* (see **Fig. 3**). Based on decreasing relative size and centromere position, a karyotype comprised of seven groups labeled A through G was devised. The X chromosome belonged to the third or "C" group, whereas the Y was often placed separately. Although still used occasionally, these letter group names are now considered obsolete.

Chromosome Banding and Identification

Unequivocal identification of individual chromosomes and chromosome regions became possible with the technical developments of the late 1960s (refer to Chapters 1 and 4). When chromosome preparations are treated with dilute solutions of proteolytic enzymes (trypsin, pepsin, etc.) or salt solutions (2X SSC) and treated with a chromatin stain such as Giemsa, alternating dark and light stained demarcations called *bands* appear along the length of each chromosome. The banding patterns produced are specific for each chromosome pair, thus enabling the identification not only of individual chromosomes but also of regions within each chromosome. Methods commonly used to produce these discriminative banding patterns include Giemsa or G-banding, quinacrine mustard or Q-banding, reverse or R-banding and constitutive heterochromatin or C-banding, each with its own uniqueness. In the United States and Canada, the most frequently used methods for routine cytoge-

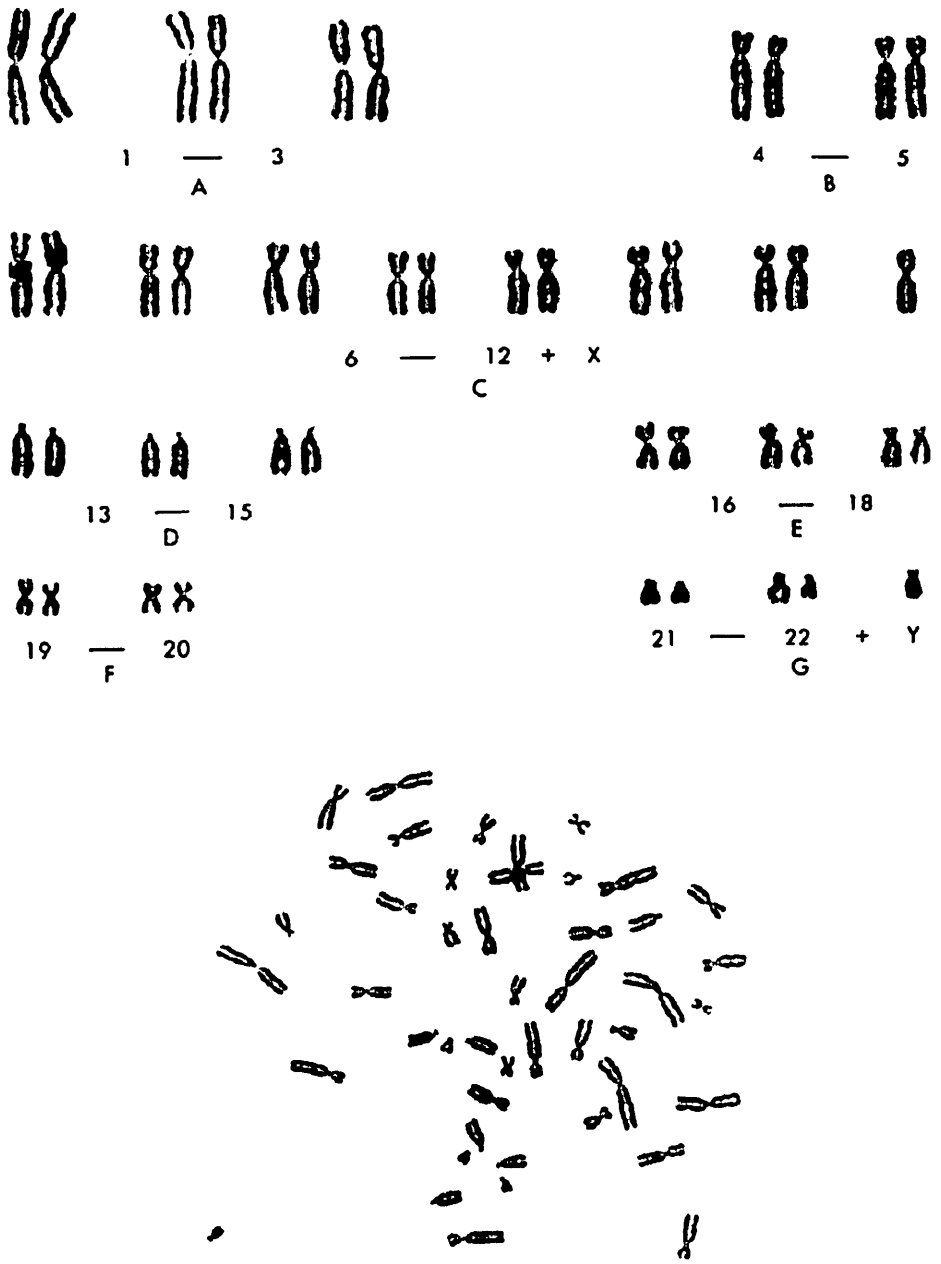


Fig. 1. Unbanded metaphase spread (**bottom**) and corresponding karyotype (**top**) per the Chicago conference.

netic analysis are G- and Q-bands (see **Fig. 2**), whereas in other countries (France, for example), R-banding is more common. Additional banding methods are occasionally employed to exemplify specific abnormalities or chromosome regions. Abbreviations commonly used to denote the various banding techniques appear in **Table 2**.

Chromosome Regions and Band Designations

The chromosomal details revealed by the new banding techniques necessitated the introduction of additional terminology and modifications of certain existing ones. This task was accomplished by a

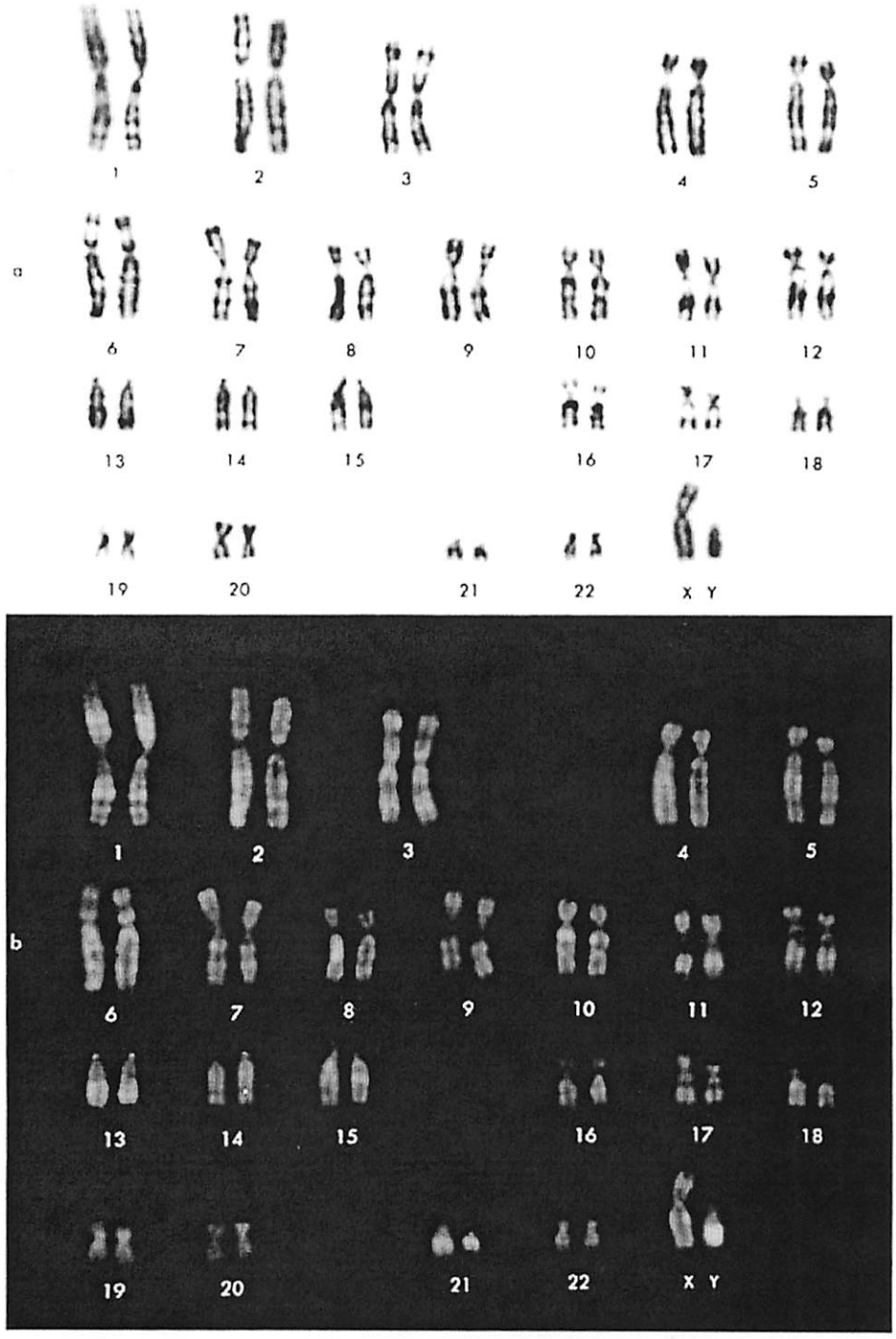


Fig. 2. Normal 46,XY male karyotype. Characteristic G-band pattern (**a**) and fluorescent Q-banding (**b**). The same cell was used for both methodologies to demonstrate the complementary banding patterns.

standing committee appointed at the Fourth International Congress of Human Genetics in Paris. The recommendations of the committee were published as *Paris Conference (1971): Standardization in Human Cytogenetics*. Through a diagrammatic representation of banding pattern, the document elucidated the typical band morphology for each chromosome *(5)* (see **Fig. 4**). The Paris Conference

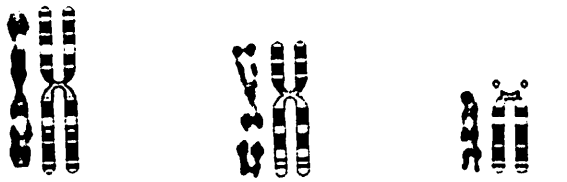


Fig. 3. Examples of metacentric, submetacentric, and acrocentric chromosomes.

Table 2
Frequently Used Banding Methods and Their Abbreviations

Banding Method	*Abbreviation*
Q-bands	Q
Q-bands by quinacrine derivatives and fluorescence microscopy	QFQ
G-bands	G
G-bands by trypsin and Giemsa	GTG
C-bands	C
C-bands by barium hydroxide and Giemsa	CBG
R-bands	R
R-bands by acridine orange and fluorescence microscopy	RFA
R-bands by BrdU and Giemsa	RBG
Telomere bands or T-bands	T

(1971) introduced a numbering system helpful in designating specific bands and regions. New terminology and abbreviations were introduced to help explain chromosome abnormalities in a more meaningful way. Other conferences then followed, with the latest held in Memphis in 1994. Descriptions of human chromosomes and their abnormalities utilize a series of symbols and abbreviations. A partial list of recommended symbols and abbreviations in ISCN 1995 appear in **Table 3.**

The centromere "cen" divides a chromosome into a short or "p" arm (from the French petit) and a long or "q" arm. For descriptive purposes, the centromere is composed of two portions. The portion of the centromere lying between its middle and the first band on the short arm is designated as "p10." Similarly, the portion of the centromere lying between its middle and the first band on the long arm is designated as "q10." The designations p10 and q10 allow us to describe accurately the nature and organization of centromeres in isochromosomes, whole-arm translocations, and Robertsonian translocations (see below). Each arm ends in a terminus ("ter," thus "pter" and "qter"), where telomeres are present to prevent the chromosomes from having "sticky ends."

Each chromosome arm is divided into *regions*. This division is based on certain *landmarks* present on each chromosome. By definition, a landmark is "a consistent and distinct morphologic area of a chromosome that aids in the identification of that chromosome." A *region* is an area that lies between two landmarks. The two regions immediately adjacent to the centromere are designated as "1" (p1 and q1), the next distal as "2," and so on. Regions are divided into *bands* and the bands into *subbands* (see **Fig. 5**). A band is that part of a chromosome that is distinctly different from the adjacent area by virtue of being lighter or darker in staining intensity. Sequential numbering of chromosome arms and

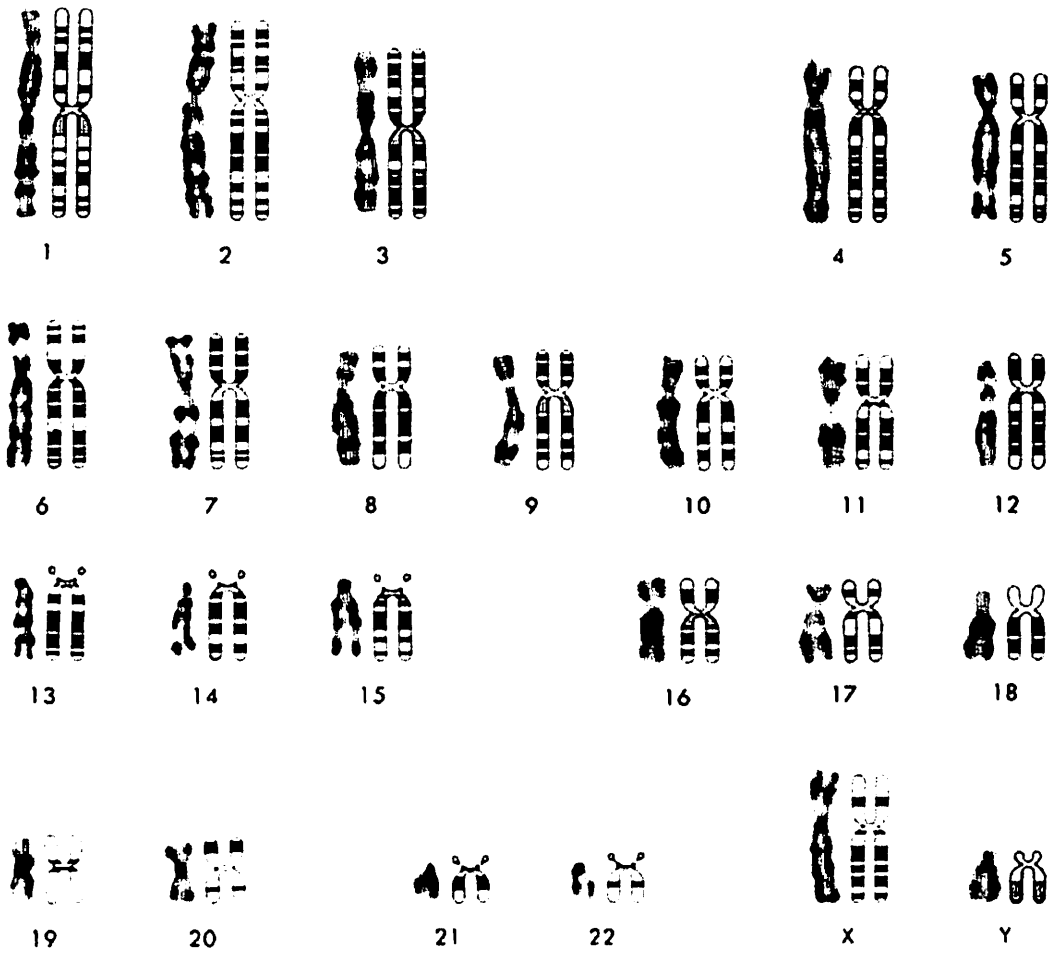


Fig. 4. A composite karyotype of G-banded chromosomes **(left)** along with the corresponding 1971 Paris Conference ideograms **(right)**.

bands helps make the designation of specific bands easy. For example, the terminal band on the long arm of chromosome 2 can be written as 2q37 to mean chromosome 2, long arm, region 3, band 7 and is referred to as "two q three-seven," not "two q thirty-seven".

Karyotype Descriptions

Karyotype descriptions follow certain basic rules. When designating a karyotype, the first item specified is the total number of chromosomes, including the sex chromosomes present in that cell, followed by a comma and the sex chromosomes in that order. Thus, a normal female karyotype is written as 46,XX and a normal male karyotype as 46,XY. The characters are contiguous, without spaces between items. Chromosome abnormalities, when present, follow the sex chromosome designation using abbreviations or symbols denoting each abnormality (see **Table 3**). These are listed in a specific order: Sex chromosome abnormalities are described first, followed by autosomal changes in numerical order. For each chromosome described, numerical changes are listed before structural abnormalities.

Most karyotypes can be described using the "short form" of the nomenclature, which is used in this chapter. However, it should be noted that for certain complex rearrangements this can produce ambiguity. ISCN therefore provides for a "long form," in which abnormal chromosomes can be

Table 3
Selected List of Symbols and Abbreviations Used in Karyotype Designations

Abbreviation or Symbol	*Description*
add	Additional material, origin unknown
arrow (_ or →)	From – to, when using long form
[ ] square brackets	Number of cells in each clone
cen	Centromere
chi	Chimera
single colon (:)	Break
double colon (::)	Break and reunion
comma (,)	Separates chromosome number, sex chromosomes, and abnormalities
del	Deletion
der	Derivative chromosome
dic	Dicentric
dmin	Double minute(s)
dup	Duplication
fis	Fission
fra	Fragile site
h	Heterochromatin
i	Isochromosome
inv	Inversion
ins	Insertion
mar	Marker chromosome
mat	Maternal origin
minus sign (–)	Loss
mos	Mosaic
multiplication sign (×)	Multiple copies; also designates copy number with ish
p	Short arm of chromosome
pat	Paternal origin
Ph or Ph1	Philadelphia chromosome
plus sign (+)	Gain
q	Long arm of chromosome
question mark (?)	Uncertainty of chromosome identification or abnormality
r	Ring chromosome
rcp	Reciprocal
rec	Recombinant chromosome
rob	Robertsonian translocation
s	Satellite
slash (/)	Separates cell lines or clones
semicolon (;)	Separates chromosomes and breakpoints in rearrangements involving more than one chromosome
stk	Satellite stalk
t	Translocation
upd	Uniparental disomy

Note: For a complete listing of symbols and abbreviations, refer to ref. *11*.

described from end to end, with all structural changes "spelled out" in detail. Some examples are provided throughout the chapter; the reader is encouraged to refer to the original document *(11)* for additional information.

The remainder of this chapter discusses the current method of using the ISCN nomenclature to describe chromosome abnormalities. A section on interpretation of karyotype descriptions follows.

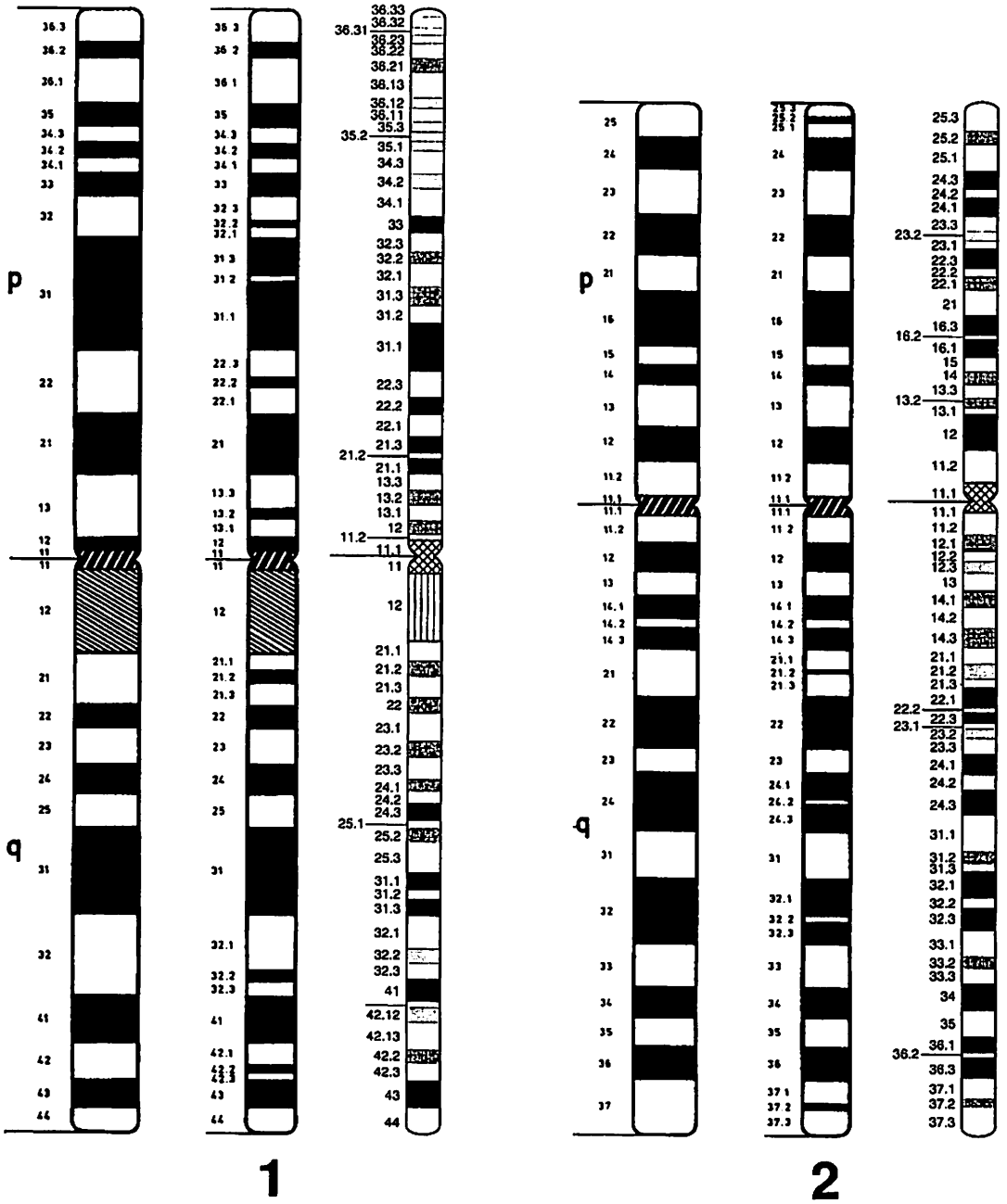


Fig. 5. Ideogram showing the G-banding pattern for normal human chromosomes at three different band resolutions. The left chromosome represents a haploid karyotype (one of each chromosome) of approximately 400 bands. The middle chromosome is at an approximately 550-band level, and the right chromosome represents about 850 bands. (Reproduced from ref. *11* with permission of S. Karger AG, Basel.)

NUMERICAL ABNORMALITIES OF CHROMOSOMES

The term "numerical abnormality" refers to gain or loss of chromosomes. As outlined above, all such abnormalities are presented in numerical order with the exception of the X and Y, which are always listed first. To designate an additional or a missing chromosome plus (+) and minus (–) signs

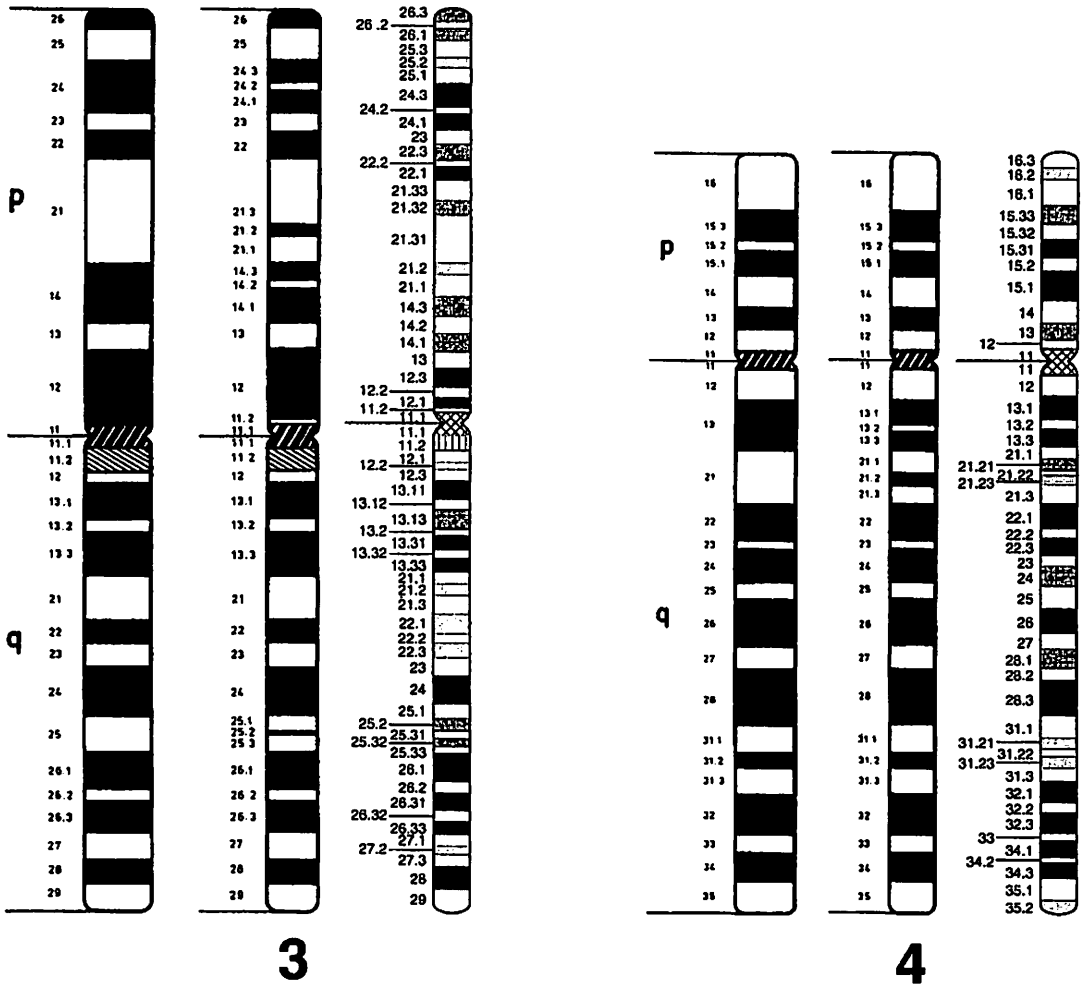


Fig. 5. (*continued*)

are placed before the specific chromosome number. Thus, –7,+18 would mean a missing chromosome 7 and an extra chromosome 18. Note that these abnormalities are presented in numerical order, regardless of whether they involve gain or loss of a chromosome. A + sign can also be used to denote additional copies of derivative chromosomes or accessory marker chromosomes, e.g., +der(6) or +mar (see below).

Numerical Abnormalities Involving the Sex Chromosomes

These can be constitutional (congenital) or acquired. ISCN 1995 provides special ways to distinguish between the two. As shown in the examples below, the + and—signs are not needed to designate constitutional sex chromosome aneuploidies.

Constitutional Sex Chromosome Aneuploidies

45,X	Classical monosomy X or Turner syndrome
47,XXY	Classical Klinefelter syndrome
47,XXX	A female with three X chromosomes
48,XXYY	Variant of Klinefelter syndrome with two X and two Y chromosomes

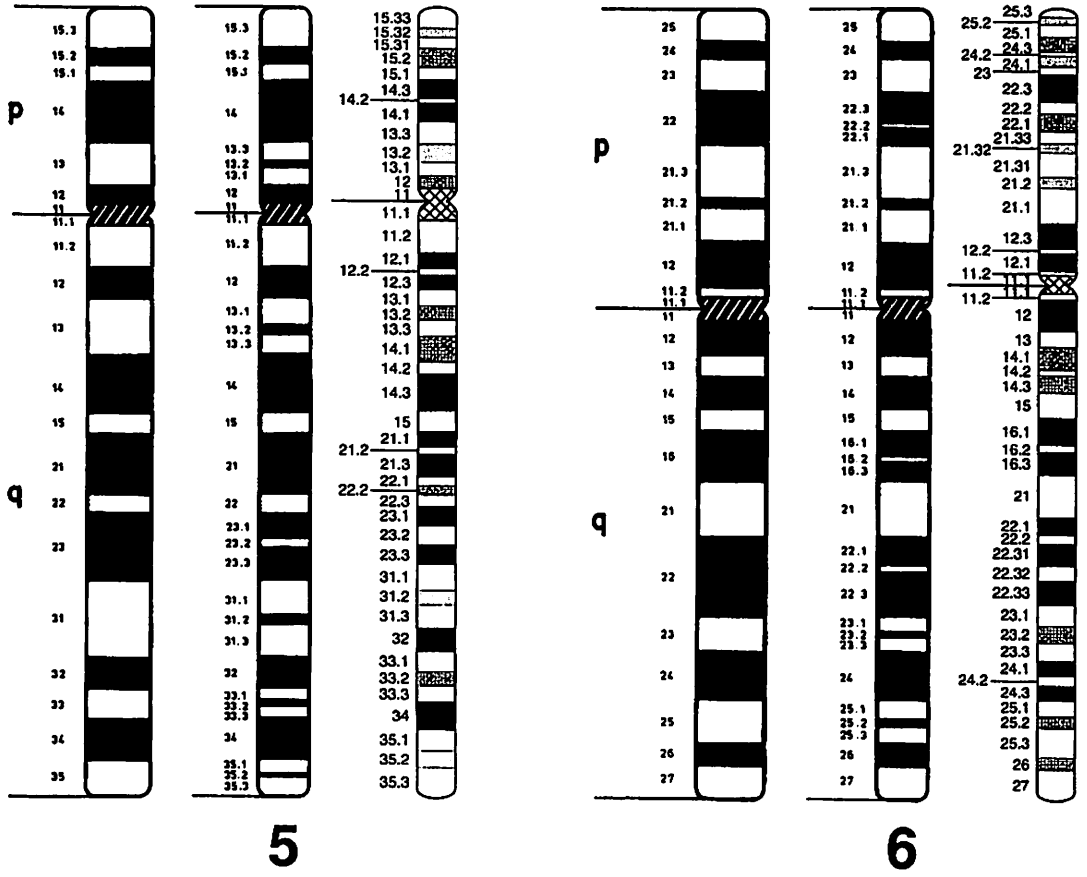


Fig. 5. (*continued*)

Acquired Sex Chromosome Aneuploidies

These involve chromosome changes seen in certain leukemias and solid tumors and are restricted to the affected tissues:

45,X,–X

This describes a normal female with two X chromosomes but with the loss of one X chromosome in her tumor cells.

47,XX,+X

This is a normal female with two X chromosomes and gain of an extra X chromosome in her tumor cells.

45,X,–Y

This is a normal male with XY chromosomes and loss of the Y chromosome in his tumor cells.

48,XY,+X,+Y

This describes a male with acquired X and Y chromosomes in his tumor cells.

48,XXYc,+X

Here, we have a patient with Klinefelter syndrome who has an acquired X chromosome in his tumor cells. The letter "c" is placed next to XXY to show that the patient's sex chromosome complement is XXY and *not* XY or XXXY.

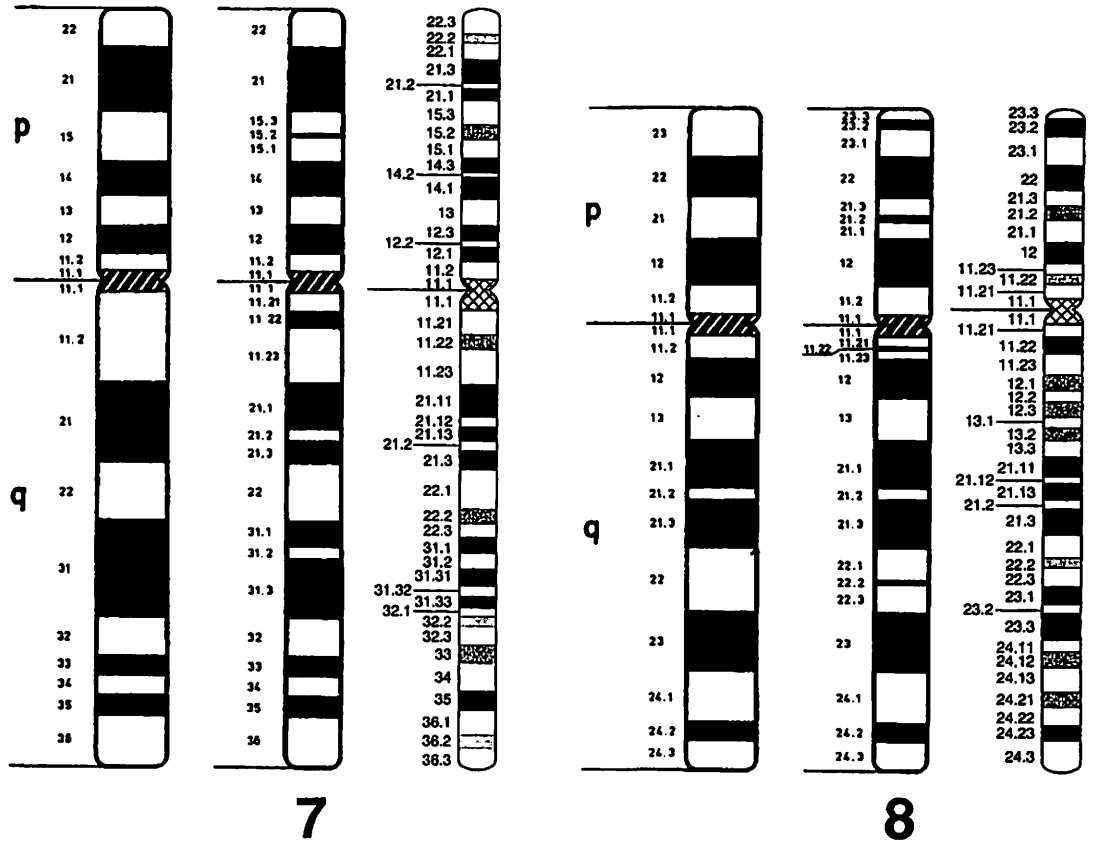


Fig. 5. (*continued*)

46,Xc,+X

This is a Turner syndrome patient (45,X) with gain of an X chromosome in her tumor cells.

Numerical Abnormalities of the Autosomes

The situation here is similar to that involving the sex chromosomes, with the exception that (+) and (–) signs are used to designate constitutional abnormalities:

47,XY,+18	Male with trisomy 18
48,XX,+18+21	Female with both trisomy 18 and trisomy 21
45,XY,–21	Male with monosomy 21
46,XY,+21c,–21	Male trisomy 21 patient with loss of one chromosome 21 in his tumor cells
48,XX,+21c,+21	Female with trisomy 21 and gain of an additional chromosome 21 in her tumor cells

Mosaics and Chimeras

An individual with two or more cell types, differing in chromosome number or structure is either a mosaic or a chimera. If the two cell types originated from a single zygote, the individual is a mosaic (mos). If the cell types originated from two or more zygotes that subsequently fused, the individual is a chimera (chi). In designating mosaic or chimeric karyotypes, a slash (/) is used to separate the cell lines. The actual number of cells detected in each clone can be given within square brackets [ ]. The largest clone is recorded first, then the next largest, and so on. Whenever a normal cell line is present, it is always recorded last, irrespective of the number of normal cells detected.

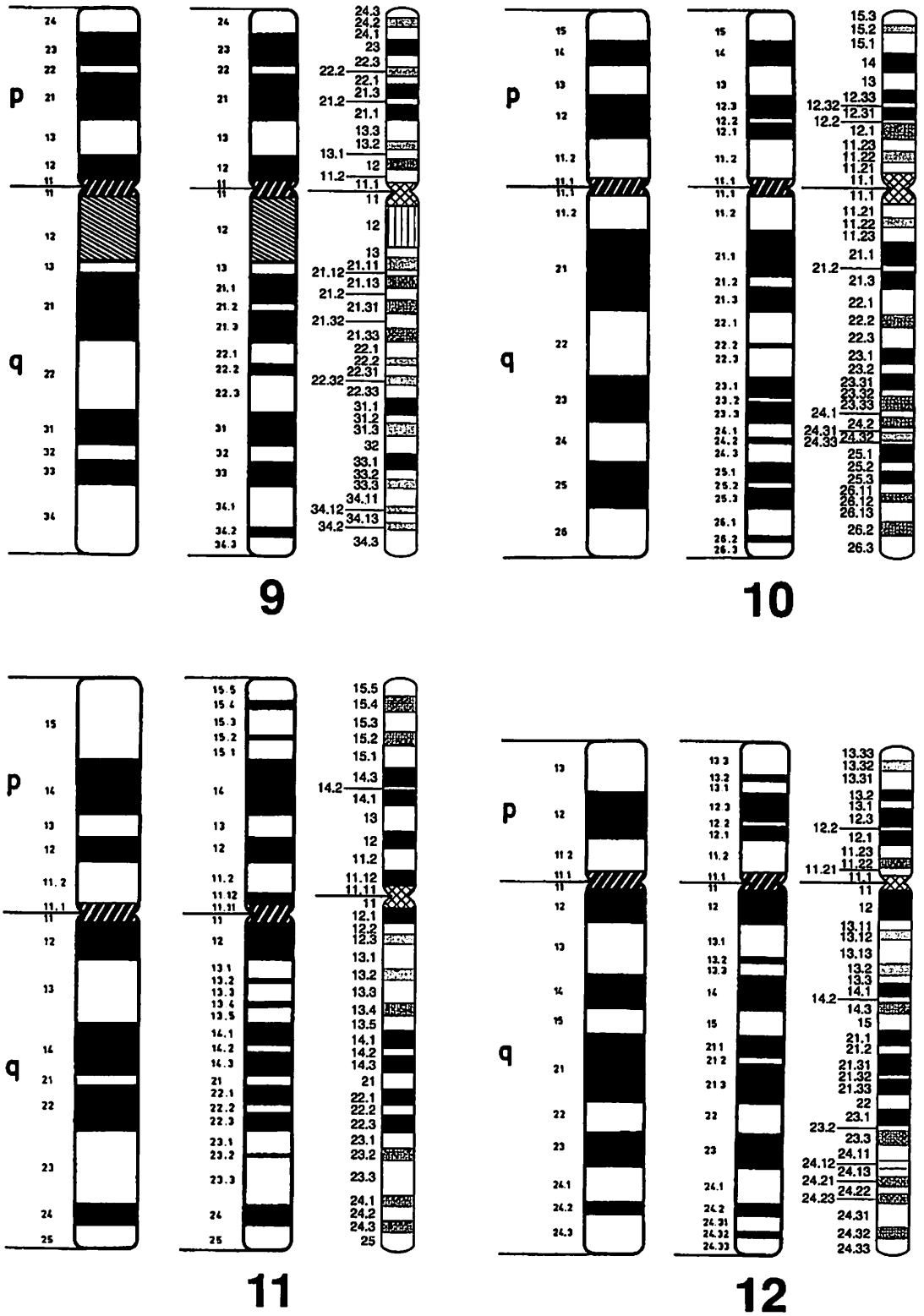


Fig. 5. (*continued*)

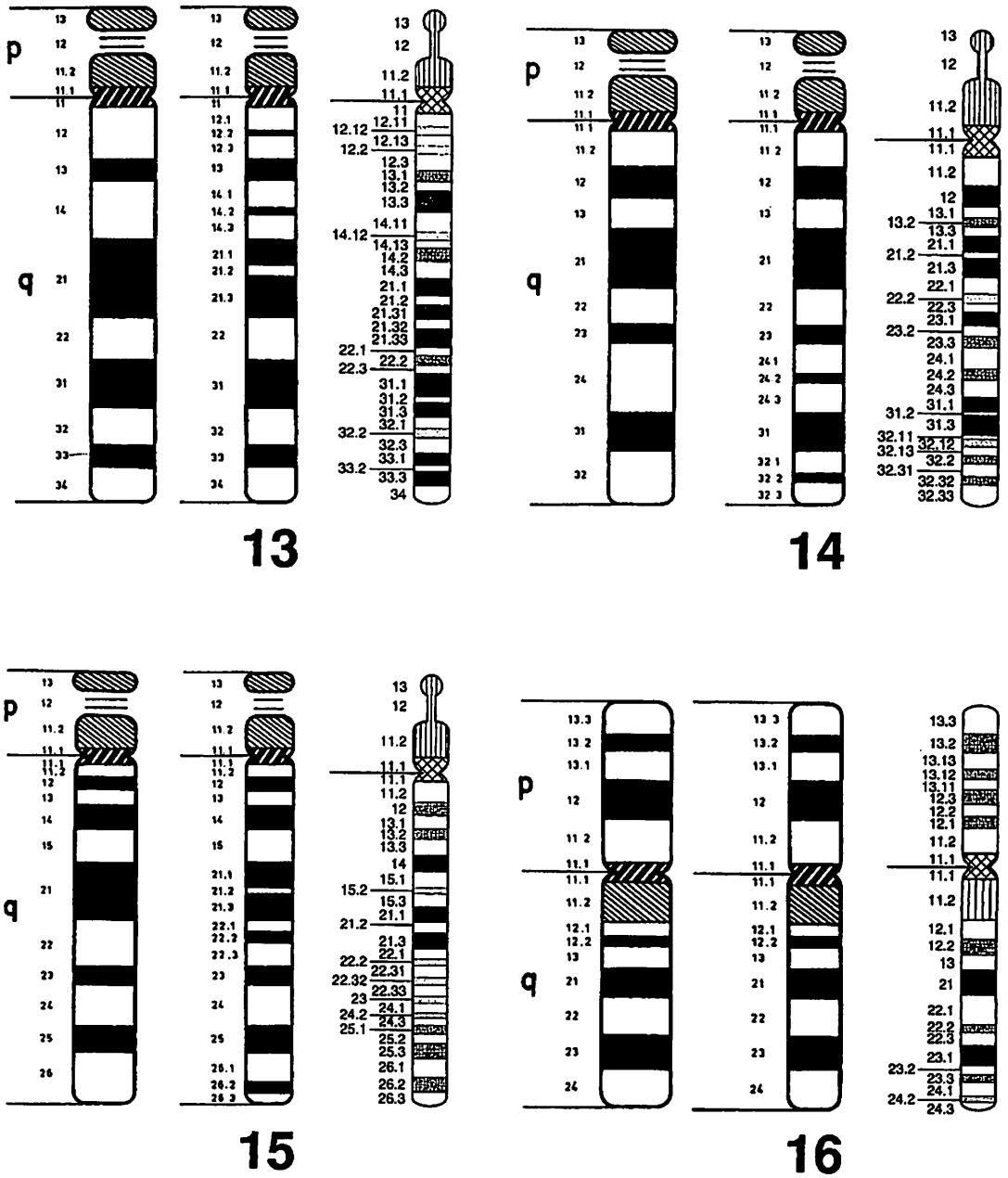


Fig. 5. (*continued*)

Examples are as follows:

mos 45,X[4]/46,XX[16]

This is a Turner mosaic with two cell lines. Analysis of 20 cells showed that this individual has 4 cells that are 45,X and 16 cells that are 46,XX.

mos 45,X[5]/47,XYY[5]/46,XY[10]

This represents a mosaic with three cell lines.

mos 47,XX,+13[15]/46,XX[5]

This is a mosaic with both trisomy 13 and normal cell lines.

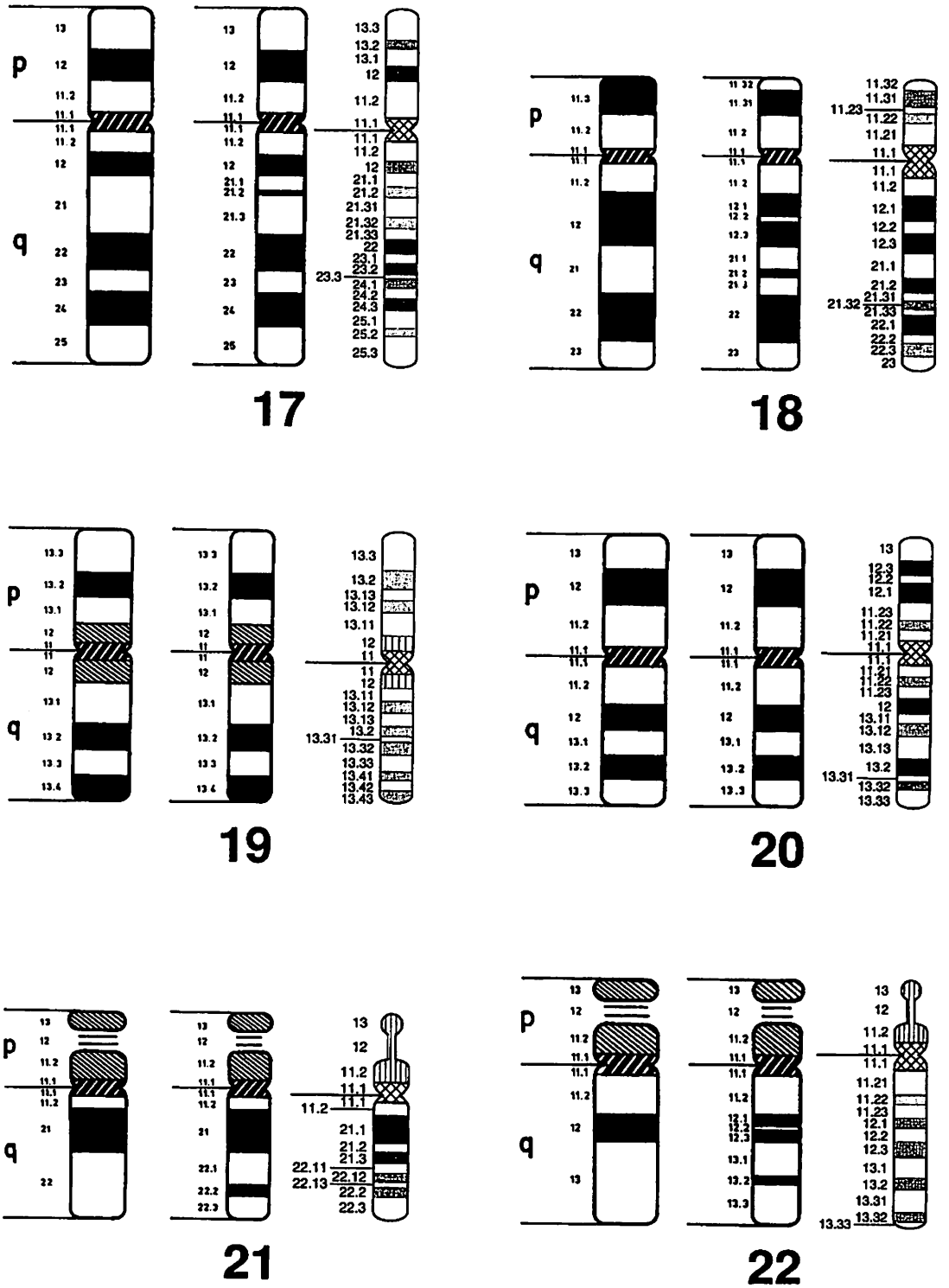


Fig. 5. (*continued*)

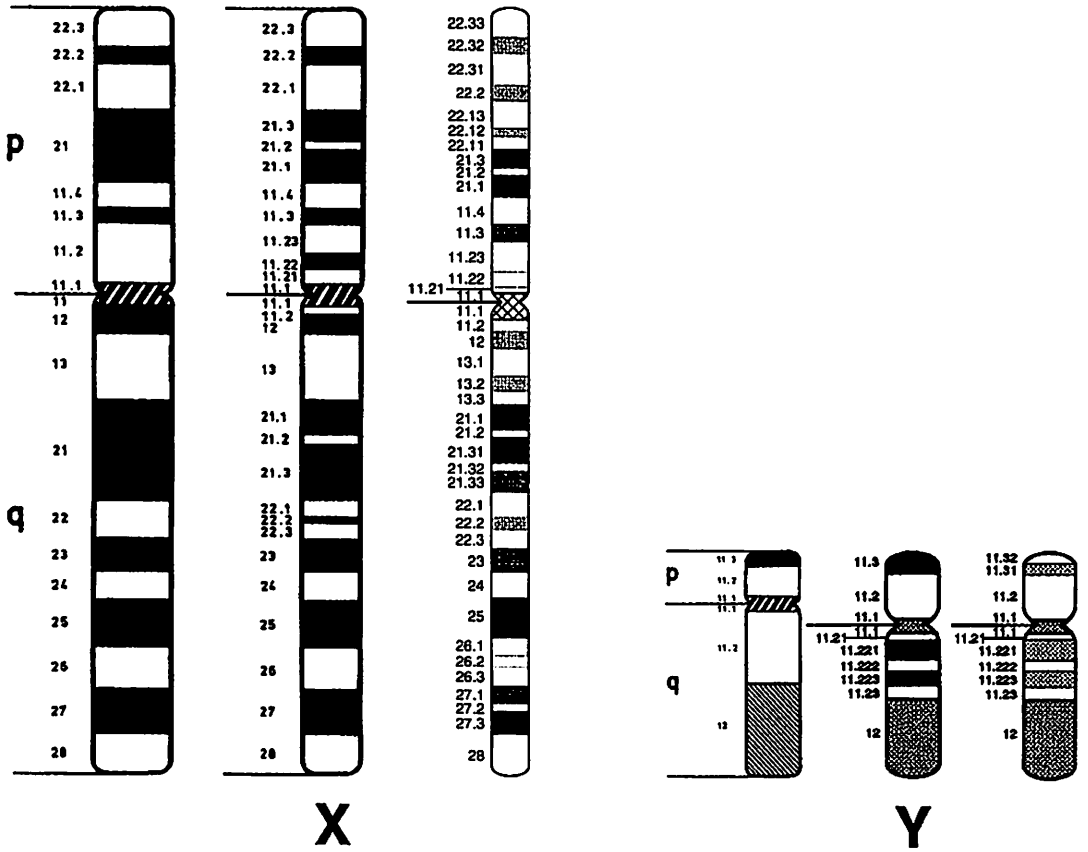


Fig. 5. (*continued*)

In a chimera where the two cell lines are normal (46,XX and 46,XY) and both are present in equal proportions, either one of them can be listed first. If one cell line is larger than the other, the larger clone is listed first.

chi 46,XX[10]/46,XY[10]
: This describes a chimera with female and male cells in equal number.

chi 47,XX+21[15]/46,XY[5]
: This is a chimera with both female and male cell lines. The female cell line shows trisomy 21, whereas the male cell line is normal.

chi 69,XXX[20]/46,XY[5]
: This represents a chimera with triploid and diploid cell lines. The triploid line is XXX, whereas the diploid line is XY.

Use of the abbreviations chi and mos is optional, as the presence of chimerism or mosaicism is usually evident from the karyotype.

STRUCTURAL CHROMOSOME ABNORMALITIES

This category of abnormalities includes several subclasses that will be discussed under separate headings. Again, as previously stated, all chromosomes involved in abnormalities are designated in numerical order, except for the X and Y, which are listed first.

When designating an abnormality that is limited to a single chromosome, the abbreviation for that abnormality is used, followed by the chromosome number in parentheses [e.g., r(X), del(2), ins(4), dup(5)]. If two or more chromosomes are involved in a rearrangement, as with translocations, a semicolon (;) is used to separate chromosome numbers within parentheses [e.g., t(3;4), t(2;5;10;) or t(15;17)]. Again, chromosomes are listed in numerical order unless a sex chromosome is involved [e.g., t(X;1) or t(Y;15)]. If, in the same cell, a specific chromosome is involved in both a numerical and a structural rearrangement, the numerical abnormality is designated first [e.g., +13,t(13;14)].

For ease of reference, the abnormalities covered will be presented in alphabetical order. For a thorough description of the mechanisms and clinical significance of structural chromosome abnormalities, see Chapter 9.

Additional Material, Origin Unknown (add)

When a chromosome has additional material attached to it, the origin of this material might not be identifiable with conventional banding methods. This is especially likely if the abnormality is subtle and originated *de novo* or is acquired. The abbreviation "add" (from the Latin *additio*) is used.

46,XX,add(17)(p13)

Additional material of unknown origin is attached to chromosome 17 at band p13.

46,XX,add(9)(q22)

Additional material of unknown origin attached to chromosome 9 at band q22. The region 9q22 → qter is missing and has been replaced by this material.

Deletions (del)

A deletion is an aberration in which a part of a chromosome is lost. Deletions can be either terminal, where all chromosomal material from the breakpoint on is lost, or interstitial, in which an internal section of one arm is missing. To introduce the reader to the long form of the nomenclature, a few of the following abnormalities will be presented using both the short and long forms.

Terminal Deletions

46,XY,del(1)(q32) (short form)
46,XY,del(1)(pter → q32:) (long form)

This karyotype describes a terminal deletion involving the long arm of chromosome 1. The colon present in the long form indicates a break at band 1q32 and deletion of the region distal to it. The rest of the chromosome, from 1pter to 1q32, is present.

Interstitial Deletions

46,XY,del(1)(p21p32) (short form)
46,XY,del(1)(pter → p21::p32 → qter) (long form)

Breakage and reunion are represented in the long form by a double colon (::). Here, this occurred involving bands 1p21 and 1p32. The segment between them has been deleted.

Derivative and Recombinant chromosomes

Derivative Chromosomes (der)

A structurally rearranged chromosome generated by events involving two or more chromosomes or the result of multiple events within a single chromosome is a derivative chromosome. Thus, each unbalanced product of a translocation event is a derivative chromosome. The identity of a derivative chromosome is determined by its centromere.

Examples are as follows:

46,XY,der(3)t(3;6)(p21;q23)

The derivative chromosome 3 in this example is the result of a translocation between the short arm of chromosome 3 at band p21 and the long arm of chromosome 6 at band q23. The der(3) replaces one

normal chromosome 3, and both chromosomes 6 are normal. This unbalanced karyotype results in monosomy (loss) of region 3p21 → pter and trisomy (gain) of 6q23 → qter. This karyotype is the product of adjacent-1 segregation (see Chapter 9).

45,XY,der(3)t(3;6)(p21;q23),–6
The der(3) is same as in the above example and again replaces one of the normal chromosomes 3. However, there is only one normal chromosome 6 in the case, resulting in monosomy for both 3p21 → pter and 6pter → q23. This is the result of 3:1 segregation (see Chapter 9).

47,XY,+der(3)t(3;6)(p21;q23)mat
The der(3) is the same as in the above examples. A 3:1 segregation in the mother resulted in a normal 3 and the derivative 3 to be retained in the ovum. The father contributed a normal 3 as well. The patient is, therefore, trisomic for both3p21 → qter and 6q23 → qter.

Recombinant Chromosomes (rec)

Recombinant chromosomes are also structurally rearranged chromosomes. They arise *de novo* from *meiotic* crossing-over between homologous chromosomes when one is structurally abnormal, often, in an inversion heterozygote.

Take, for example, an individual with the karyotype 46,XY,inv(3)(p21q27). As described below, this man has one chromosome 3 with a pericentric inversion involving the segment between bands p21 and q27. During meiosis, crossing-over within the inverted segment could result in two recombinant chromosomes, each of which has a duplication of one part of the chromosome and deletion of another part; this is described in detail in Chapter 9:

46,XY,rec(3)dup(3p)inv(3)(p21q27)
One normal chromosome 3 has been replaced by a recombinant chromosome 3. The segment 3p21 → pter is duplicated, and the segment from 3q27 → qter is deleted. The key to interpreting this karyotype is "dup(3p)"; dup indicates a duplication (see **Table 3**).

46,XY,rec(3)dup(3q)inv(3)(p21q27)
Here, the other possible recombinant chromosome is present, resulting in duplication of the segment 3q27 → qter and loss of the segment 3p21 → pter. In this case, note "dup(3q)."

Fragile Sites

As discussed in Chapters 14 and 18, fragile sites exist in many areas of the human karyotype. Although the fragile site responsible for fragile X syndrome is no longer diagnosed via cytogenetic analysis, the nomenclature occasionally can still be seen. A male would be described as 46,Y,fra(X)(q27.3), and a female would be 46,X,fra(X)(q27.3). Other fragile sites are described in the same way [e.g., 46,XY,fra(12)(q13.1)].

Insertions (ins)

An insertion is a structural rearrangement in which a part of a chromosome is typically interstitially repositioned into a different area of the karyotype. Insertions can occur within a chromosome or between two chromosomes. They can also be direct, in which the inserted segment retains its orientation relative to the centromere, or inverted, where the inserted segment has been "flipped over." Although the symbols "dir" and "inv" can be used to distinguish between the two, they are optional, as the orientation of the inserted material is typically evident from the nomenclature.

Insertion Within a Chromosome

In these cases, only one chromosome need be described. The first band listed is the break at the point of insertion, followed by the breakpoints that define the inserted segment itself. No punctuation is used:

46,XX,ins(3)(p21q27q32)
This represents a direct insertion. The long-arm segment between bands 3q27 and 3q32 has broken away and has been inserted into the short arm of the same chromosome at band p21. The

orientation of the inverted segment has not changed (i.e., band q27 is still proximal to the centromere relative to band q32).

46,XX,ins(3)(p21q32q27)
In this case, the inserted segment is inverted; band q32 is now closer to the centromere than band q27.

Insertion Between Two Chromosomes

Here, both chromosomes are listed, with the recipient chromosome presented first, irrespective of numerical order. As with other rearrangements, a semicolon separates the chromosome numbers.

46,XX,ins(4;9)(q31;q12q13)
The long-arm segment between bands 9q12 and 9q13 has been inserted, in its original orientation, into the long arm of chromosome 4 at band q31.

Inversions (inv)

A chromosomal aberration in which a segment of a chromosome is reversed in orientation but not relocated is called an inversion. There are two types of inversion. Paracentric inversions involve only one arm of a chromosome, whereas pericentric inversions involve both arms of a chromosome and, therefore, *include the centromere*. The type of inversion does not have to be specified, as this will be evident from the breakpoints.

Paracentric Inversions

46,XY,inv(3)(q21q27)
Break and reunion occurred at bands q21 and q27 in the long arm of chromosome 3. The segment lying between these breakpoints has been reattached with its bands in reverse (inverted) order.

Pericentric Inversions

46,XY,inv(2)(p21q31)
Break and reunion occurred at bands p21 (short arm) and q31 (long arm) of chromosome 2. The segment between these bands, including the centromere, was reattached with its bands in inverted order.

Isochromosomes (i)

An abnormal chromosome in which one arm is duplicated (and the other lost) is an isochromosome, abbreviated as "i" in the nomenclature. The breakpoint in an isochromosome is assigned to the centromere, at band p10 or q10, depending on which arm is duplicated:

46,XX,i(18)(p10)
This describes an isochromosome for the short arm of chromosome 18, as evident by assigning the breakpoint to band p10.

46,XX,i(18)(q10)
This describes an isochromosome for the long arm of a chromosome 18; the breakpoint is assigned to q10.

Isodicentric Chromosomes (idic)

Unlike isochromosomes, isodicentric chromosomes contain two copies of the same centromere. One of the two centromeres might be inactive, in which case the chromosome is pseudodicentric (psu dic). The breakpoints in isodicentric chromosomes are usually on the band adjacent to the centromere *on the opposite arm*:

46,XX,idic(18)(q11.2)

Here, we have an isodicentric chromosome comprised of two copies of the entire short arm of chromosome 18, two copies of the centromere, and two copies of the small portion of the long arm between the centromere and band q11.2.

Marker Chromosomes (mar)

Marker chromosomes (mar) are supernumerary, structurally abnormal chromosomes of which no part can be identified. If any part of such a chromosome is identifiable, it is not a marker but a derivative chromosome. The presence of a "mar" in a karyotype is always recorded by a plus (+) sign:

47,XY,+mar

This is a male karyotype with a marker chromosome.

48,XY,+2mar

This is a male karyotype with two marker chromosomes.

48,XY,t(5;12)(q13;p12),+21,+mar

This describes a male karyotype with a translocation involving chromosomes 5 and 12, an extra chromosome 21, and a marker chromosome.

Ring Chromosomes (r)

A structurally abnormal chromosome with two breaks, one on the short arm and one on the long arm, in which the broken ends are attached to form a circular configuration is a ring chromosome. The net result is deletion of at least the terminal ends of both arms, and potentially more (or most) of either or both arms:

46,X,r(X)

This is a female karyotype with only one normal X chromosome and a ring X chromosome with no information on breakpoints.

46,X,r(X)(p22q24)

This describes a female karyotype with one normal X chromosome and a ring X chromosome with break and reunion at bands p22 and q24. The material distal to both breakpoints is lost.

Translocations (t)

The interchange or transfer of chromosomal segments between two nonhomologous chromosomes is defined as a translocation.

Reciprocal Translocations

If the translocation involves mutual exchange of segments between two chromosomes, it is referred to as a reciprocal translocation. To describe a reciprocal translocation, the abbreviation "rcp" can be substituted for the "t," but this is generally not done, as all translocations are, in one sense, theoretically reciprocal, even if this is not readily apparent visually. As always, sex chromosomes are listed first, with autosomes presented in numerical order. If a translocation involves three or more chromosomes, the same rule applies to the first chromosome listed; however, in these rearrangements, the second chromosome specified will be the one that received the segment from the first and so on:

46,XX,t(7;10)(q22;q24)

Break and reunion occurred at bands 7q22 and 10q24. The segments distal to these bands were interchanged. The translocation event has not altered the total DNA content of this cell. Therefore, the translocation is microscopically (cytogenetically) balanced.

46,X,t(X;1)(p21;q32)

Break and reunion occurred at bands Xp21 and 1q32. The segments distal to these bands were interchanged. The translocation is balanced. Note that the X chromosome is specified first.

46,X,t(Y;15)(q11.23;q21.2)

Break and reunion occurred at subbands Yq11.23 and 15q21.2. The segments distal to these bands were interchanged. This translocation is cytogenetically balanced. Here, again, the sex chromosome is specified first.

46,XY,t(9;22)(q34;q11.2)

Break and reunion has occurred at bands 9q34 and 22q11.2. The segments distal to these bands have been interchanged. This represents the typical "Philadelphia" rearrangement associated with CML and also seen in ALL and AML.

46,XX,t(1;7;4)(q32;p15;q21)

This is an example of a complex translocation involving three chromosomes. The segment on chromosome 1 distal to band q32 has been translocated onto chromosome 7 at band p15, the segment on chromosome 7 distal to band p15 has been translocated onto chromosome 4 at band q21, and the segment on chromosome 4 distal to band q21 has been translocated onto chromosome 1 at band q32. The translocation is cytogenetically balanced.

These same general principles also apply to describing translocations involving more than three chromosomes.

Whole-Arm Translocations

Whole-arm translocations are a type of reciprocal translocation in which the entire arms of two nonacrocentric chromosomes are interchanged. Such rearrangements are described by assigning the breakpoints to the arbitrary centromeric regions designated as p10 or q10, as the actual ultimate composition of the centromeres is not known. If both chromosomes have exchanged the same arms, so that the resultant rearranged chromosomes are still comprised of one short arm and one long arm, the breakpoint p10 is assigned to the chromosome with the lowest number (or a sex chromosome, if applicable). Consequently, the other chromosome will have the breakpoint at q10:

46,XX,t(3;8)(p10;q10)

This represents a balanced whole-arm translocation between chromosomes 3 and 8. In this example, the short arm of chromosome 3 and the long arm of chromosome 8 have been fused. Reciprocally, the long arm of chromosome 3 has fused with the short arm of chromosome 8, but only one combination need be written. The composition of the resultant centromeres is not known.

46,XX,t(3;8)(p10;p10)

This is a balanced whole-arm translocation in which the short arms of chromosomes 3 and 8 have been fused, as have both long arms of these chromosomes. Note that the breakpoints designate the short arms of both chromosomes. Here, again, the reciprocal product [t(3;8)(q10;q10)] need not be written, as its presence is obvious from the chromosome number of 46.

Whole-arm translocations are not always balanced, as in the following examples:

45,X,der(X;3)(p10;q10)

Here, we have a derivative chromosome consisting of the short arm of an X and the long arm of chromosome 3. The reciprocal product consisting of the long arm of the X and the short arm of 3 is missing. Note: The total chromosome number is 45, indicating the loss of the reciprocal product; no (–) sign is used. The net result is monosomy for both the long arm of X and short arm of 3.

47,XX,+der(X;3)(p10;q10)

This karyotype has an extra derivative chromosome consisting of the short arm of an X and the long arm of chromosome 3, the same derivative chromosome as in the previous example. However, in this case, two normal X chromosomes and two normal chromosomes 3 are also present, and so the derivative chromosome is extra (note that the total number of chromosomes is 47). The net result is trisomy for both the short arm of the X and the long arm of chromosome 3.

Robertsonian Translocations

Although long believed to originate through centric fusion of the long arms of acrocentric chromosomes (pairs 13, 14, 15, 21, and 22), recent data suggest this might not always be so (see Chapter 9). They were first described by Robertson, whose name they have been given. The short arms, which all contain redundant copies of ribosomal genes, are lost in these rearrangements; this is of no clinical significance. Because Robertsonian translocations are still treated as a type of whole-arm translocation, they can be adequately described using the same nomenclature:

45,XX,der(13;14)(q10;q10)

This describes a Robertsonian translocation between chromosomes 13 and 14. The centromere origin is unknown, and so the breakpoints are designated as 13q10 and 14q10 to indicate that both long arms are involved. This derivative chromosome has replaced one chromosome 13 and one chromosome 14; there is no need to indicate the missing chromosomes. The karyotype now contains one normal 13, one normal 14, and the der(13;14). The short arms of the 13 and 14 are lost, which is why the abbreviation "der" is used instead of "t" to describe the translocation. One can also use "rob" to describe Robertsonian translocations. The loss of these short arms is not clinically significant and, therefore, this description represents a balanced Robertsonian translocation (an individual with this karyotype is referred to as a balanced carrier) even though only 45 chromosomes are present.

46,XX,+13,der(13;14)(q10;q10)

The derivative chromosome consists of the long arms of chromosomes 13 and 14, as in the above example. However, in this karyotype, there are two normal 13s and one normal 14, plus the der(13;14). The net result is trisomy for the long arm of chromosome 13, clinically identical to trisomy 13. The additional chromosome 13 is shown by the designation +13. Here, we have an example of both numerical and structural abnormalities that involve the same chromosome number, and so the numerical abnormality is designated first.

Uniparental Disomy (upd)

Representation of both maternally and paternally inherited genes is required in many areas of the genome in order for normal development to occur. This phenomenon is referred to as genomic imprinting and involves selective inactivation of certain genes by methylation. Uniparental disomy is a situation in which both homologs of a specific chromosome pair are inherited from the same parent and, in some cases, is associated with an abnormal phenotype. Uniparental disomy can occur, for example, in an embryo that starts out trisomic for a given chromosome and then loses one copy of this chromosome early enough in development to "rescue" what would have been a pregnancy doomed to abort spontaneously. If, by chance, the two remaining copies were inherited from one parent, the individual is said to have upd for that chromosome. For example, some patients with Prader–Willi/Angelman syndrome and no deletion of chromosome 15 have been shown to have upd for this chromosome. Inheriting two paternal chromosomes 15 results in Angelman syndrome, whereas receiving two maternal 15s results in Prader–Willi syndrome. See Chapter 19.

Nomenclature examples are follows:

46,XY,upd(15)pat

This is a male patient with uniparental disomy for paternally derived chromosomes 15.

46,XY,upd(22)pat[10]/47,XY,+22[6]
: This represents a mosaic male karyotype involving one cell line that contains two paternally derived chromosomes 22 and the other with trisomy 22. Here, both cell lines are abnormal and, therefore, the larger clone is recorded first.

46,XX,upd pat
: This describes a complete hydatidiform mole with XX sex chromosomes (very rare). All 46 chromosomes are paternally derived.

46,XY,upd pat
: This describes a complete hydatidiform mole with XY sex chromosomes. All 46 chromosomes are paternally derived.

46,XX,upd mat
: This is an ovarian teratoma. All 46 chromosomes are maternally derived.

NEOPLASIA

The basic rules for using the nomenclature apply when describing the karyotypes associated with cancer. However, special situations, requiring additional guidelines, might arise in these cases. Therefore, special ISCN definitions and rules have been devised for use with neoplasia.

Clones

A clone is defined as two cells that share the same abnormality or abnormalities, unless the change involves loss of a chromosome, in which case three such cells are required (because of the possibility of coincidental random chromosome loss). During tumor progression, related subclones can evolve; related or unrelated clones are separated by slashes "/" and the number of cells observed for each is given in square brackets "[ ]".

Mainline, Stemline, Sideline, and Clonal Evolution

These terms can be confusing and are often misunderstood. The mainline (ml) is the term used to describe the most common clone (i.e., the one represented by the most cells). This is a quantitative issue only. It does not necessarily indicate the most basic clone in tumor progression, which is referred to as the *stemline* (sl). Clones that evolve from the stemline are referred to as *sidelines* (sdl):

46,XY,t(9;22)(q34;q11.2)q34;q11.2)[5]/47,XY,+8,t(9;22)(q34;q11.2)[11]/46,XY,t(9;22)(q34;q11.2),i(17)(q10)[4]
⇔ ⇑ ⇒
stemline mainline sidelines

When more than one clone is present but no clear clonal progression is evident, the mainline is listed first, followed by each clone in order of relative size. When clonal evolution is present, the stemline is listed first, with sidelines listed in order of increasing complexity whenever possible, or by clone size when more than one sideline evolves independently from the stemline, as in the preceding example.

Composite Karyotype (cp)

When a clone contains multiple abnormalities, a frequent occurrence is that not all changes are present in every cell, yet the interpretation can be made that these cells do, in fact, represent a single abnormal clone rather than an evolving process. To report such a phenomenon, the clone is described as a *composite*, using the abbreviation "cp" before the number in brackets. It should be noted that this can occasionally produce seemingly contradictory data, as some cells will contain additional copies of a chromosome that is missing in others.

INTERPRETING A KARYOTYPE DESCRIPTION

Receiving a cytogenetic report that contains the description of a patient's karyotype can create confusion, particularly if complex rearrangements or multiple clones are present. Interpretation of the description of a karyotype can be facilitated by breaking this description into its component parts.

First, determine whether more than one cell line is present. This will happen if constitutionally the patient is a mosaic or a chimera as is often the case with acquired cytogenetic abnormalities, particularly in patients whose neoplasm is progressing. Because the first item described is always the number of chromosomes present, each clone or cell line present will start with this number, and each is separated by a slash (/). Each cell line can then be examined individually. If abnormalities present in the first clone listed are also present in others, the description can be simplified by using the abbreviation "idem" to indicate this; note that idem always refers to the first cell line described, which will be the stemline in these cases.

As discussed above, the sex chromosome complement follows the chromosome count. Sex chromosome abnormalities are listed first, followed by autosomal abnormalities in numerical order. When abnormalities involve the same chromosome, numerical changes are presented first, followed by structural abnormalities listed in alphabetical order, using the abbreviations listed in **Table 3.**

Commas separate each abnormality listed, and so by examining the karyotype from comma to comma, the abnormalities involved can be interpreted.

Consider the following example from a patient with AML:

47,XY,del(5)(q13q33),+8,t(9;22)(q34;q11.2)[4]/48,idem,+9,i(17)(q10)[12]/46,XY[4]

At first blush, receiving a report with this karyotype might be enough to scare away even the most confident clinician! However, let us break this karyotype down into its component parts, which will simplify its interpretation.

The slashes, brackets, and listings of number of chromosomes tell us that three different clones are present:

47,XY,del(5)(q13q33),+8,t(9;22)(q34;q11.2)**[4]**
/48,idem,+9,i(17)(q10)**[12]**
/46,XY**[4]**

Of the 20 cells examined, the first clone has 47 chromosomes and is represented by 4 cells. The second clone has 48 chromosomes; 12 of these cells were observed. Finally, four normal 46,XY cells are present.

Now, let us look again at the first cell line, the *stemline* in this case. It has an XY sex chromosome complement. It also has three cytogenetic abnormalities: It has one chromosome 5 with an interstitial deletion of the material between bands q13 and q33 (on the long arm):

47,XY,**del(5)(q13q33)**,+8,t(9;22)(q34;q11.2)[4]/48,idem,+9,i(17)(q10)[12]/46,XY[4]

It has an extra copy of chromosome 8,

47,XY,del(5)(q13q33),**+8**,t(9;22)(q34;q11.2)[4]/48,idem,+9,i(17)(q10)[12]/46,XY[4]

and it has a translocation involving the long arms of chromosomes 9 and 22, at band q34 of chromosome 9 and band q11.2 of chromosome 22:

47,XY,del(5)(q13q33),+8,**t(9;22)(q34;q11.2)**[4]/48,idem,+9,i(17)(q10)[12]/46,XY[4]

Yes, this is the "Philadelphia" rearrangement, which is sometimes also seen in patients with AML.

The second cell line contains the sex chromosomes and all of the abnormalities present in the first:

47,XY,del(5)(q13q33),+8,t(9;22)(q34;q11.2)[4]/48,**idem**,+9,i(17)(q10)[12]/46,XY[4]

plus an additional copy of chromosome 9:

47,XY,del(5)(q13q33),+8,t(9;22)(q34;q11.2)[4]/48,idem,+**9**,i(17)(q10)[12]/46,XY[4]

and an isochromosome for the long arm of chromosome 17:

47,XY,del(5)(q13q33),+8,t(9;22)(q34;q11.2)[4]/48,idem,+9,**i(17)(q10)**[12]/46,XY[4].

Because this is the largest clone present (with 12 cells), it represents the *mainline*.

Finally, as mentioned above, the third cell line represents cells with a normal male karyotype:

47,XY,del(5)(q13q33),+8,t(9;22)(q34;q11.2)[4]/48,idem,+9,i(17)(q10)[12]/**46,XY**[4]

Thus, we see that by examining the components of a reported karyotype using the above-outlined rules, together with the abbreviations listed in **Table 3** or in the nomenclature document itself *(11)*, what initially might appear as an indecipherable compilation of numbers and symbols becomes a concise, universal method of describing the results of a patient's chromosome analysis.

FLUORESCENCE AND OTHER *IN SITU* HYBRIDIZATION

Recent advances in human cytogenetics include the development and application of *in situ* hybridization (ish) protocols to incorporate and bind labeled, cloned DNA or RNA sequences to cytological preparations. These techniques facilitate the localization of specific genes and DNA segments onto specific chromosomes, ordering the position and orientation of adjacent genes along a specific chromosome, identification of microduplications or microdeletions of loci that lie beyond the resolution of conventional cytogenetics but manifest themselves as abnormal clinical phenotypes, and the detection of aneuploidies involving whole chromosomes or chromosomal regions (see Chapter 17). For these reasons, nomenclature to designate various ish applications was introduced in ISCN 1995. The symbols and abbreviations used in ish nomenclature are listed in **Table 4.**

Prophase or Metaphase Chromosome In Situ *Hybridization (ish)*

Even though fluorescence microscopy is most commonly used to view *in situ* hybridization signals, the abbreviation ish, not FISH, is used in the karyotype description. If chromosome analysis was done prior to ish, the karyotype is first designated using conventional rules. A period (.) is then placed to record the end of the cytogenetic findings. This is then followed by the ish results. If a standard cytogenetic analysis was not done and only ish studies were done, the ish results are presented directly.

When presenting an abnormal ish result, the abbreviation for that specific abnormality is recorded (e.g., ish del) followed by the chromosome number, the breakpoints, and a designation for the probe used, all listed in separate parentheses [e.g., ish del(4)(p16.p16)(D4S96–]. Whenever possible, Genome Data Base (GDB) designations for loci are used. These consist of the letter "D" (for DNA), the chromosome of origin, the letter "S" (segment), and the GDB number of the probe. The above example uses the 96th DNA segment assigned to chromosome 4, D4S96. The locus designation must be given using capital letters only. When a GDB designation is not available, a probe name can be

Table 4
Selected List of Symbols and Abbreviations Used for *In Situ* Hybridization (ish) Nomenclature

Abbreviation or Symbol	*Description*
–	Absent on a specific chromosome
+	Present on a specific chromosome
++	Duplication on a specific chromosome
x	Precedes the number of signals seen
.	Period, separates cytogenetic results from ish results
con	Connected or adjacent signals
ish	Refers to *in situ* hybridization; when used by itself, ish refers to hybridization to chromosomes
nuc ish	Nuclear or interphase *in situ* hybridization
pcp	Partial chromosome paint
sep	Separated signals (which are usually adjacent)
wcp	Whole chromosome paint

Note: For a complete listing of symbols and abbreviations, refer to ref. *11*.

used. If more than one probe from the same chromosome is used, these are listed in order from pter to qter. If probes from two different chromosomes are used, they are separated by a semicolon.

Given below are a series of examples that illustrate the ish karyotype designations one might see, using as examples patients suspected of having various disorders.

Patients with Possible DiGeorge/VCF Syndrome

46,XX.ish 22q11.2(D22S75x2)

This example illustrates the basic rules in describing an ish karyotype when both chromosome and ish results are normal. The test was performed on prophase/metaphase chromosomes. The probe used, D22S75, detects about 80% of deletions leading to DiGeorge/velocardiofacial (VCF) syndrome. First, the cytogenetics result 46,XX is recorded, followed by a period and then the abbreviation ish. A single space is left, after which the chromosome and region numbers are given together without parentheses, 22q11.2, followed by the GDB locus designation of the probe used, within parenthesis (D22S75), and the number of times the probe signal is observed (x2, because in a normal cell, neither chromosome 22 would have a deletion).

46,XX.ish del(22)(q11.2q11.2)(D22S75–)

This patient has a normal karyotype resulting from standard chromosome analysis, but a deletion in the DiGeorge region of chromosome 22, at band q11.2, was detected by ish using a probe for that locus, D22S75. Note: The chromosome 22 and the region tested are now placed within parentheses because an abnormality (no signal, indicated by a minus sign) is being described.

46,XX,del(22)(q11.2q11.2).ish del(22)(q11.2q11.2) (D22S75–)

Here, we have a karyotype in which a deletion was identified with standard chromosome analysis and confirmed with ish using a probe for locus D22S75.

Patients with Possible Prader–Willi/Angelman Syndrome

46,XX.ish 15q11.2q13(D15S11x2,GABRB3x2)

This patient has normal chromosomes, but was suspected of having a microdeletion in the Prader–Willi/Angelman syndrome region. She was studied by *in situ* hybridization using probes D15S11 and GABRB3, both of which map to the region 15q11.2 → q13. Hybridization showed two copies each of the two probes, suggesting no deletion for either locus.

46,XX.ish 15q11.2q13(D15S11x2,GABRB3x2D15S10x2,SNRPNx2,)

Because of the negative ish results but continued clinical suspicion, the above patient was retested using the additional probes D15S10 and SNRPN. There is still no deletion detected. Because of the high degree of suspicion, this patient is a candidate for uniparental disomy analysis (see Chapter 19).

46,XX,del(15)(q11.2q13).ish del(15)(q11.2q13)(D15S10–,SNRPN–)

Here, a deletion of 15q11.2 → q13 was detected with cytogenetic analysis and was confirmed with ish. The probes used were D15S10 and SNRPN. Both were absent from one chromosome 15. The ish "deletion" is denoted by a minus sign.

Patients with Possible Williams Syndrome

46,XX.ish 7q11.23(ELNx2)

This patient had a diagnosis of Williams syndrome and normal chromosomes. *In situ* hybridization with a probe for the Elastin–Williams syndrome (ELN) locus produced hybridization at band 7q11.23 on both chromosomes 7. There is no deletion.

46,XX.ish del(7)(q11.23q11.23)(ELN–)

As above, this is a patient with Williams syndrome and normal cytogenetic results. *In situ* hybridization with a probe for the ELN locus showed a deletion on one chromosome 7.

46,XX.ish del(7)(q11.23q11.23)(ELN–x2)

Again, this is a patient with Williams syndrome and normal cytogenetic results. However, in this case, ish with a probe for the ELN locus showed deletions on both chromosomes 7.

Patients with Possible Charcot–Marie–Tooth Syndrome

46,XX.ish 17p11.2(CMT1Ax2)

This is a patient with Charcot–Marie–Tooth syndrome and normal chromosomes. *In situ* hybridization with a probe for the CMT1A locus showed normal hybridization on both chromosomes 17 and, thus, no deletion or duplication of the locus.

46,XX,ish dup(17)(p11.2p11.2)(CMT1A++)

This Charcot–Marie–Tooth syndrome patient also has normal chromosomes. *In situ* hybridization with a probe for the CMT1A locus showed duplication of the locus on one chromosome 17(++).

Chromosome Abnormalities Identified with Whole Chromosome Paints

In situ hybridization can be performed using a cocktail of chromosome-specific probes that will hybridize along the entire length of that chromosome pair, effectively "painting" them. Because the procedures used ensure that no other chromosomes are "painted," these probes provide a way to identify or confirm the identity of chromosomal material:

46,XX,add(20)(p13).ish dup(5)(p13p15.3)(wcp5+)

In this patient, one chromosome 20 has extra material attached to it at band p13. By using a whole chromosome paint for chromosome 5 (wcp5), the extra segment was identified as a partial duplication of chromosome 5. Subsequent analysis of the band morphology using Giemsa banded preparations allowed the duplicated material to be identified as the segment 5p13 → p15.3. The diagnosis is essentially made by going from G-banding to ish and then back to G-banding.

Both whole chromosome paints and locus-specific ish probes can be used in combination in order to determine the composition of an abnormal chromosome:

46,X,r(X).ish r(X)(p22.3q13.2)(wcpX+,DXS1140+,DXZ1+,XIST+,DXZ4–)

This is an example of a ring X that was identified with G-banding and then further defined by ish. First, a whole chromosome paint for the X confirmed the origin of the ring. Next, probes

localized to Xp22.3 (DXS1140), the X centromere (DXZ1), Xq13.2 (XIST), and Xq24 (DXZ4) were used. The last probe, DXZ4, produced no hybridization signal (–), narrowing down the portion of the X that was lost during formation of the ring.

46,X,r(?).ish r(X)(DYZ3–, wcpX+)

In this case, a small ring chromosome of indeterminate origin was detected with G-banding. Hybridization with the Y probe DYZ3 showed that the ring was not derived from the Y. Follow-up hybridization with a whole chromosome paint for the X showed that it originated from an X.

47,XX,+mar.ish der(12)(wcp12+,D12Z1+)[10]/46,XX[10]

This patient is a mosaic, with both normal cells and cells with an extra marker chromosome. The marker was identified with ish as being derived from chromosome 12, using a whole chromosome paint for chromosome 12 and chromosome 12 centromere probe D12Z1.

Painting probes that hybridize to specific parts of chromosomes have also been developed and are referred to as partial chromosome paints (pcp). Consider the following example:

46,XX.ish inv(16)(p13.1q22)(pcp16q sp)

In this case, what appeared to be a normal female karyotype with routine G-banding was found to have a pericentric inversion of chromosome 16 using ish. When a partial chromosome paint for band 16q22 was used, this band was shown to be split (sp) between the long and short arms.

Identification of Cryptic Translocations Using ish

Some translocations are beyond the limits of microscopic resolution. Take, for example, an individual who has a child with Miller-Dieker syndrome. Although routine chromosome analysis produced a normal karyotype, the child was shown to have a microdeletion for this locus on chromosome 17 using ish:

46,XX.ish del(17)(p13.3p13.3)(D17S379–)

The patient and her husband wish to know if this condition could have been inherited as the result of a microscopically undetectable (cryptic) translocation carried by one of them. Both of their karyotypes are normal with standard chromosome analysis, but ish analysis demonstrates that the mother carries such a cryptic translocation.

46,XX.ish t(16;17)(q24;p13.3)(D17S379+;wcp16+)

After hybridizing the Miller–Dieker locus probe D17S379 to previously banded cells, one signal was observed in its proper location on the short arm of chromosome 17, but the other appeared on the long arm of chromosome 16. Subsequent hybridization with a whole chromosome paint for chromosome 16 showed that part of this chromosome is now on chromosome 17, confirming the presence of a reciprocal cryptic rearrangement.

Sometimes, a translocation appears to be present with standard cytogenetics, but it is so subtle and must be confirmed with ish:

46,XX,?t(4;7)(p16;q36).ish (wcp7+,D7S427+,D4S96–;wcp4+,D4S96+,D7S427–)

Here, a cryptic translocation between the short arm of chromosome 4 and the long arm of chromosome 7 was suspected with G-banding, but was not a certainty via cytogenetics alone, hence the "?." The presence of this rearrangement was confirmed with ish using probe D7S247 localized to 7qter, D4S96 localized 4pter, and whole chromosome paints for both chromosomes 4 and 7. The distal short arm of the der(4) was wcp7+, D7S247+, and D4S96–. The distal long arm of the der(7), on the other hand, was wcp4+, D4S96+, and D7S247–.

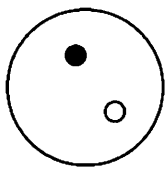
Interphase or Nuclear In situ *Hybridization (nuc ish)*

In situ hybridization can be performed on interphase nuclei to provide information concerning the number and/or relative positions of the probes (and therefore the loci) involved. Thus, it can be used as a screening method for the rapid detection of aneuploidies and gene rearrangements. Typically performed prior to or in the absence of standard chromosome analysis, interphase ish results are abbreviated nuc ish.

Designation of the Number of Signals

When designating interphase ish results, the abbreviation nuc ish is followed by a space, the chromosome band to which the probe is mapped, and then, in parentheses, by the GDB locus designation, a multiplication sign, and the number of signals detected:

nuc ish Xcen(DXZ1x1,DYZ3x1)

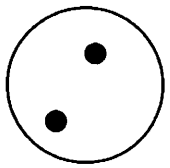


● = probe for DXZ1

○ = probe for DYZ3

One copy of the X centromere probe DXZ1 is detected, as is one copy of the Y chromosome probe DYZ3. This implies the presence of one X and one Y chromosome, suggesting an XY sex chromosome complement. No other information is presented, and so this report cannot specify whether these sex chromosomes are normal. These types of data are therefore generally used when the sex chromosome information itself is of value (e.g., when monitoring the progress of a mixed-gender bone marrow transplant).

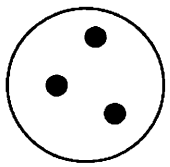
nuc ish Xcen(DXZ1x2)



● = probe for DXZ1

Here, two copies of the DXZ1 locus were detected. This implies the presence of two X chromosomes.

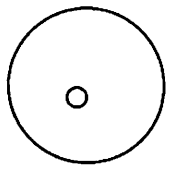
nuc ish Xcen(DXZ1x3)



● = probe for DXZ1

Three copies of the DXZ1 locus are detected, implying the presence of three X chromosomes.

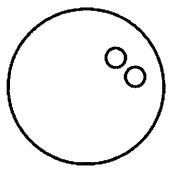
nuc ish 13q14(Rb1x1)



○ = probe for Rb1

Only one copy of the retinoblastoma locus probe Rb1 is detected. This implies a deletion of the Rb1 gene from one chromosome 13.

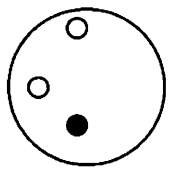
nuc ish Yp11.2(DYZ3x2)



○ = probe for DYZ3

In this case, two copies of DYZ3 are detected, implying that an extra copy of this locus is present. It is not clear whether the extra copy is the result of the presence of two Y chromosomes or an isochromosome involving the short arm of the Y.

nuc ish 4cen(D4Z1x2),4p16.3(D4S96x1)

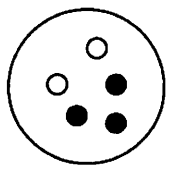


○ = probe for D4Z1

● = probe for D4S96

Here, we have an example of a structural abnormality identified with ish. Two copies of chromosome 4 are implied by two D4Z1 signals. However, only one copy of D4S96 is detected, implying a deletion of this locus from one chromosome 4. In the nomenclature, two or more probes for the same chromosome are separated by commas.

nuc ish Xp22.3(STSx2),13q14(Rb1x3)



○ = probe for STS

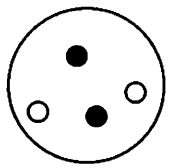
● = probe for Rb1

This is an example of ploidy detection. Two copies of the steroid sulfatase locus on the X chromosome and three copies of the Rb1 locus are detected. This implies the presence of two X chromosomes and trisomy 13. Probes from different chromosomes are separated by commas.

Designation of Relative Positions of the Signals

Under normal conditions, if probes from two chromosomes are tested simultaneously, the signals are expected to appear separated. However, chromosome rearrangements, such as the BCR/ABL gene fusion, can bring signals together:

nuc ish 9q34(ABLx2),22q11.2(BCRx2)

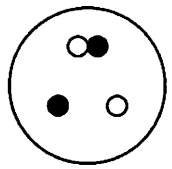


○ = probe for ABL

● = probe for BCR

Two ABL and two BCR loci seen and they are well separated. No gene rearrangement is evident.

nuc ish 9q34(ABLx2),22q11.2(BCRx2)(ABL con BCRx1)



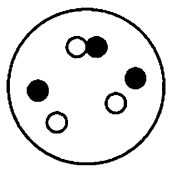
○ = probe for ABL

● = probe for BCR

○● = ABL con BCR

Here, signals from two ABL and two BCR loci are seen. However, one ABL signal and one BCR signal are juxtaposed (or connected, "con"), suggesting that they now reside on the same chromosome. This is the pattern observed when a t(9;22) or "Philadelphia rearrangement" is present.

nuc ish 9q34(ABLx3),22q11.2(BCRx3)(ABL con BCRx2)



○ = probe for ABL

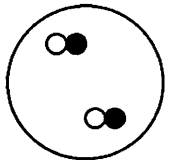
● = probe for BCR

○● = ABL con BCR

Here, three ABL and three BCR signals are present. However, two pairs of BCR/ABL signals are juxtaposed. This is the pattern observed when both a t(9;22) and an additional der(22) ["Philadelphia chromosome"] are present.

Sometimes, a rearrangement can be detected when signals that are normally juxtaposed become separated:

nuc ish Xp22.3(STSx2,KALx2)

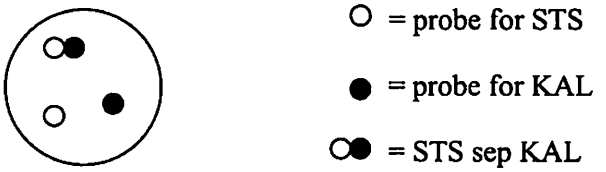


○ = probe for STS

● = probe for KAL

STS and KAL are two loci on Xp22.3 that are adjacent to each other. Because they map to the same band, they are reported within parentheses. Under normal circumstances, ish signals will appear side by side, as they do here. However, the signals might appear to be independent of each other.

nuc ish Xp22.3(STSx2,KALx2)(STS sep KALx1)



In this example, one STS and one KAL locus are separated, most likely as the result of a rearrangement involving this area of the X chromosome. The nomenclature term "sep" is used to designate this change.

ISCN 1995 has, indeed, made a good beginning concerning nomenclature for various *in situ* hybridization scenarios. However, it has become obvious in clinical practice that this document requires substantive revision in order to accommodate the technical explosion we are witnessing in this arena (see Chapter 17). Primed *in situ* labeling (PRINS), comparative genomic hybridization (CGH), use of five or more probes simultaneously for rapid aneuploidy screening, multiplex FISH, neoplasia panels, and arm-specific subtelomeric detection screening, to name a few, will all need to be included in future versions. At the time of publication, the next revision of ISCN is not expected until 2005.

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