

# Cytogenetic Nomenclature: Changes in the ISCN 2013 Compared to the 2009 Edition

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## Key Words

Array · Cytogenetic nomenclature · FISH · ISCN 2009 · ISCN 2013 · Karyotype

## Abstract

The latest edition of the International System for Human Cytogenetic Nomenclature, ISCN 2013, has recently been published following a thorough revision of the 2009 issue and the incorporation of suggestions from the community by the current standing committee. This review will highlight the multiple nomenclature changes in the respective chapters of the 2013 version compared to the previous version of the ISCN published in 2009. These highlights are meant as a guide for the cytogeneticist to assist in the transition in the use of this updated nomenclature for describing cytogenetic and molecular cytogenetic findings in both clinical and research reports.

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The International System for Human Cytogenetic Nomenclature (ISCN) has served as the central reference for describing the human chromosome complement since 1960 [Denver Conference, 1960]. Multiple iterations of

this system have evolved, and a historical record of this evolution is shown in the first chapter of the book. The latest version of ISCN, ISCN 2013, was published in November 2012. The world-wide cytogenetic community strives for consistency in the descriptive and interpretive reporting of both normal and abnormal karyotypes, regardless of which technical evaluation method was used. As the field of cytogenetics continues to expand to include several molecular-based technologies, concurrent revisions of cytogenetic nomenclature are critical for accurate descriptions of abnormalities with the new technologies. In addition, as the use of cytogenetics in oncology continues to increase, the use of cytogenetic nomenclature for neoplasms continues to become more well-defined.

The ISCN committee is comprised of an elected panel of expert (cyto)geneticists representing each continent of the world and convenes periodically to address changes in the field which are summarized in updated versions of the ISCN. The use of the most current ISCN nomenclature is strongly recommended or sometimes required for diagnostic cytogenetic reports, cytogenetic publications, proficiency-testing (or external quality assessment) and for laboratory accreditation. When ISCN versions are updated, the cytogenetics community en-

**Table 1.** Symbol and abbreviated term changes (specific sections are specified), with the new and expanded definitions denoted in bold

Symbol/abbreviation	Description
<b>cth</b>	<b>Chromothripsis (14.2.2)</b>
<b>hg</b>	<b>Human genome build or assembly (14)</b>
minus sign (-)	Loss (4.1, 8.1); <b>decrease in length (7.1.1); locus absent from a specific chromosome (13.2)</b>
<b>neg</b>	<b>No presence of the rearrangement for which testing was conducted (15.3)</b>
plus sign, single (+)	<b>Additional normal or abnormal chromosomes (4.1, 8.1); increase in length (7.1.1); locus present on a specific chromosome (13.2)</b>
<b>plus sign, double (++)</b>	<b>Two hybridization signals or hybridization regions on a specific chromosome (13.2)</b>
<b>pos</b>	<b>Detection of a rearrangement for which testing was conducted (15.3)</b>
<b>pter</b>	<b>Terminal end of the short arm</b>
<b>qter</b>	<b>Terminal end of the long arm</b>
<b>rsa</b>	<b>Region-Specific Assay (15)</b>
semicolon (;)	Separates altered chromosomes and breakpoints in structural rearrangements involving more than one chromosome (4.1, 4.3.1, 12.1); <b>separates probes on different derivative chromosomes (13.2)</b>
slant line, single (/)	Separates clones (4.1, 11.1.1, 11.1.6, 11.3), <b>or contiguous probes (13.2, 13.3)</b>

**Table 2.** Abbreviations removed from ISCN 2013 (with sections specified) because they were no longer used in the nomenclature

Symbol/abbreviation	Description
ml	Mainline (11.1.3)
mlpa	Multiplex ligation-dependent probe amplification (MLPA) (14.1, 14.4)
mn	Modal number (11.2)
tan	Tandem

ters a learning curve during a transition period while the changes are adapted for use in both research and clinical reporting.

This report highlights the major changes in the most current version of the ISCN compared to ISCN 2009. Karyotype as well as FISH and microarray examples are critical for illustrating nomenclature concepts, and nearly all chapters are expanded with new examples reflecting unique situations.

Descriptions of the changes to the nomenclature, with references to corresponding ISCN 2013 sections, can serve as a starting point in understanding and converting to ISCN 2013 nomenclature. For each chapter of the ISCN 2013, the major changes are specified below.

## Chapter 2: Normal Chromosomes

No changes.

## Chapter 3: Symbols and Abbreviated Terms (Pages 36–38)

Several symbols and abbreviations used in the description of chromosomes and chromosome abnormalities listed in chapter 3 were redefined or clarified as shown in table 1.

Abbreviations which were removed because they were no longer used in the nomenclature are listed in table 2.

## Chapter 4: Karyotype Designation

In section 4.1 (General Principles) where text has been added, it is denoted in bold:

Page 40, paragraph 5: ...and a *chimera* (cell lines originating from different zygotes) **in constitutional cases...**

Page 40, paragraph 6: ...separated by a double slant line (/) **as shown in the following examples.**

Page 41, paragraph 2: ...the abnormality may be designated *de novo* (dn), e.g., 46,XY,t(5; 6)(q34;q23)mat,inv(14)(q12q31)dn. **When dn follows another abbreviation, a space is inserted, e.g., 47,XY,+mar dn[14]/46,XY[16].**

## Chapter 5: Uncertainty in Chromosome or Band Designation

No changes.

## Chapter 6: Order of Chromosome Abnormalities in the Karyotype

The following new example was added to the top of the list of examples on page 52:

50,X,+X,-Y,+10,+14,+17,+21[5]/46,XY[15]

The numerical abnormality of the X is listed before that of the Y.

## Chapter 7: Normal Variable Chromosome Features

In section 7.1.2 (Variation in Number and Position), the following new nomenclature was added to the top of the list on page 54:

22pvar

Variable presentation of the short arm of chromosome 22.

## Chapter 8: Numerical Chromosome Abnormalities

No changes.

## Chapter 9: Structural Chromosome Rearrangements

In section 9.2.3 (Derivative Chromosomes), the following new examples were added to the bottom of the paragraph ‘When homologous chromosomes cannot be distinguished within this nomenclature system, one of the numerals may be underlined (single underlining)...’ on page 66:

46,XX,der(1)t(1;1)(p31;q32)

46,XX,der(1)t(1;1)(p31;q32)

The two derivative chromosomes can be distinguished by underlining. In the first example, the derivative observed is the homologue with a break at q32. In the second example, the derivative is the homologue with a breakpoint in p31.

In section 9.2.5 (Duplications), the first paragraph was rewritten, on page 69:

The symbol **dup** indicates a duplication. Duplications are a gain of a chromosome segment observed at the original chromosome location. When a gain of a chromosome segment is found elsewhere in the genome, der or ins should be used depending on the rearrangement. The orientation of the duplicated segment,

whether it is *direct* or *inverted*, is indicated by the order of the bands with respect to the centromere. Note that no arrow is used in the short system to indicate the orientation.

In section 9.2.9 (Insertions), the first paragraph was rewritten, on page 71:

The symbol **ins** is used for insertions. The orientation of the inserted segment, whether it is *direct* or *inverted*, is indicated by the order of the bands of the inserted segment with respect to the centromere.

Some examples were added to the end of the section ‘Insertion between two chromosomes’ on page 72, among which:

46,XY,der(5)ins(5;2)(q31;p23p13)mat

A derivative chromosome 5 resulting from malsegregation of a maternal insertion. There is one derivative chromosome 5 containing the insertion from chromosome 2, one normal chromosome 5, and two normal chromosomes 2.

46,XX,del(2)(p13p23)mat

An interstitial deletion resulting from malsegregation of a maternal insertion.

In section 9.2.13 (Neocentromeres), the following text was added below the first two examples on page 75:

Unlike duplications in which the orientation of the duplicated segment, whether it is *direct* or *inverted*, is indicated by the order of the bands with respect to the centromere, supernumerary marker chromosomes may require the use of *inv* or *dir* depending on the circumstance.

## Chapter 10: Chromosome Breakage

In section 10.1.1 (Chromatid Aberrations; Non-Banded Preparations) on page 85, in the paragraph on chromatid exchange, the wording was changed from:

...The number of centromeres might be indicated within parentheses...

to

...The number of centromeres may be indicated within parentheses...

In section 10.2.1 (Chromosome Aberrations; Non-Banded Preparations) on page 87, the following text was added to the end of the paragraph on pulverization:

The term *chromothripsis* (**cth**) describes complex patterns of alternating copy number changes (normal, gain or loss) along the length of a chromosome or chromosome segment (Stephens et al., 2011). As these complex rearrangements cannot be visualized on banded or non-banded chromosomes, this symbol is used after microarray analysis (see Section 14.2.2).

## Chapter 11: Neoplasia

In section 11.1.1 (Clones and Clonal Evolution; Definition of a Clone), the following text was changed/added to paragraph 1 on page 88:

Loss of a single chromosome must be detected in at least three such cells. However, two cells with identical losses of one or more chromosomes and the same structural aberration(s) may be considered clonal and included in the nomenclature.

46,XY,del(5)(q13q33),-7,+8[2]/46,XY[18]

The following text was added to the end of section 11.1.1, on page 89 (after the final example):

When additional abnormalities are seen in a single cell, but not proven to be present with another method, they should not be listed in the nomenclature but should be discussed in the interpretation.

In section 11.1.4 (Clones and Clonal Evolution; Stemline, Sideline and Clonal Evolution), the following examples were added to page 91 (after the 4th set of examples):

46,XY,t(9;22)(q34;q11.2)[3]/47,sl,+8[10]/48,sdl,+der(22)t(9;22)[4]/47,sl,+19[3]

46,XY,t(9;22)(q34;q11.2)[3]/47,idem,+8[10]/48,idem,+8,+der(22)t(9;22)[4]/47,idem+19[3]

The clone with the t(9;22) as the sole abnormality is the stemline. Three additional abnormal subclones are identified, one with a trisomy 8 from the stemline (sl) (now termed sdl), one that has an additional derivative chromosome 22 in the previous clone or sideline (sdl), and one with trisomy 19 of the stemline.

In section 11.1.6 (Clones and Clonal Evolution; Unrelated Clones), the following text was added after the first sentence on page 94:

If there are two equal sized clones, they are listed as follows: clones with abnormalities of the sex chromosomes first and then those with the smallest to largest numbered autosomes.

## Chapter 12: Meiotic Chromosomes

No changes.

## Chapter 13: In situ Hybridization

Note: Section 13.2 (List of Symbols and Abbreviations) in ISCN 2009 has been removed in ISCN 2013, since symbols and abbreviations have been included in chapter 3. Therefore subsequent paragraphs have been renumbered in the new ISCN 2013.

In section 13.2 (Prophase/Metaphase in situ Hybridization (ish)), the following text was added to the second paragraph and can be found on page 106:

If the clone name is not available, the locus designated according to GDB (Genome Database) should be used in order as they would appear on a normal chromosome from pter to qter.

and

Thus, at the discretion of the investigator or laboratory director, the probe or clone name or accession number, gene name, or GDB D-number can be used.

Some examples were added to pages 108 and 109, among which:

46,XX.ish ins(15;17)(q22;q21q21)(PML+,RARA+;RARA+)

A cryptic insertion of the segment 17q21 from the long arm of chromosome 17 into the 15q22 band of the long arm of chromosome 15 identified using probes for *PML* and *RARA*.

The following text was added to the end of the section on page 110 and some examples have been added, among which:

An exception to using the multiplication sign can occur in cancer, as shown in these examples. When the number of signals can be counted, the number of signals should be listed.

ish dmin(MYCN×20~50)[20]

Double minutes, identified to contain *MYCN*, are found in 20–50 copies per cell.

The abbreviation amp can be used if the number of signals cannot be enumerated.

ish der(21)(RUNX1 amp)

A derivative chromosome 21 that has an increase in *RUNX1* copies so numerous that they cannot be reliably quantified.

In section 13.3.1 (Interphase/Nuclear in situ Hybridization (nuc ish); Number of Signals), the following was added to the second paragraph on page 112:

...separated by commas. For a single locus visualized with probes to the 3' and 5' ends of a gene, they should be listed as they reside on the chromosome pter to qter.

The following example was changed on page 112 from:

nuc ish amp(MYCN)[200]

to

nuc ish(MYCN amp)[200]

The following example was changed on page 113 from:

nuc ish(D17Z1×2~3), amp(ERBB2)[100/200]/(D17Z1,ERBB2)×3[20/200]

to

nuc ish(D17Z1×2~3),(ERBB2 amp)[100/200]/(D17Z1,ERBB2)×3[20/200]

Some more examples were added to pages 113 and 114, among which:

nuc ish(DXZ1×2,DYZ3×1,D18Z1×3),(RB1,D21S259/D21S341/D21S342)×3

Three copies of 13, 18 and 21, two copies of X and one copy of Y were found, which may indicate a triploid 69,XXY. Note that the chromosome 21 contig probe shows each locus listed, separated by slashes.

In section 13.3.2 (Interphase/Nuclear in situ Hybridization (nuc ish); Relative Position of Signals), new examples are given on amplification (with supporting diagrams) and on nomenclature of results from dual fusion and break-apart probes, pages 116 to 118, among which:

Amplification of the probe for one of the loci when juxtaposed to a normal signal is expressed as follows:

nuc ish(IGH@×3,BCL2×2,BCL2 amp),(IGH@ con BCL2×1)(IGH@ con BCL2 amp×1)

nuc ish(3'DDIT3×2,5'DDIT3×1,5'DDIT3 amp)(3'DDIT3 con 5'DDIT3×1)(3'DDIT3 con 5'DDIT3 amp×1) [192/200]

Using the *DDIT3* break-apart probe, a *DDIT3* rearrangement was observed with amplification of the 5' signal. Note that the orientation is from pter to qter.

## Chapter 14: Microarrays

The original title of this chapter in ISCN 2009 was Copy Number Detection. The chapter has been largely rewritten and now includes the following sections:

### 14.1 Introduction

### 14.2 Examples of Microarray Nomenclature

#### 14.2.1 Nomenclature Specific to SNP Arrays

#### 14.2.2 Complex Array Results

Note: Section 14.2 in ISCN 2009 (List of Symbols and Abbreviations) has been removed in ISCN 2013 since symbols and abbreviations have been included in chapter 3.

In section 14.1 (Introduction), the SNP-based array has been given more attention, because this type of array has become more commonly used, which is also the reason for adding a separate paragraph on the corresponding nomenclature for regions of homozygosity and heterozygosity.

The use of the genome build in describing microarray results is introduced in this chapter:

arr[hg19] 4q32.2q35.1(163,146,681–183,022,312)×1

It is also allowed to display complex array results using ISCN nomenclature in a table instead of in a string.

Because most array platforms used these days are whole genome arrays, the ISCN committee decided to re-

move the use of arrays restricted to a particular chromosome or chromosomal region (targeted arrays), and previous examples of such nomenclature in ISCN 2009 are removed from the array chapter, because nomenclature for such targeted tests is now covered in chapter 15 (Region-Specific Assays).

In section 14.2 (Examples of Microarray Nomenclature), starting on page 122, many new examples are given, among which:

arr(8)×3,(21)×3

Microarray analysis shows a single copy gain of chromosomes 8 and 21.

arr(X)×2,(Y)×1

Microarray analysis shows a single copy gain of the X chromosome in a male.

arr(1–22)×3,(X)×2,(Y)×1

Microarray analysis shows triploidy 69,XXY.

arr[hg18] Xq28 or Yq12(154,584,238–154,913,754 or 57,443,438–57,772,954)×1

Microarray analysis shows a single copy loss of the pseudoautosomal region that is found at Xq28 and Yq12. It is not possible to determine if the loss is from X or Y in a male; FISH or chromosome analysis is required to confirm the origin of the loss.

In section 14.2.1 (Nomenclature Specific to SNP Arrays), pages 127 and 128, new examples are added in which different regions of homozygosity can be combined to shorten nomenclature.

In addition, examples are added in which constitutional and acquired aberrations are present, among which:

arr 11p15.5p15.4(2,265,338–6,275,434)×2 hmzc,  
19q13.33qter(55,069,569–63,779,291)×2 hmz

This is a possible example of a Beckwith-Wiedemann syndrome patient with inherited, segmental UPD for 11p15.5p15.4 and an acquired region of homozygosity of 19q13.33qter. Segmental UPD may be better referred to in cancer cases as copy neutral loss of heterozygosity (LOH) and in constitutional cases as absence of heterozygosity (AOH).

In section 14.2.2 (Complex Array Results), page 128, the use of the abbreviations cx for complex and cth for chromothripsis is introduced in array nomenclature with some examples, among which:

arr(1–22,X)cx

Microarray analysis shows multiple complex rearrangements across the entire genome in a female.

arr 1p36q44(1–247,249,719)cth

Microarray analysis shows multiple alternating changes (normal segments, gains, and/or losses, within the region) in chromosome 1 at bands p36 through q44. All material is from chromosome 1.

## Chapter 15: Region-Specific Assays

This is a new chapter with the following sections:

15.1 Introduction

15.2 Examples of RSA Nomenclature for Copy Number Detection

15.3 Examples of RSA Nomenclature for Balanced Translocations or Fusion Genes

The term *rsa* or region-specific assay is introduced as generic or non-specific term to be used for any type of (targeted) assay. As a consequence, the nomenclature *mlpa*, as existing in ISCN 2009, is not longer used; it is replaced by *rsa*. Below some examples of region-specific assays in ISCN 2013, pages 129 and 130:

46,XY.rsa(13,18,21)×2,(X,Y)×1

Normal male karyotype and normal copy number of chromosomes 13, 18, 21, X and Y using a region-specific assay.

When a kit is used, the name of the kit can be designated if the genomic coordinates are not known:

rsa 22q11.2('kit name')×1

Abnormal result showing a loss of 22q11.2 using an MLPA kit. The name of the kit can be inserted in the parentheses without the quotation marks.

rsa(BCR::ABL1)neg

Normal result using a region-specific assay to identify a BCR-ABL1 translocation or juxtaposition.

## References

Denver Conference (1960): A proposed standard system of nomenclature of human mitotic chromosomes. *Lancet* i:1063–1065 (1960).

ISCN (2009): An International System for Human Cytogenetic Nomenclature, Shaffer LG, Slovak ML, Campbell LJ (eds), (S Karger, Basel 2009).

## Chapter 16: References

The references section has changed from chapter 15 in ISCN 2009 to chapter 16. The following 2 references have been added to page 131 and page 132, respectively:

ISCN (2009): An International System for Human Cytogenetic Nomenclature, Shaffer LG, Slovak ML, Campbell LJ (eds), (S Karger, Basel 2009).

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).

## Conclusion

In conclusion, as the field of cytogenetics and molecular genetics evolves, a standardized nomenclature is critical for describing karyotypes and genomic changes accurately and concisely. This report summarizes the major changes noted in ISCN 2013. The ISCN is an indispensable tool in clinical and research cytogenetic use for accurate communication and reporting normal and abnormal karyotypes (including e.g. FISH and microarray data). Cytogeneticists are encouraged to carefully review the new version and become familiar with all differences introduced. In addition, users of the ISCN 2013 are invited to contact the committee on omissions and needs for the next edition of ISCN.

ISCN (2013): An International System for Human Cytogenetic Nomenclature, Shaffer LG, McGowan-Jordan J, Schmid M (eds), (S Karger, Basel 2013).