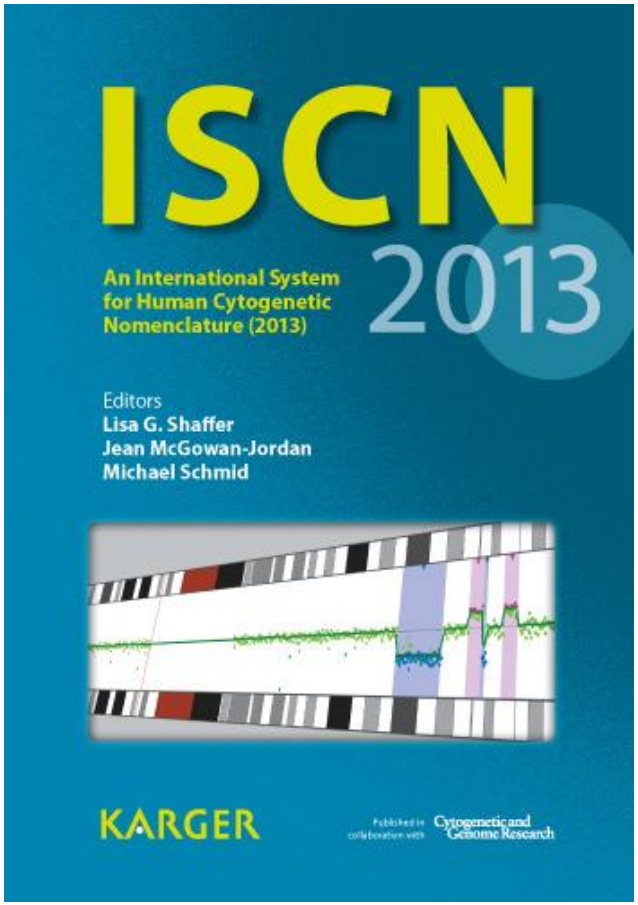
UMC St Radboud

ISCN (2013):

An International System for Human Cytogenetic Nomenclature

1st International workshop on
Cancer Genetic & Cytogenetic Diagnostics

March 20-22, 2013
Radboud University Nijmegen Medical Centre,
The Netherlands



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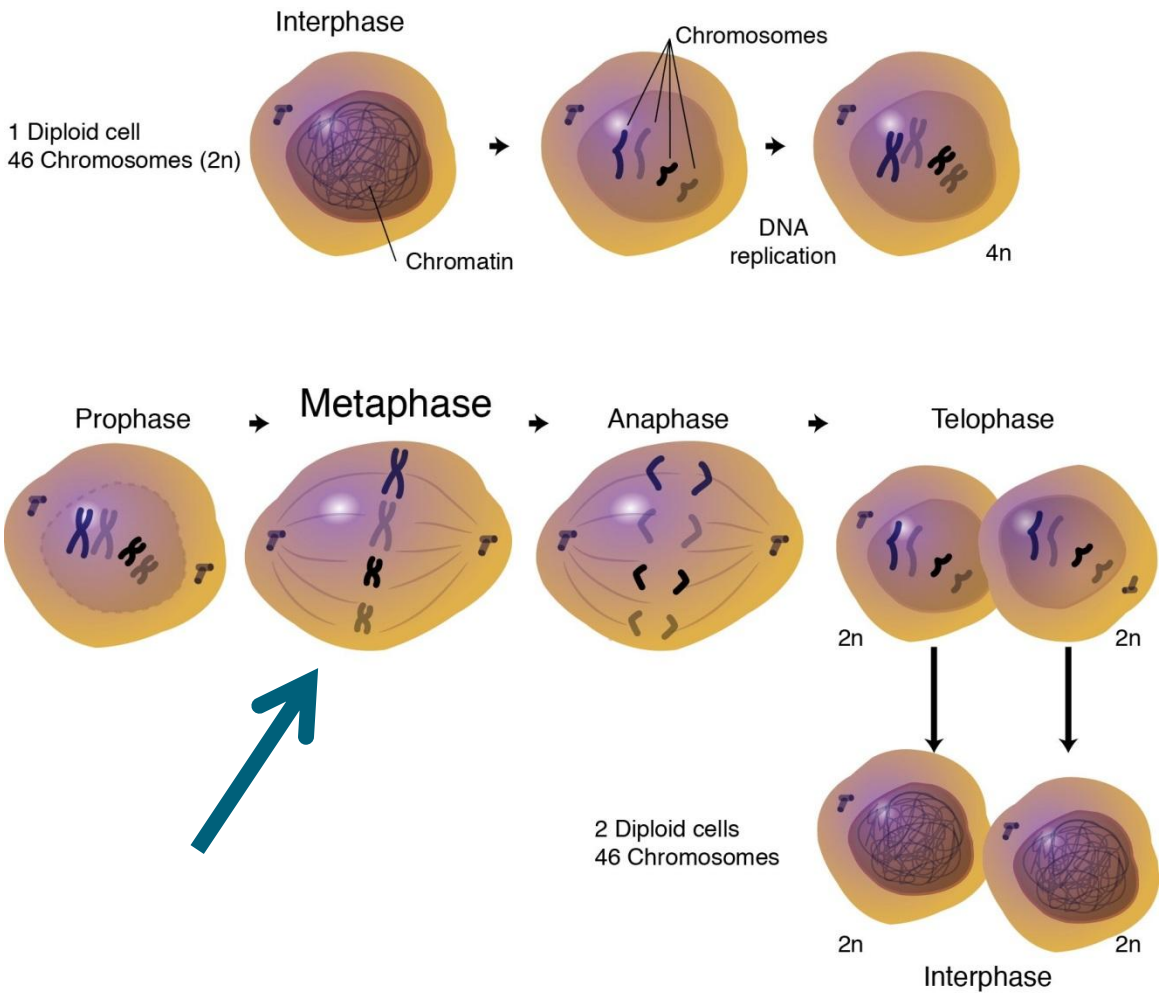
Chromosomes and cell division

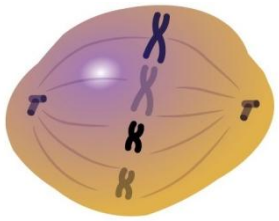


Source: Darryl Leja, NHGRI (NIH)

Historical overview about chromosomes

- 1879 human chromosomes
- 1923 48 chromosomes
- 1956 46 chromosomes (lung tissue)
- 1956 23 bivalents (spermatocytes)
- 1959 Down's syndrome (trisomy G)

- 46 chromosomes
  - 22 pairs of autosomes (1-22)
  - 2 sex chromosomes (XX or XY)



History of nomenclature

- 1956 human 46 chromosomes (no 48!)
- 1959 variety of classification and nomenclature systems
- 1960 Denver Conference: basis for all subsequent nomenclature reports
- 1963 London: classification of chromosomes in 7 groups (A-G)
- 1966 Chicago: improvement of nomenclature non-banded chromosomes
- 1968 banding techniques in plants
- 1970 first banded human karyotype
- 1971 Paris: nomenclature for chromosomal regions and bands
- 1976 Mexico: 1st international standing committee on human cytogenetic nomenclature

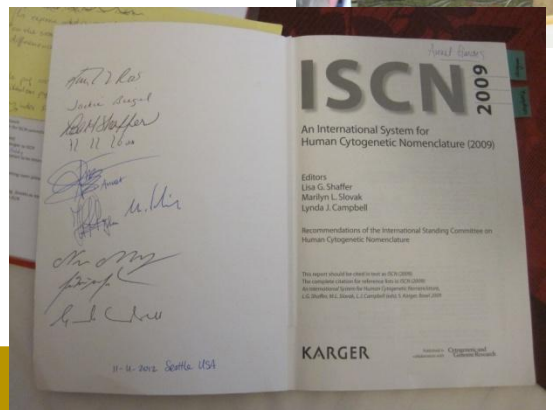
- ISCN (1978), 1st book!
- ISCN (1981), High resolution, separate book
- ISCN (1985), combination of 1st and HR
- ISCN (1991), Cancer cytogenetic, separate book
- ISCN (1995), combination of 1985 and 1991 into one document
- ISCN (2005), + G and R banding, + FISH
- ISCN (2009), + large expansion of cancer nomenclature, + array, + MLPA
- ISCN (2013), + large expansion of nomenclature array, FISH, cancer, rsa

ISCN meeting in Seattle, April 2012

- Lisa Shaffer, Chair (USA)
- New members:
  - 3 America (N+S)
    Jaclyn Biegel (USA)
    Kathleen Rao (USA)
    Jean McGown-Jordan (Canada),
    elected new chair!
  - 3 Europe
    Nils Mandahl (Sweden)
    Annet Simons (NL)
    Johan den Dunnen (NL)
  - 1 Asia
    Jin Yeong Han(Korea)
  - 1 Africa/Australia/NZ
    Myriam Chaabouni (Tunesia) (not present in Seattle)

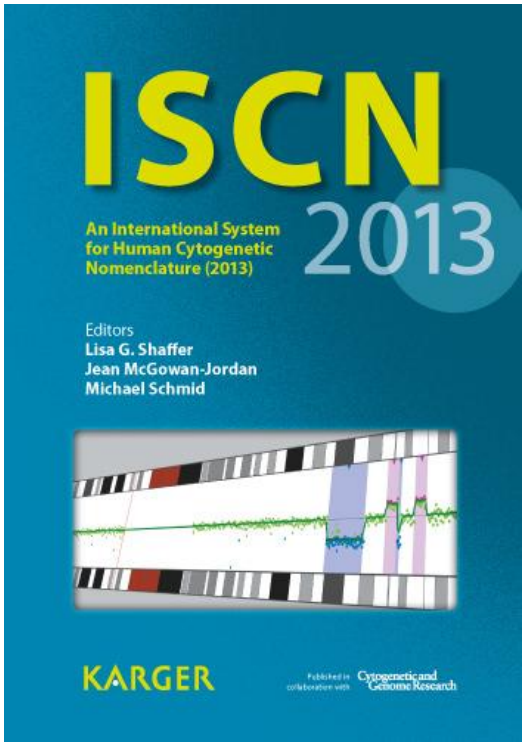
- Advisors:
  Lynda Campbell (Australia), member of previous committee
  Michael Schmid (Germany), representative Karger (publisher)
  Michelle Caldwell (USA), editor (textual, lay out)

Seattle, April 10-11, 2012



➔ ISCN (2013)

Published in November 2012



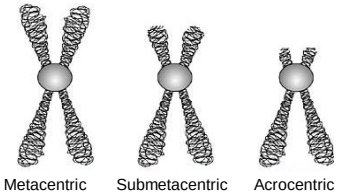
Purpose of the book

- only guidelines for nomenclature!
- practical or clinical guidelines are NOT in the book

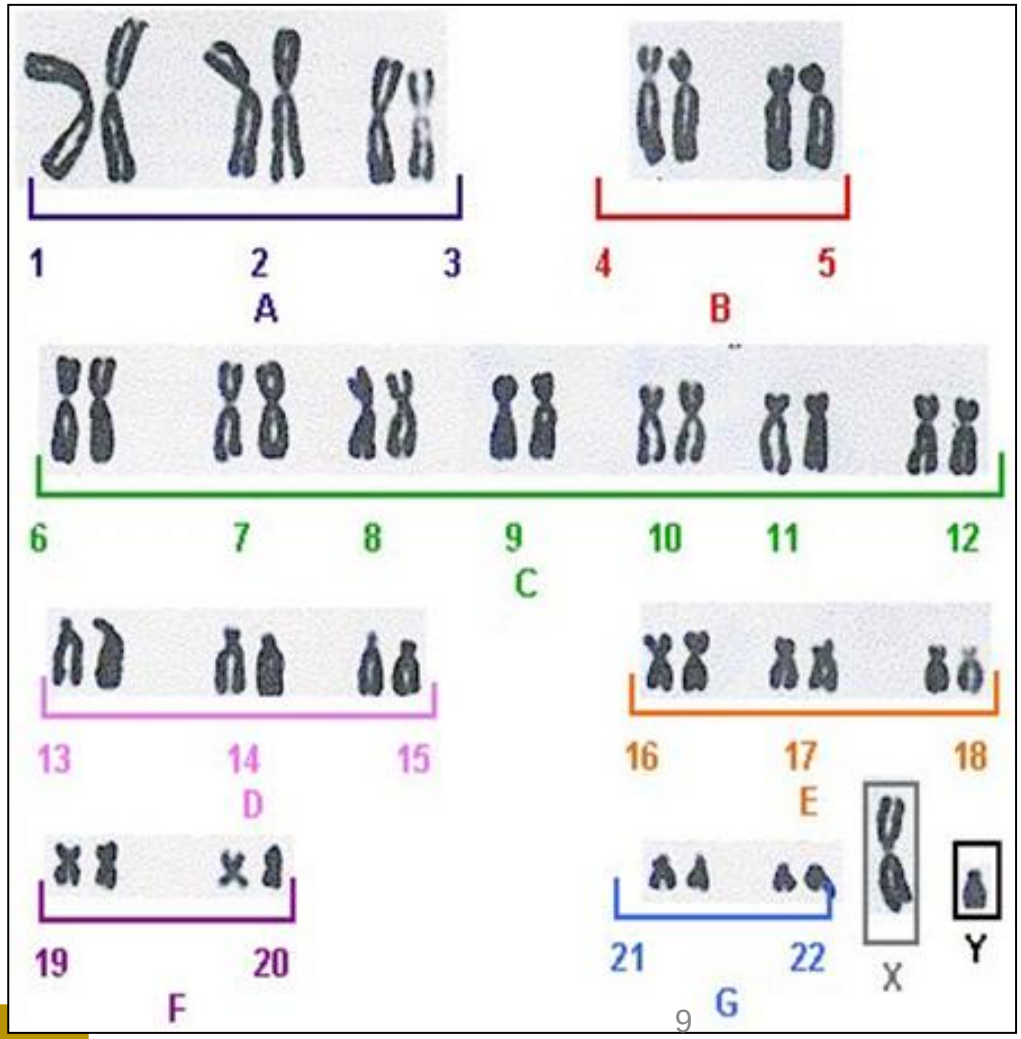
ISCN 2013 Table of Contents

Non-banded human chromosomes (until 1970)

- length
- centromere position and arm ratio

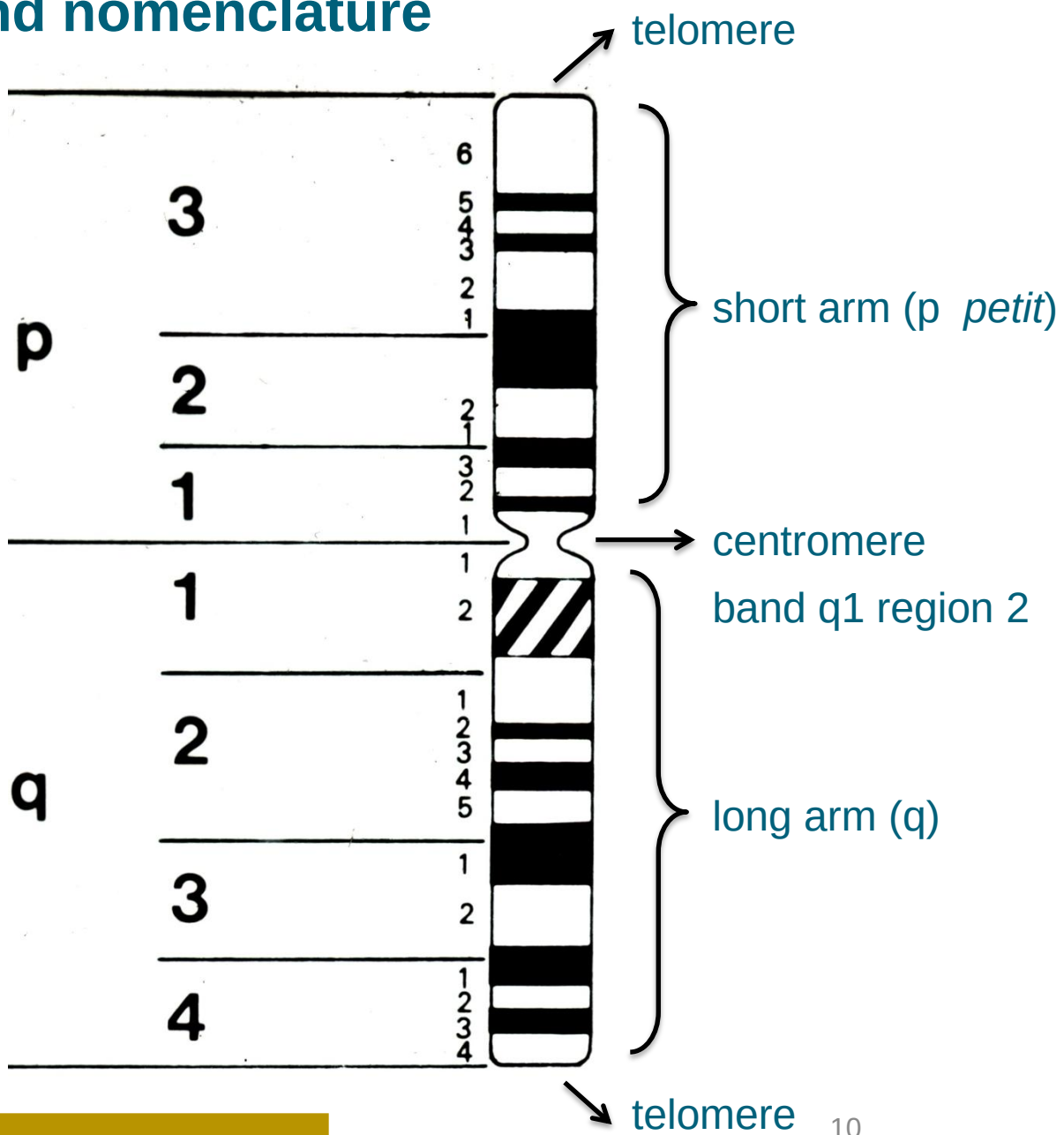


- classification: groups A-G



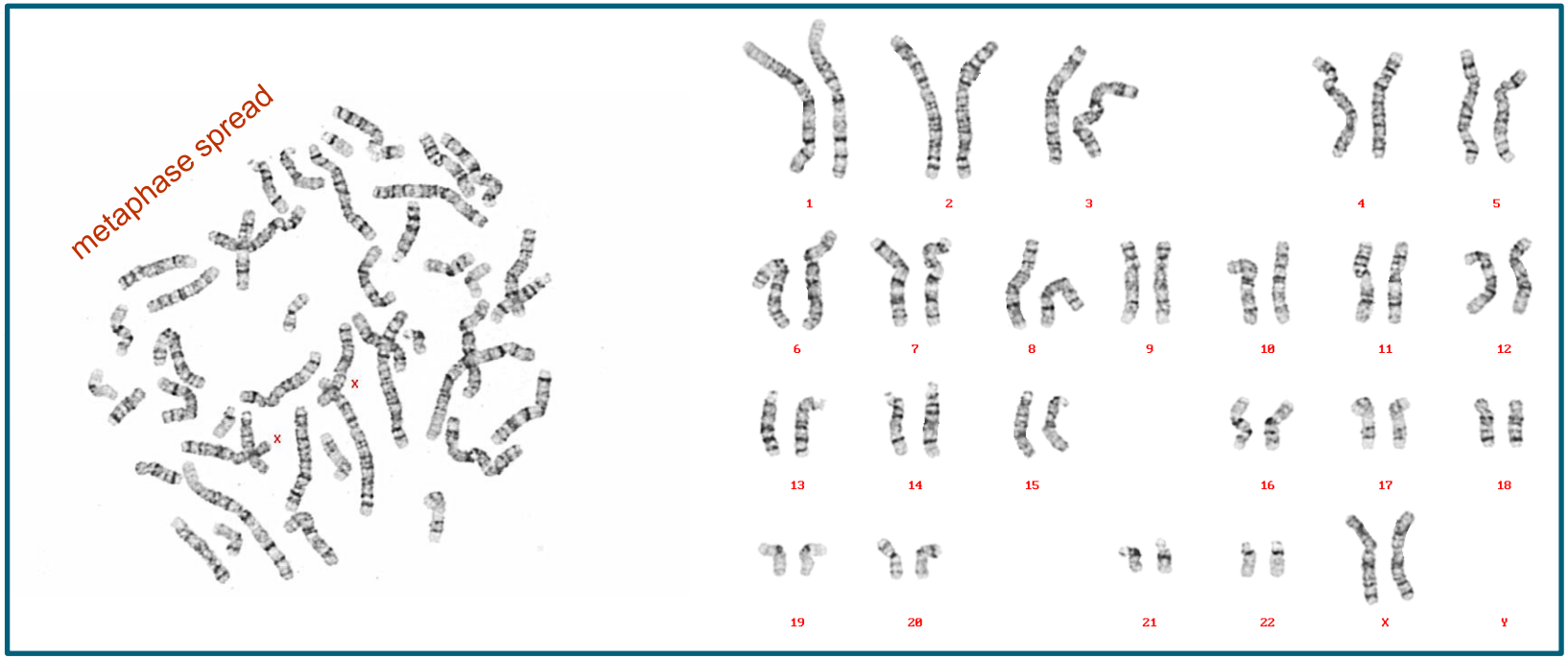
Chromosome band nomenclature

chromosome 1



Definitions

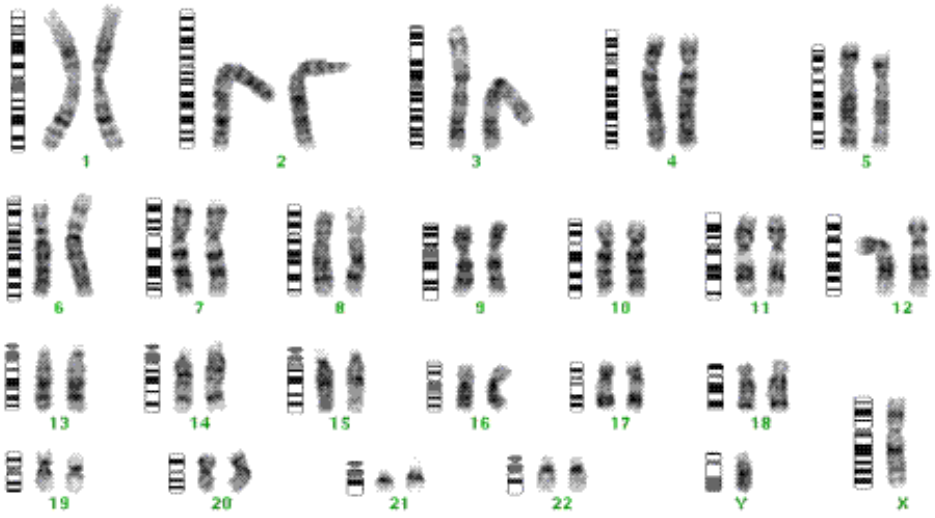
karyogram = systematized array of the metaphase chromosomes



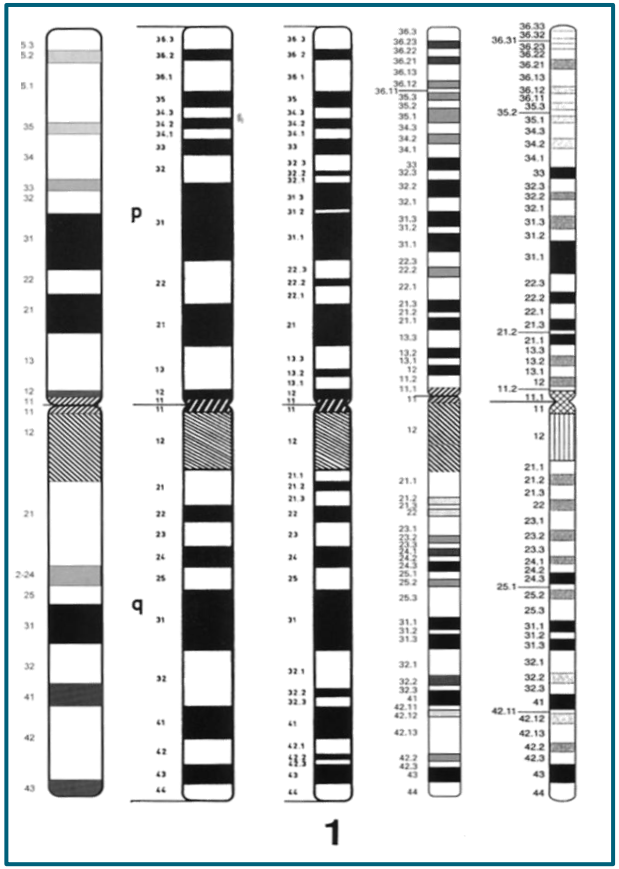
karyotype = is the use of nomenclature to describe the normal or abnormal, constitutional or acquired, chromosomal complement of an individual, tissue or cell line.

Definitions

idiogram = the diagrammatic representation of a karyotype or chromosome



400-band level



300-, 400-, 550-, 700- and 850-band levels

Chromosomes in each group represent a haploid karyotype of the approximately indicated band levels

Cytogenetic Abnormalities

Numerical

- gain of whole chromosome (trisomy)
- loss of whole chromosome (monosomy)

Structural

- deletion
- insertion
- inversion
- isochromosome
- dicentric chromosome
- addition
- derivative
- marker
- ring
- translocation
- duplication
- amplification (dmin, hsr)

Numerical Chromosome Abnormalities

- Plus (+) or minus (-) to indicate gain or loss

- Constitutional numerical sex chromosome abnormalities are designated by listing all sex chromosomes after the chromosome number

  (without the use of + or -)

  47,XXY

  45,X

- All numerical changes expressed in relation to the appropriate ploidy level (most often 2n, which may be indicated in the karyotype)

  68,XXY,-13

  71,XXX,+8,+10

  58<2n>,XY,+X,+4,+6,+10,+11,+14,+14,+17,+18,+21,+21[10]

- Acquired cytogenetics: constitutional anomalies are distinguished by the letter c

  47,XXYc,t(9;22)(q34;q11.2)[10]

  47,X,t(X;18)(p11.1;q11.1),+21c[20]

Karyotype designation_Order_1

Normal order:

1. total number of chromosomes
2. sex chromosome constitution

46,XX 46,XY

Abnormal order:

1. total number of chromosomes
2. sex chromosomes
3. aberrations (see next slide)

47,XX,abberations

47,XX,t(1;3)(p32;q21),+21

- use commas
- no spaces!

Karyotype designation_Order_2

Abnormal

order of aberrations:

1. Sex chromosomes (X before Y)
2. Autosomes in numerical order (irrespective of aberration type)
   46,XY,der(13;21)(q10;q10),+21
   48,XY,+X,+8[10]
3. Numerical before structural
4. Multiple structural changes: alphabetical order (del,dup,inv,t)
   a) Identified abnormalities
   b) Derivative(s) with unknown centromere der(?)
   c) Unidentified abnormalities: r, mar, dmin (this order)
5. Aberrations within same chromosome: order from pter to qter

52,XX,+1,+del(1)(p13),+dup(1)(q21q32),+inv(1)(p31q41),+8,t(9;22)(q34;q11.2),-21,+r,+mar,12~20dmin

{Note: NOT +dmin}

Karyotype designation_Order_3

Abnormal: Two or more chromosomes involved (sex chr. and autosome):

1. Sex chromosome
2. Autosome(s)

46,X,t(X;15)(p11.1;p11.1)	{NOT: 46,XX,t(X;15)(p11.1;p11.1)}
46,Y,t(X;15)(p11.1;p11.1)	{NOT: 46,XY,t(X;15)(p11.1;p11.1)}
46,XY,t(9;22;17)(q34;q11.2;q22)	{start lowest number, order dependent on movement of chromosomal segments}

Symbols and Abbreviations

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. Symbols utilized in describing results obtained by in situ hybridization are given again in Chapter 13 and those utilized in describing microarray results are given again in Chapter 14. When more than one symbol or abbreviation is used together, a space is placed between the two (e.g. psu dic). When the symbol precedes the total number of chromosomes and no parenthesis is present, a space is placed between the symbol and the number of chromosomes (e.g. mos 47,XXX[25]/46,XX[5]). There is no space when a symbol immediately precedes a parenthesis.

AI	First meiotic anaphase (12.1)
AII	Second meiotic anaphase (12.1)
ace	Acentric fragment (9.2.12, 10.2.1)
add	Additional material of unknown origin (9.2.1)
amp	Denotes an amplified signal (13.3.1)
approximate sign (~)	Denotes intervals and boundaries of a chromosome segment or number of chromosomes, fragments, or markers (5.2); denotes a range of number of copies of a chromosomal region when the exact number cannot be determined (14.2.1)
arr	Microarray (14.2.1)
arrow (→ or ->)	From – to, in detailed system (4.3.2.1)
b	Break (10.1.1, 10.2.1)
brackets, angle (< >)	Surround the ploidy level (8.1)
brackets, square ([ ])	Surround number of cells (4.1, 11.1.2)
c	Constitutional anomaly (4.1, 8.3, 11.3)
cen	Centromere (2.3.2, 4.3.2.1)
cgh	Comparative genomic hybridization (13.6)
chi	Chimera (4.1)
chr	Chromosome (10.2)
cht	Chromatid (10.1)
colon, single (:)	Break, in detailed system (4.3.2.1)
colon, double (::)	Break and reunion, in detailed system (4.3.2.1)
comma (,)	Separates chromosome numbers, sex chromosomes, and chromosome abnormalities (4.1, 14.2); separates locus designations (13.2, 13.3.1)
con	Connected signals (13.3.2)
cp	Composite karyotype (11.1.5)
cth	Chromothripsis (14.2.2)
cx	Complex rearrangements (10.1.1, 14.2.2)
decimal point (.)	Denotes sub-bands (2.3.2)
del	Deletion (9.2.2)
der	Derivative chromosome (4.4, 9.2.3, 9.2.17.2, 9.2.17.3)
dia	Diakinesis (12.1)
dic	Dicentric (9.2.4)
dim	Diminished (13.2.1, 13.5)
dip	Diplotene (12.1)
dis	Distal (12.1)
dit	Dictyotene (12.1)
dmin	Double minute (9.2.12, 10.2.1)
dn	Designates a chromosome abnormality that has not been inherited (de novo) (4.1)
dup	Duplication (9.2.5)
e	Exchange (10.1.1, 10.2.1)
end	Endoreduplication (4.1)
enh	Enhanced (13.2.1, 13.5)
equal sign (=)	Number of chiasmata (12.1)
fem	Female (12.1)
fib	Extended chromatin/DNA fiber (13.4)
fis	Fission, at the centromere (9.2.6)
fra	Fragile site (7.2, 9.2.7)
g	Gap (10.1.1, 10.2.1)
h	Heterochromatin, constitutive (7.1.1)
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) (14.2.1)
hsr	Homogeneously staining region (9.2.8)
htz	Heterozygous, heterozygosity (14.2.1)
i	Isochromosome (9.2.11)
idem	Denotes the stemline karyotype in a subclone (11.1.4)
ider	Isoderivative chromosome (9.2.3)
idic	Isodicentric chromosome (9.2.4, 9.2.11)
inc	Incomplete karyotype (5.4)
ins	Insertion (9.2.9)
inv	Inversion or inverted (9.2.10)
ish	In situ hybridization; when used without a prefix applies to chromosomes (usually metaphase or prometaphase) of dividing cells (13.2)
lep	Leptotene (12.1)
MI	First meiotic metaphase (12.1)
MII	Second meiotic metaphase (12.1)
mal	Male (12.1)
mar	Marker chromosome (9.2.12)
mat	Maternal origin (4.1)
med	Medial (12.1)
min	Minute acentric fragment (10.2.1)
minus sign (−)	Loss (4.1, 8.1); decrease in length (7.1.1); locus absent from a specific chromosome (13.2)
mos	Mosaic (4.1)
multiplication sign (×)	Multiple copies of rearranged chromosomes (9.3);designate aberrant polyploidy clones in neoplasias (11.1.4); with number to indicate number of signals seen (13.2, 13.3.1); multiple copies of a chromosome or chromosomal region (14.2.1)
neg	No presence of the rearrangement detected (15.2)
neo	Neocentromere (9.2.13)
nuc	Nuclear or interphase (13.3)
oom	Oogonial metaphase (12.1)
or	Alternative interpretation (5.3)

General rules: Symbols and Abbreviations

- When more than one abbreviation, a space between the two abbreviations.

  psu dic
  +mar c

- A space between the abbreviation and the number of chromosomes when the abbreviation precedes the total number of chromosomes and no parenthesis is present

  mos 45,X[15]/46,XX[13]

- No space when an abbreviation immediately precedes (or follows) a parenthesis.

  t(1;3)(p32;q21)pat

Mosaicism versus Chimeras

Mosaic cell lines originating from the same zygote

mos 45,X/46,XX

Chimera cell lines originating from different zygotes

chi 46,XX/46,XY

Chimerism secondary to bone marrow transplantation:

recipient cell clone(s)***//***donor cell line(s)

46,XY,t(9;22)(q34;q11.2)[3]//46,XX[17]

//46,XX[20] {all cells from donor}

46,XY[20]// {all cells from recipient}

- use slant lines /
- use double slant lines //
- slant lines also used to separate different clones in neoplasia

Structural Chromosome Rearrangements_deletion

del deletion

denotes either a terminal or an interstitial deletion

terminal

46,XX,del(5)(q13)

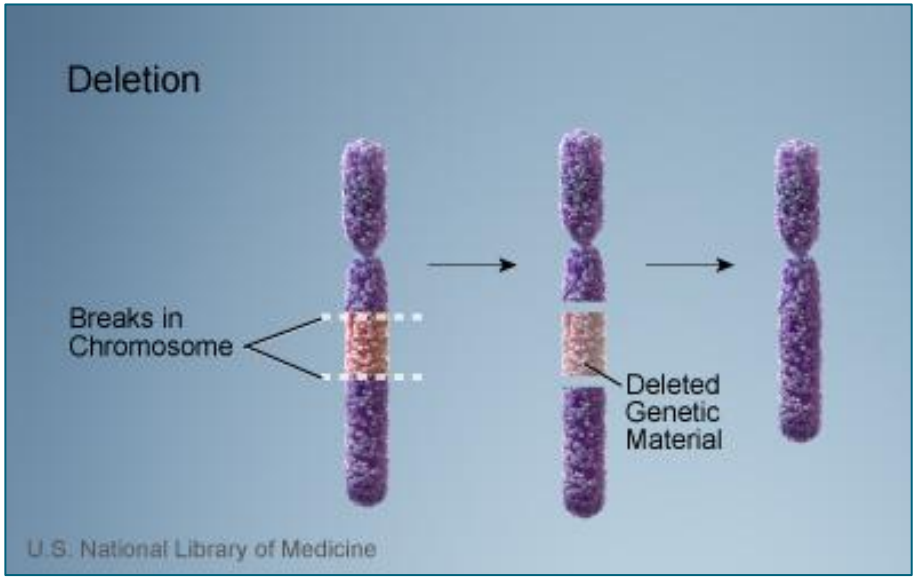
interstitial

46,XX,del(5)(q13q33)

46,Y,del(X)(p21p21)

Note:

"5q-" or "del(5q)" may NOT be used in karyotypes (only in text)



- multiple deletions of the same chromosome → use der

  46,XX,der(5)del(5)(p14)del(5)(q13q33)

Structural Chromosome Rearrangements_insertion

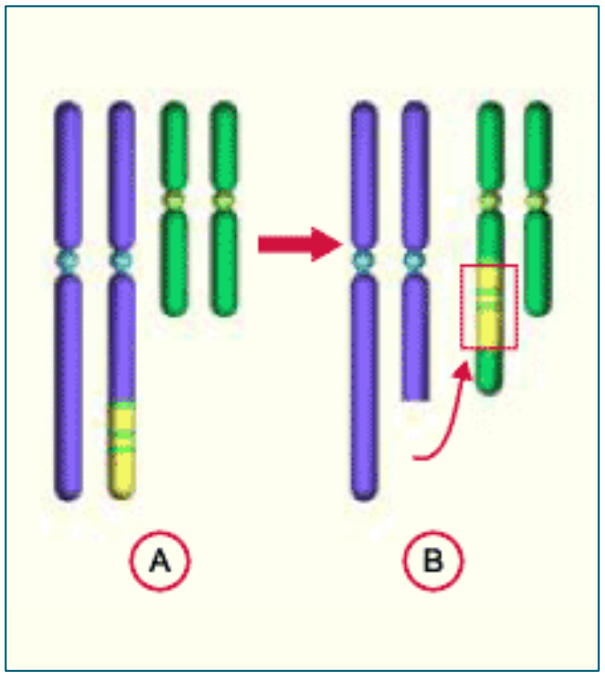
ins insertion

- orientation will be apparent from the order of the bands with respect to the centromere

46,XX,ins(2)(p13q21q31)
46,XX,ins(2)(p13q31q21)

- between two chromosomes: recipient is specified first

46,XY,ins(5;2)(p14;q32q22)



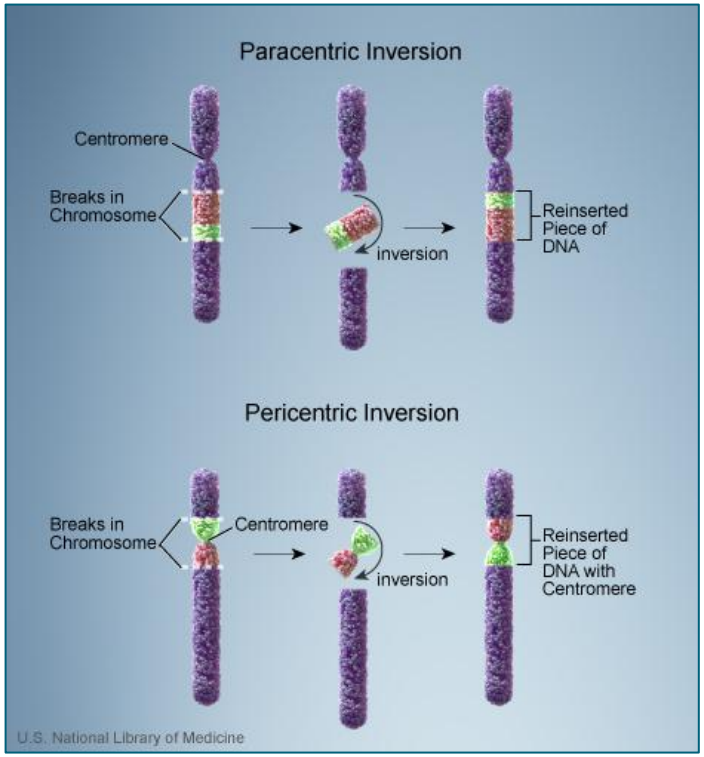
Structural Chromosome Rearrangements_inversion

inv inversion

- denotes either paracentric or pericentric inversion: apparent from the band designations

46,XX,inv(2)(p13p23)

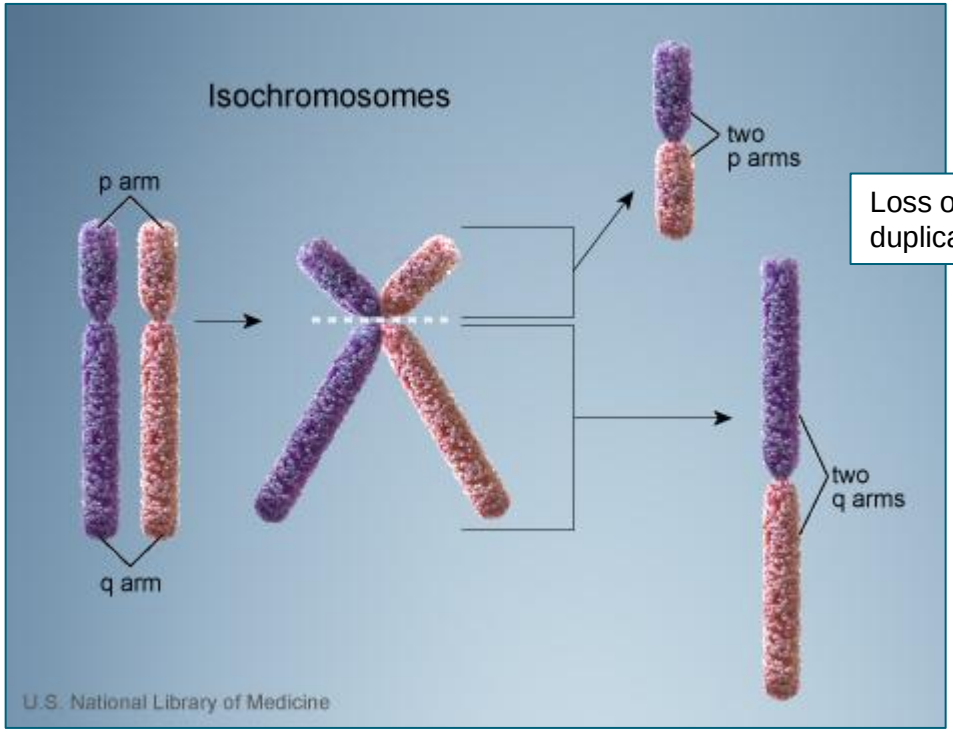
46,XX,inv(2)(p21q31)



Structural Chromosome Rearrangements_isochromosome

i isochromosome

46,XY,i(17)(q10) {isochromosome of the entire q-arm of chromosome 17}



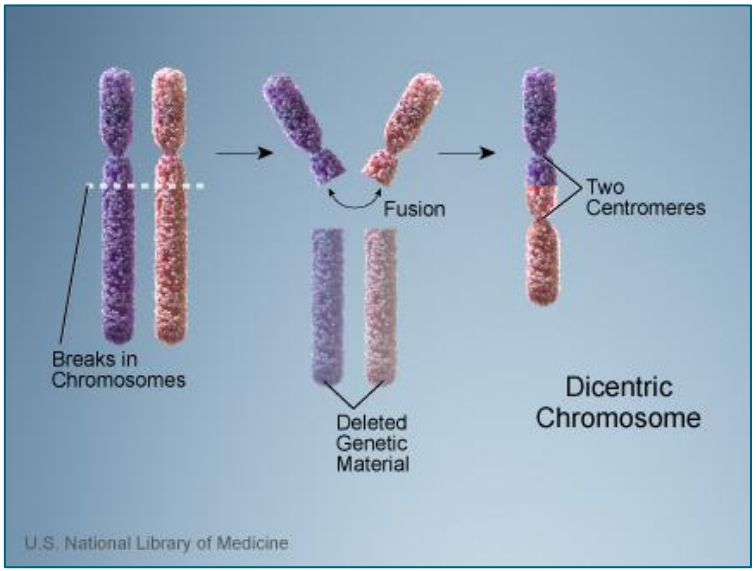
Loss of one arm and duplication of the other

Structural Chromosome Rearrangements_dicentric

dic dicentric chromosome

45,XX,dic(9;20)(p13.2;q11.2)

trc tricentric chromosome



idic isodicentric chromosome

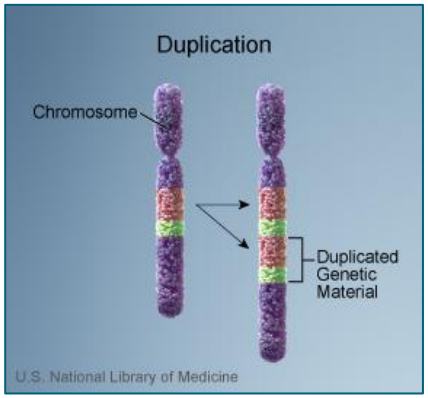
- It is apparent from (i)dic that the dicentric chromosome(s) involved replaces one or two normal chromosomes. No need to indicate the missing chromosome
- A dicentric chromosome is counted as one chromosome
- der instead of dic, but NOT “der dic”

psu dic pseudodicentric chromosome, in which only one centromere is active

- the segment with presumptively active centromere is written first

Structural Chromosome Rearrangements_dup_neo_fra

dup duplicated segment
trp triplicated segment
qdp quadruplicated segment



orientation will be apparent from the order of the bands with respect to the centromere

46,XY,dup(1)(q22q25)
46,XY,dup(1)(q25q22)

neo neocentromere = functional centromere that has arisen or been activated within a region not known to have a centromere

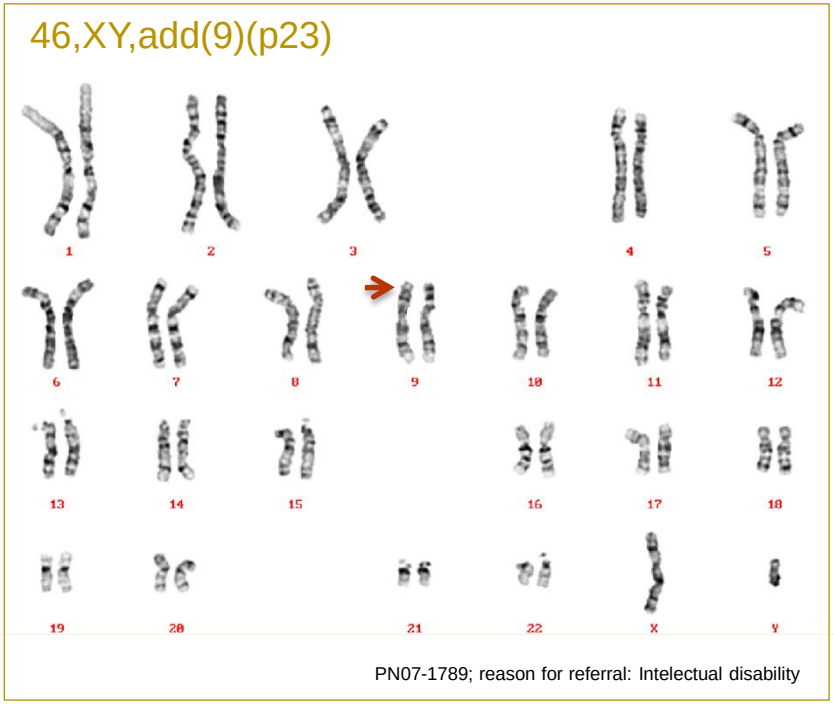
- der instead of neo is allowed

fra denotes a fragile site, which may occur as a normal variant or be associated with specific diseases

fra(X)(q27.3)

Structural Chromosome Rearrangements_addition

add additional material of unknown origin attached to a chromosome region



Note: "9p+" may NOT be used in karyotypes (only in text)

- additional material attached to both arms → use der
  46,XX,der(5)add(5)(p15.3)add(5)(q23)
- additional material inserted in a chromosome → use ins
  46,XX,der(5)ins(5;?)(q13;?)

Structural Chromosome Rearrangements_derivative _1

der derivative = structurally rearranged chromosome generated by

- >1 rearrangement within a single chromosome

  46,XX,der(5)del(5)(p14)del(5)(q13q33)

- rearrangements involving ≥ 2 chromosomes

  46,XX,der(1)t(1;3)(p22;q13.1)

  46,XX,der(1)t(1;3)(p32;q21)t(1;11)(q25;q13)

- "der" refers to the chromosome that has in an intact centromere

- aberrations should be listed according to the breakpoints of the der from pter to qter and should not be separated by a comma

- breakpoints in derivative chromosomes generated by the same rearrangement need not to be repeated in each individual der

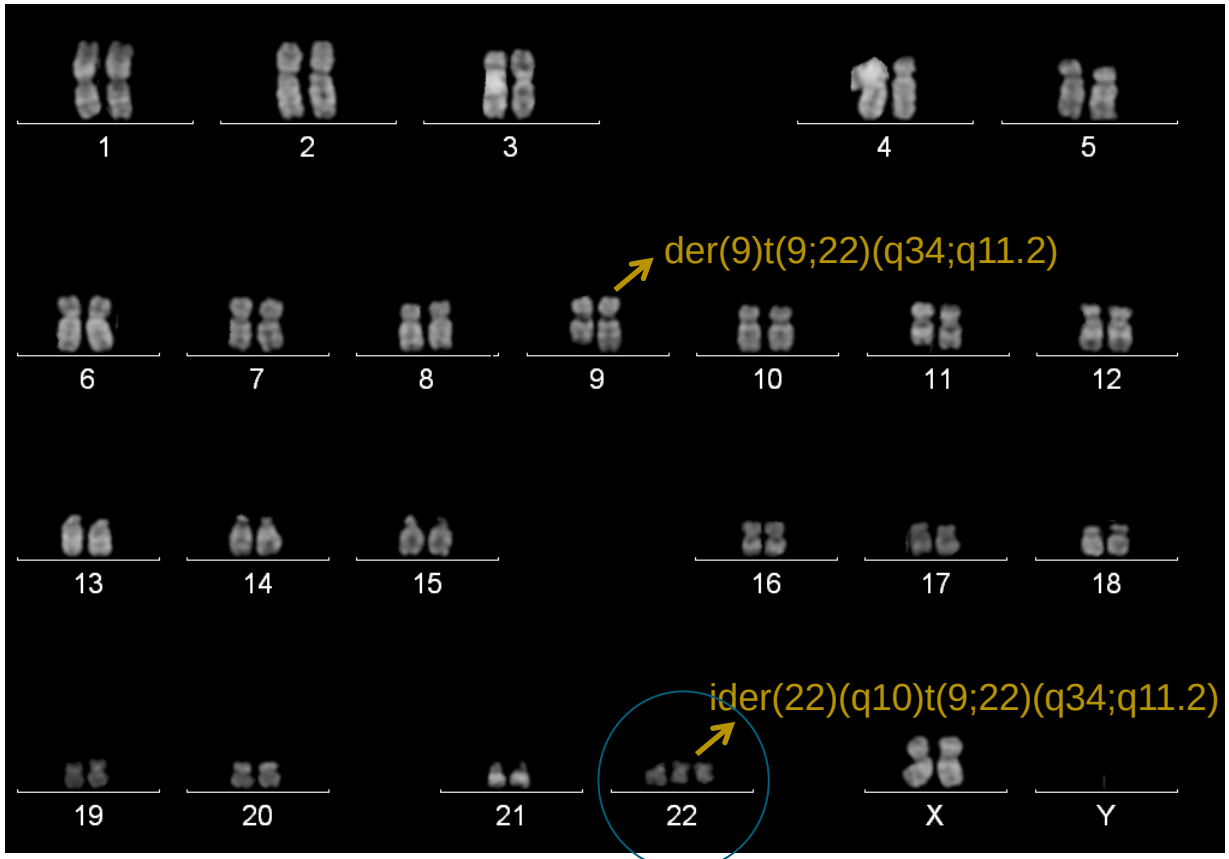
  47,XX,t(9;22)(q34;q11.2),+der(22)t(9;22)

Structural Chromosome Rearrangements_derivative_2

ider isoderivative chromosome

= isochromosome of one of the arms of a derivative chromosome

46,XX,ider(22)(q10)t(9;22)(q34;q11.2)



Structural Chromosome Rearrangements_derivative_3

- Dicentric derivative: use der

  46,XY,der(5;7)t(5;7)(q22;p13)t(3;7)(q21;q21)

- Centromere of derivative unknown: der(?)

  46,XY,der(?)t(?;9)(?;q22)

- Both homologues involved:

  der(9)del(9)(p12)t(9;22)(q34;11.2),der(9)t(9;12)(p13;q22)inv(9)(q13q22)

- Both homologues indistinguishably involved:

  der(1)t(1;3)(p34.3;q21),der(1)t(1;3)(p34.3;q21)

Structural Chromosome Rearrangements_marker

mar marker chromosome

a structurally abnormal chromosome in which no part can be identified

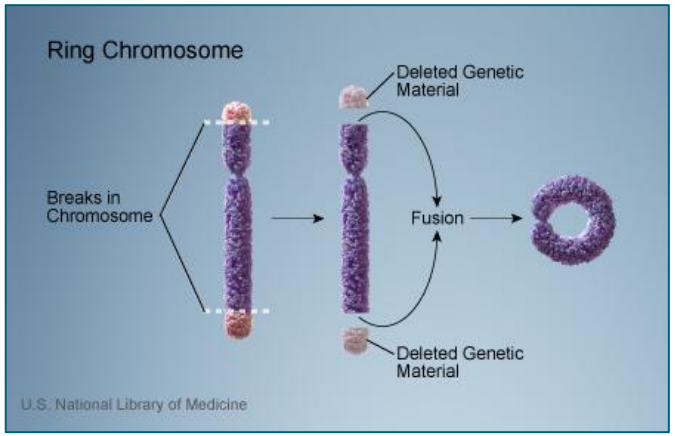
- In karyotype ”+mar”
- Different markers present → +mar1,+mar2,+mar3
- Multiple copies of the same marker → +mar1x3

- In case of (partial) identification → use der instead of mar

Structural Chromosome Rearrangements_ring

r ring chromosome

- Monocentric ring chromosomes derived from >1 chromosome are treated as der, the chromosome that provides the centromere is listed first
- If the centromere is unknown, but other segments are identified → der(?)
- Dicentric ring = dic r
- Tricentric ring = trc r
- Different unidentified rings present: r1,r2, etc.



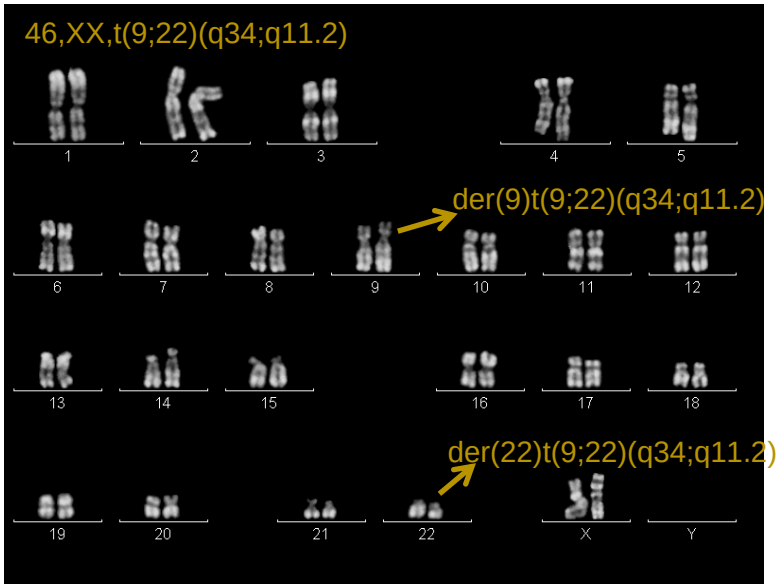
r(18)

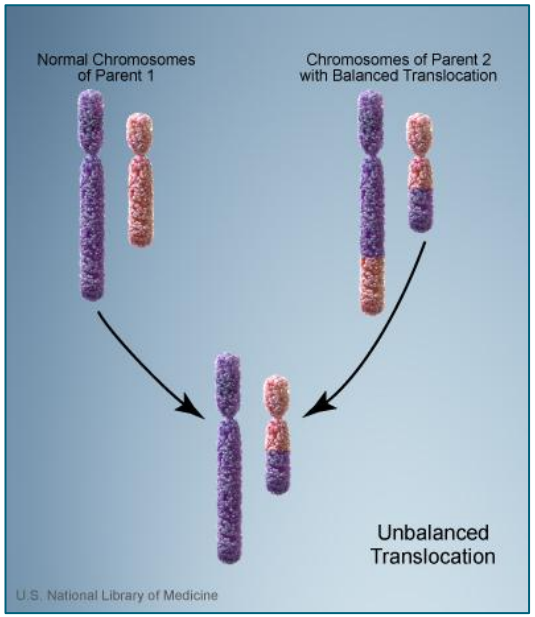
Structural Chromosome Rearrangements_translocation_1

t translocation

reciprocal

- two-break

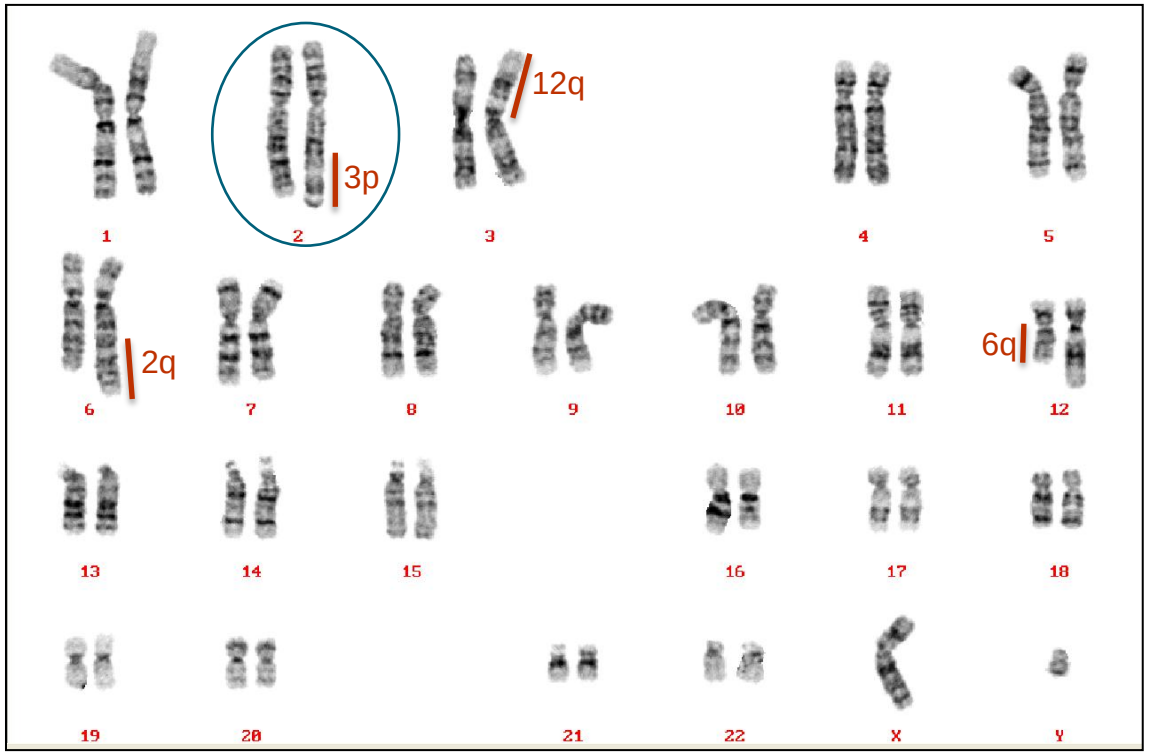




- three-break
- four-break and more complex (example next slide)

Structural Chromosome Rearrangements_translocation_2

- General rules apply; >2 chromosomes involved: t(2;3;7)

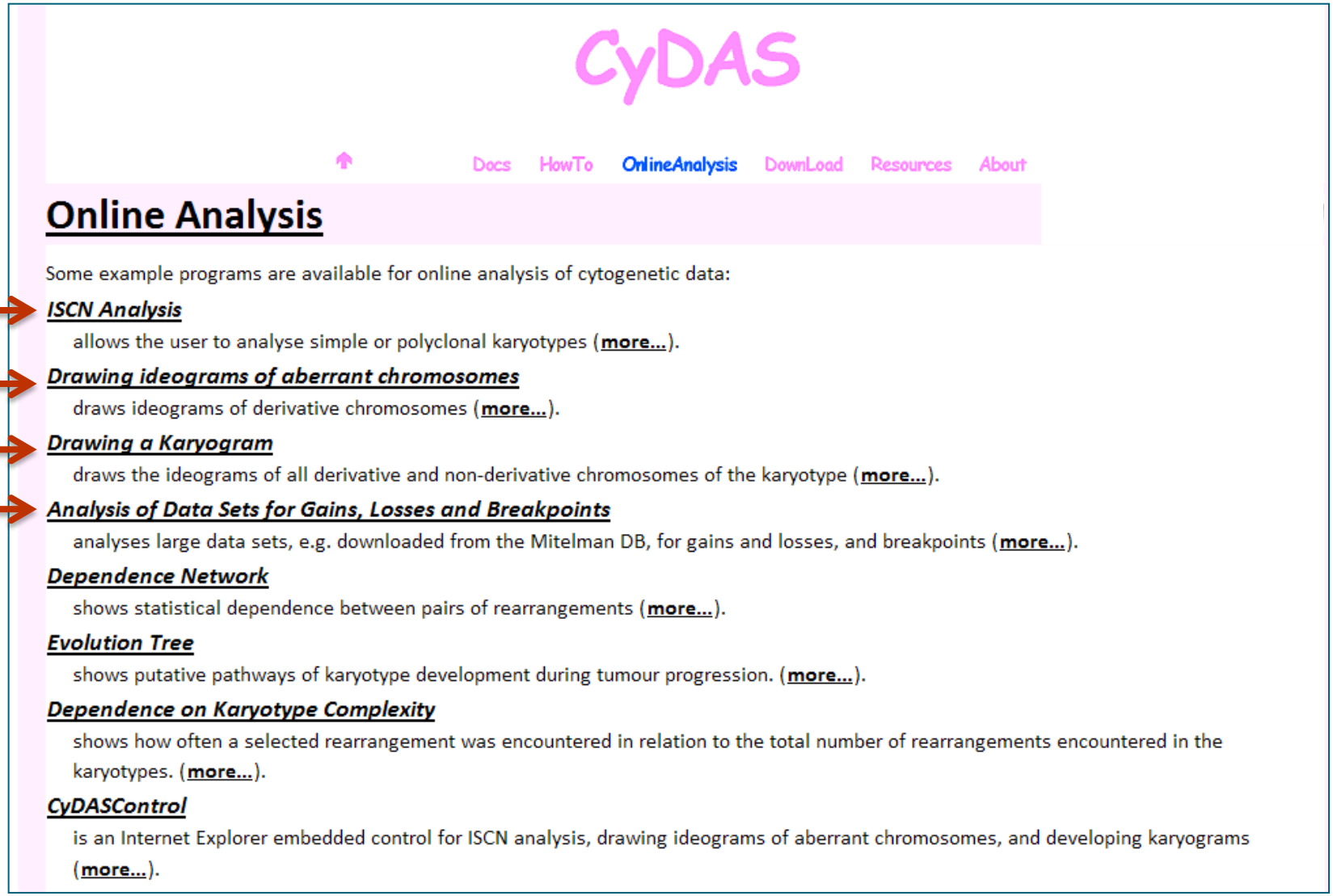


t(2;6;12;3)(q24;q23;q12;p13)

start with lowest chromosome number

- Homologues are distinguished by single underlining

Useful website: CyDAS = Cytogenetic Data Analysis System at www.cydas.org



CyDAS

Docs HowTo OnlineAnalysis DownLoad Resources About

Online Analysis

Some example programs are available for online analysis of cytogenetic data:

ISCN Analysis

allows the user to analyse simple or polyclonal karyotypes (**more...**).

Drawing ideograms of aberrant chromosomes

draws ideograms of derivative chromosomes (**more...**).

Drawing a Karyogram

draws the ideograms of all derivative and non-derivative chromosomes of the karyotype (**more...**).

Analysis of Data Sets for Gains, Losses and Breakpoints

analyses large data sets, e.g. downloaded from the Mitelman DB, for gains and losses, and breakpoints (**more...**).

Dependence Network

shows statistical dependence between pairs of rearrangements (**more...**).

Evolution Tree

shows putative pathways of karyotype development during tumour progression. (**more...**).

Dependence on Karyotype Complexity

shows how often a selected rearrangement was encountered in relation to the total number of rearrangements encountered in the karyotypes. (**more...**).

CyDASControl

is an Internet Explorer embedded control for ISCN analysis, drawing ideograms of aberrant chromosomes, and developing karyograms (**more...**).

➔ISCN 2013?

Useful website: CyDAS = Cytogenetic Data Analysis System at www.cydas.org

Drawing a Karyogram Online

Enter an ISCN formula in the text field below, select the desired map viewer with which chromosomal bands are to be linked, banding resolution, color style, and the sequence of the chromosomes, then click "Draw". The CyDAS software will then compute an image map containing the ideograms of all derivative and non-derivative chromosomes of the karyotype (= "karyogram"), with links to the NCBI or Ensembl map viewer.

It is absolutely indispensible that **break points** are specified; denoting them at a lower resolution than the resolution for the image may yield inconsistencies. **Ring** chromosomes of defined band composition are shown **linearized**; marker chromosomes (linear or ring shaped) are not shown. Minor errors in the formula are automatically corrected.

Background information on Known Problems and the technics of calculating a karyogram are available in the documentation section.

An experimental page for step by step development of a karyogram is also available.

46<2n>,XY,t(2;6)(q24;q23)

Link to MapViewer: ◉NCBI ○Ensembl

Banding Resolution:○2 Digits ◉400 Bands ○550 Bands ○800 Bands

☑Color

Scale: 0.2

The Drawing sequence denotes the sequence in which chromosomes are to be drawn. Chromosomes are limited by commata, "BR" is used to denote a line break.

Drawing Sequence:

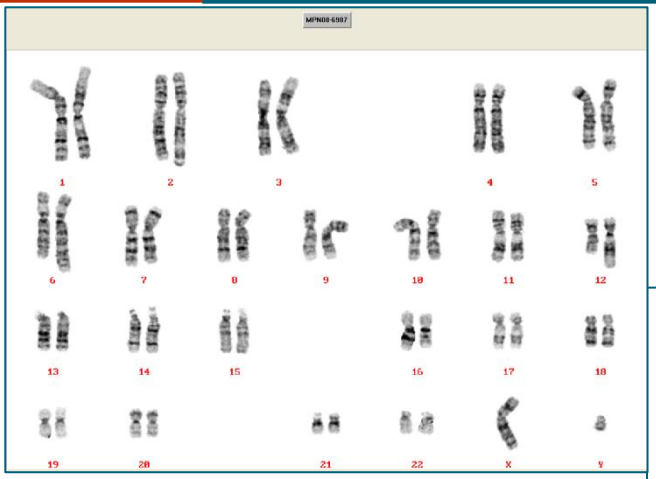
1,2,3,4,5,6,7,X,8,9,10,11,BR,12,13,14,15,16,17,18,19,20,21,22,Y,?

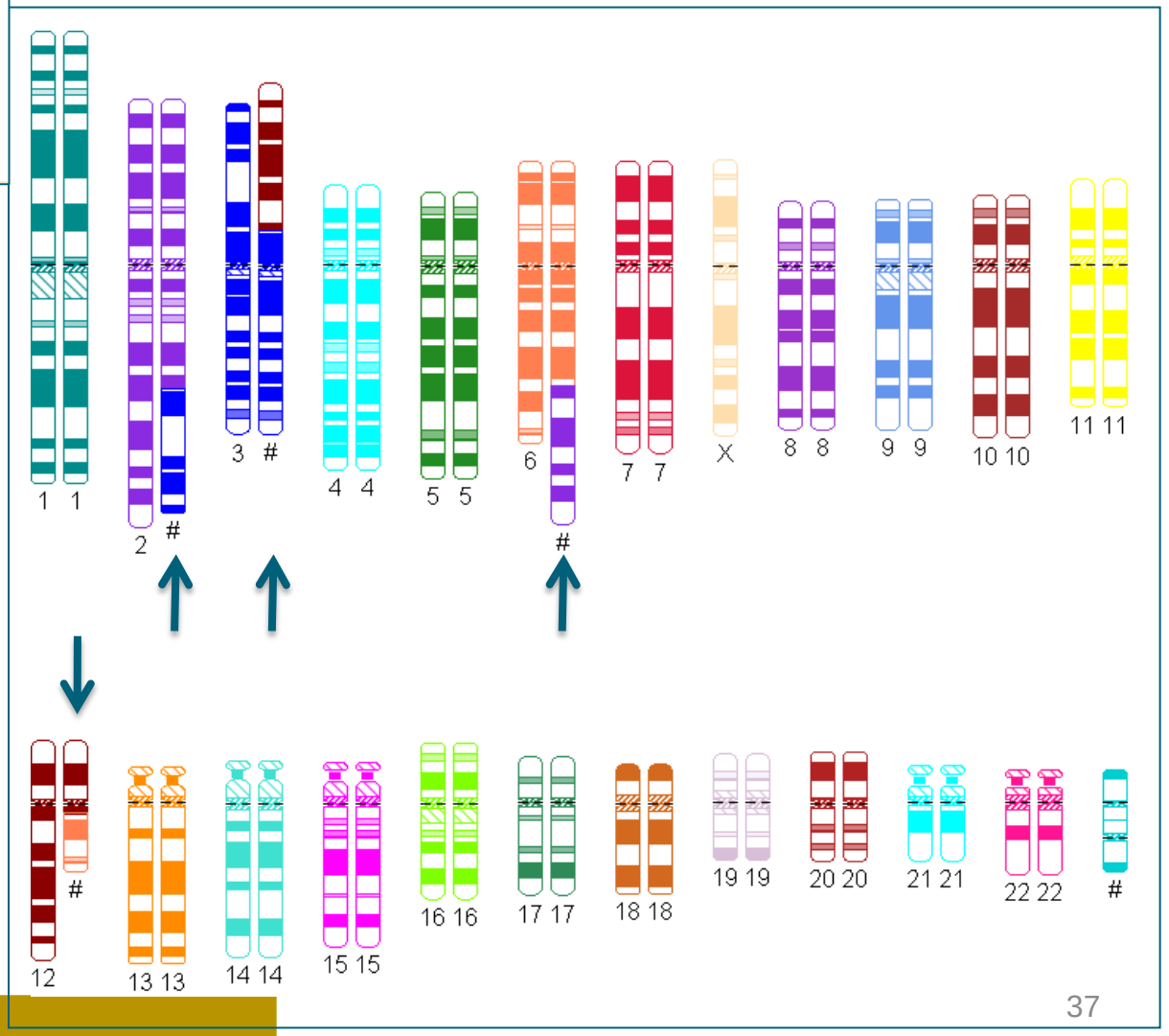
Draw

1 1 # 2 3 3 4 4 5 5 6 # 7 7 X 8 8 9 9 10 10 11 11

12 12 13 13 14 14 15 15 16 16 17 17 18 18 19 19 20 20 21 21 22 22 Y

➔ISCN 2013?

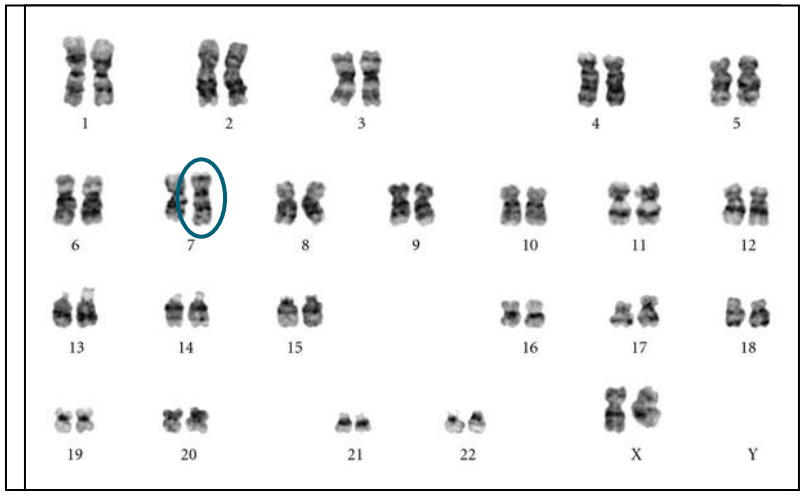



1 1
2 #
3 #
4 4
5 5
6 #
7 7
X
8 8
9 9
10 10
11 11
12 #
13 13
14 14
15 15
16 16
17 17
18 18
19 19
20 20
21 21
22 22
#

Structural Chromosome Rearrangements_translocation_3

- Whole-arm
  - Breakpoints are assigned to centromeric bands p10 and 10q according to the morphology of the abnormal chromosomes
  - Balanced whole-arm exchanges: breakpoint in chromosome which has the lowest number, or X or Y, is assigned to p10
  - A der resulting from unbalanced whole-arm translocations by convention replaces the two normal chromosomes involved. The two missing ones are not specified.

45,XX,der(1;7)(q10;p10) {one #1, one #7, one der(1;7)➔ monosomy 1p, monosomy 7q}



46,XX,+1,der(1;7)(q10;p10)

{two #1, one #7, one der(1;7)
➔ trisomy 1q, monosomy 7q}

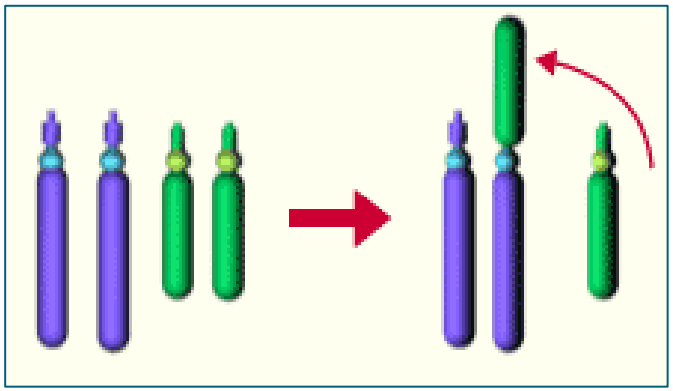
Structural Chromosome Rearrangements_translocation_4

- Robertsonian → der or rob

  45,XX,der(13;21)(q10;q10)

  46,XX,+13,rob(13;21)(q10;q10)

  - If breakpoints are assigned to p11.2 or q11.2 → use dic



Structural Chromosome Rearrangements_General

- All structural changes are expressed in relation to the appropriate ploidy level

  70,XXY,+del(7)(p11.2) {three normal chromosomes 7 and an additional abnormal 7 in a triploid cell}

- When normal chromosomes are replaced by structurally altered chromosomes, the normal ones should not be recorded as missing! (including whole arm translocations)

- The multiplication sign (**x**): to describe more copies of structural rearrangements

  46,XX,del(6)(q13q23)x2

  48,XX,+del(6)(q13q23)x2

  48,XX,del(6)(q13q23)x2,+7,+7 {NOT: 48,XX,del(6)(q13q23)x2,+7x2}

Structural Aberrations: Specification of Breakpoints

- Two-break rearrangements
  - 1 chromosome: breakpoint in p-arm before breakpoint in q-arm

    46,XX,inv(2)(p21q31)
  - 1 chromosome-arm: breakpoint more proximal to centromere before distal breakpoint

    46,XX,inv(2)(p13p23)
  - 2 chromosomes: lowest number chromosome is specified first

    46,XX,t(12;16)(q13;p11.1)

- Semicolon '**;**'

  separates altered chromosomes and breakpoints in structural rearrangements involving more than one chromosome
- No semicolon

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

Structural Aberrations: Specification of Breakpoints

6

13

- A break suspected to be at an interface between two bands
  is assigned arbitrarily to the higher of the two band numbers,
  i.e. the band more distal to the centromere.

- Break in either of two consecutive bands →'or'

  46,XX,add(19)(p13 or q13)

- When an extra copy of a rearranged chromosome is present, the breakpoints are specified only once, at the first time it appears in the karyotype.

  48,XX,+1,+der(1)t(1;16)(p13;q13),t(1;16)

- Uncertainty in chromosome or band designation →'?'

  45,XX,-?21
  46,XX,del(1)(q?2)

- Incomplete karyotype →'inc'

  53~57,XY,+1,+3,+6,t(9;22)(q34;q11.2),+21,+3mar,inc[cp10]

Structural Aberrations: Complex Structural Abnormalities

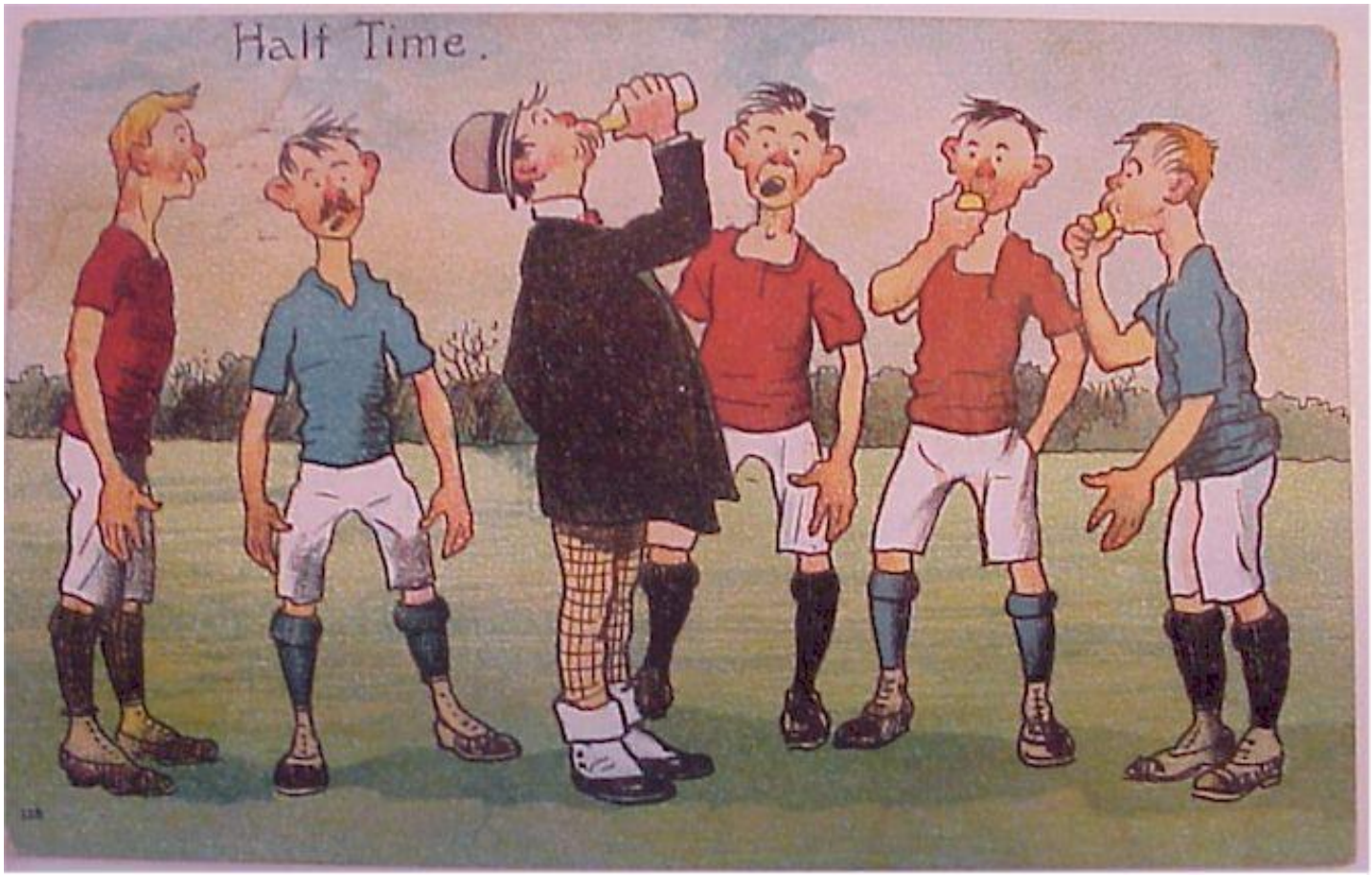
- Short system
- Detailed system:
  - useful in case of very complex abnormalities
  - start at end of short arm and proceeds to end of long arm
  - 1 chromosome: number not repeated in band description
  - >1 chromosome: bands and ends identified with appropriate numbers
  - double colon '**::**' break and reunion

Short: 46,XX,der(9)inv(9)(p13p23)del(9)(q22q33)
Detailed: 46,XX,der(9)(pter->p23::p13->p23::p13->q22::q33->qter)

Short: 46,XX,der(1)t(1;3)(p22;q13.1)
Detailed: 46,XX,der(1)(3qter->3q13.1::1p22->1qter)

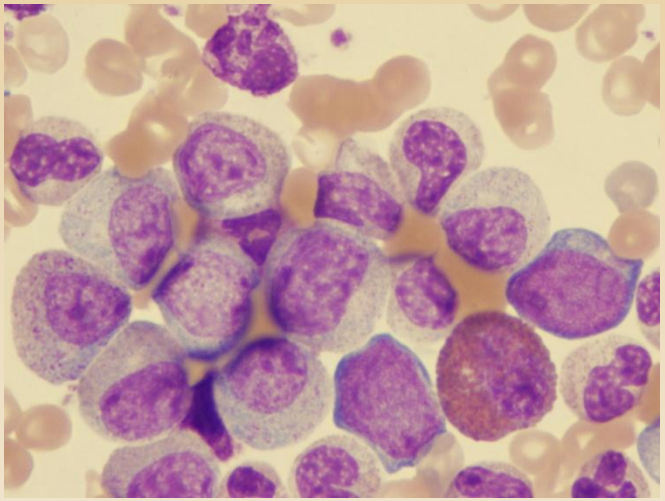
- Acceptable to combine both in complex karyotypes

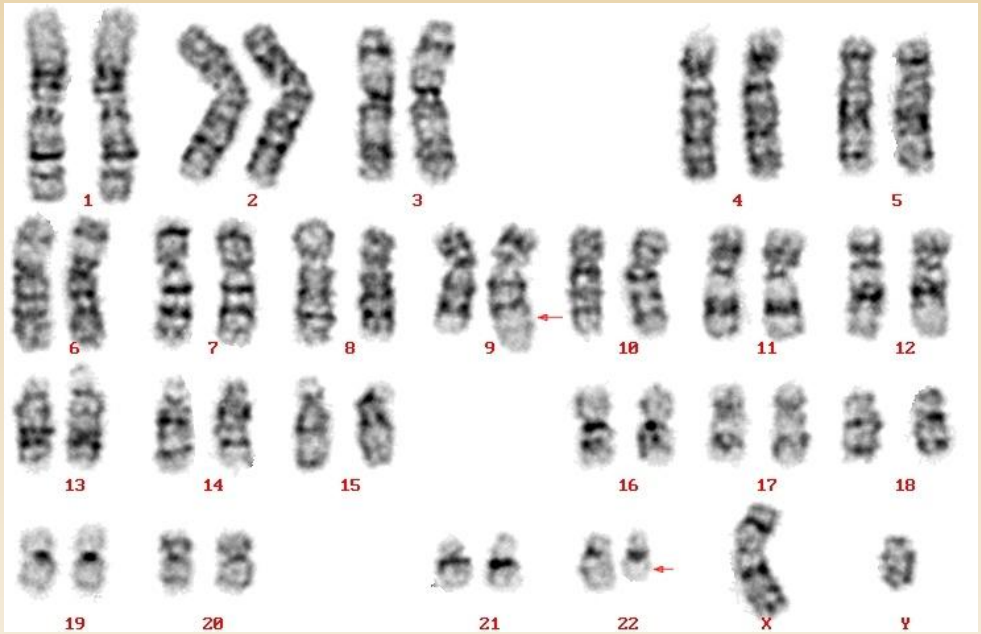
We're about half-way…



Neoplasia

Acquired cytogenetics





Neoplasia_Karyotype Designation

- The number of cells constituting a clone given in square brackets [ ]

  46,XX,t(9;22)(q32;q11.2)[15]
  46,XY[23]

- Slant line ***/*** to separate different clones and subclones

  46,XX,t(9;22)(q32;q11.2)[15]/46,XX[5]

- Constitutional; Down syndrome patient with ALL and normal karyotype:

  47,XY,+21c[10]

Neoplasia_Definition of a Clone or Clonal

- Gain or structural: same aberration in at least 2 cells
- Loss of a single chromosome: in at least 3 cells
- However, 2 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]

  51,X,-Y,der(1;13)(p10;q10)x2,i(1)(q10),+2,-8,-9,-10,-11,+12,+19,+20,+21,-22,+1~7mar[2]/46,XY[5]
- Similarly, if a single abnormal cell is confirmed by a different method (e.g., FISH), and thus shown to be clonal, it should be reported in the karyotype

  46,XX,del(20)(q11.2q13.3)[1]/46,XX[19].nuc ish(D20S108 1)[40/200]

Note: If additional abnormalities are seen in the single cell, but not proven to be present with another method, they should NOT be listed in the nomenclature but may be discussed in the interpretation.

Neoplasia_One Aberrant Cell at Follow-up

- When the same abnormal clone has been found in an initial and follow-up study, even in a single cell, it should be reported in the karyotype

46,XX,t(9;22)(q34;q11.2)[1]/46,XX[19]

Neoplasia_Clonal Evolution

- **mainline** — the largest clone (purely quantitative)
- **idem** — used to describe subclones (=sideline), always refers to the first karyotype listed

  47,XX,+1[4]/48,idem,+2[6]/49,idem,+2,+3[4]

- **sl** — **stemline**, most basic clone (“qualitative”), used to describe subclones
- **sdl** — **sideline**, used to describe subclones
- **sdl1,sdl2,…** — **sidelines**, when more than one sidelines are present

  47,XX,+1[4]/48,sl,+2[6]/49,sdl1,+3[4]

  ➔ order: increasing complexity

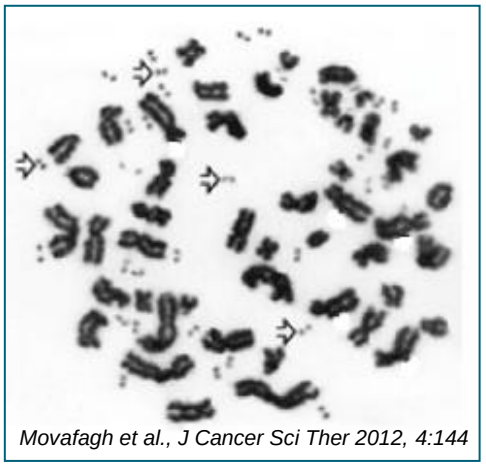
Neoplasia_aberrant polyploid clones_dmin_hsr

- The multiplication sign (**x**): to describe aberrant polyploid clones

  46,XY,t(9;22)(q34;q11.2)[3]/92,slx2[5]/93,sdl,+8[2]

  or

  46,XY,t(9;22)(q34;q11.2)[3]/92,idemx2[5]/93,idemx2,+8[2]



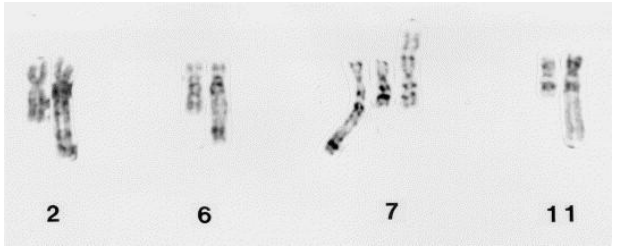
Movafagh et al., J Cancer Sci Ther 2012, 4:144

- **dmin** double minutes
  - dmin, NOT +dmin
  - idem includes dmin
  - dmin NOT included in total chromosome number

  49,XY,t(9;22)(q34;q11.2),+3mar,9~34dmin[cp5]/50,idem,+8

- **hsr** describes presence (not size) of homogeneously staining region

  46,XX,hsr(1)(p22)



Yoshida et al., 1999 Cancer Genet Cytogenet 109:40–44

Neoplasia_Composite karyotype

- Every effort should be made to describe clones and subclones, so that clonal evolution is made evident
- However, this is not always possible

- ➔ **cp** composite karyotype
  - contains all clonal aberrations
  - contains the range of chromosome numbers
  - total number of cells given as [cp…]

45~48,XX,del(5)(q13q33),-5,+8,+11[cp7]
or
45~48,XX,del(5)(q13q33)[2],-5[4],+8[2],+11[3][cp7]

Neoplasia_Unrelated clones

- Unrelated clones are listed according to their size (largest first)
- Equal sized clones: sex chromosomes first, then those with smallest to largest numbered autosomes
- Normal diploid clone always listed last
- Combination of related and unrelated clones:
  - 1st related clones in order of increasing complexity
  - 2nd unrelated clones in order of decreasing frequency
- Follow up: a previously identified abnormality should always be listed first

46,XY,t(9;22)(q34;q11.2)[6]/46,XY,t(1;3)(p22;p14)[14]

ISCN is guideline for nomenclature, not a law!

- Monosomal karyotype

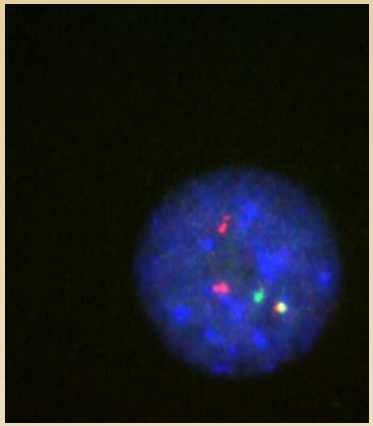
  Breems et al., JCO 2008

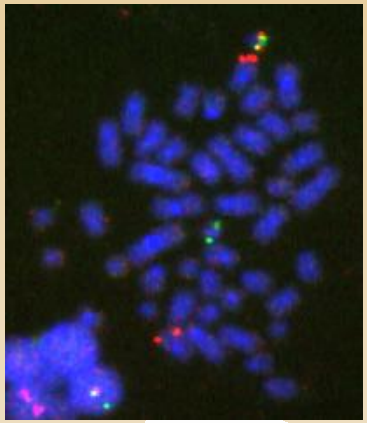
- Complex karyotype: >3 or >4 or >5 structural aberrations?

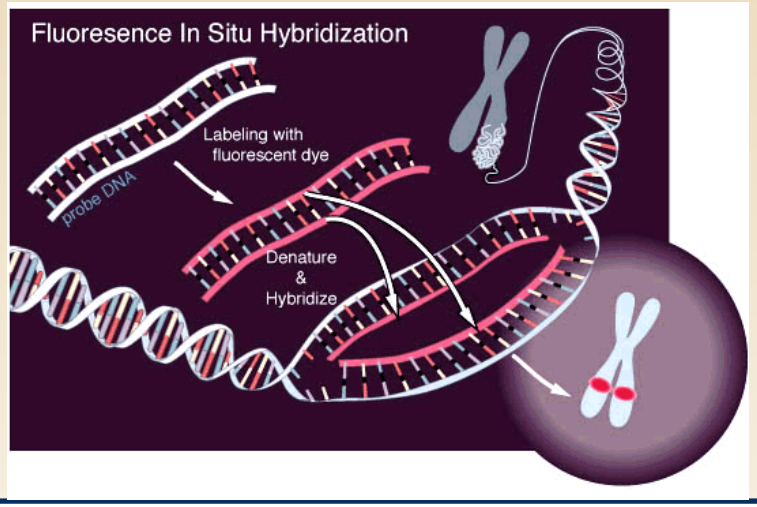
  differs between trials and publications

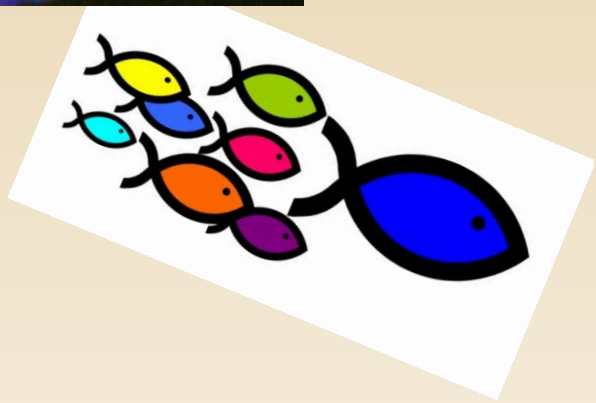
➔ NOT in ISCN!

(Fluorescence) In situ Hybridisation









In situ Hybridisation_metaphase_1

- **ish** ish del(7)(q31q31)(D7S486-)

  → probe or clone name, accession nr, gene name (HUGO), GDB D-nr)

  1. Locus designations (capital letters)
  2. Status given: present (+), absent (-), multiple signals (++)
  3. Separated by commas
  4. No spaces

- **.ish** normal: 46,XX.ish 7q31(D7S486x2)

  → chromosome locus NOT in parentheses,
  probe designation IN parentheses

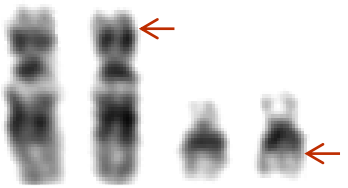
  abnormal: 46,XX.ish del(22)(q11.2q11.2)(D22S75-)
  46,XY.ish dup(17)(p11.2p11.2)(RAI1++)
  46,XX,add(4)(q35).ish dup(4)(q33q35)(wcp+)

In situ Hybridisation_metaphase_2

- If FISH further clarifies the karyotype and, in retrospect, the abnormality can be visualised with banding, the karyotype may be re-written (example next slide).

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

Wrong: 46,XX,t(12;21)(p13;q22)
Right: 46,XX.ish t(12;21)(p13;q22)(ETV6+,RUNX1+;RUNX1+,ETV6+)



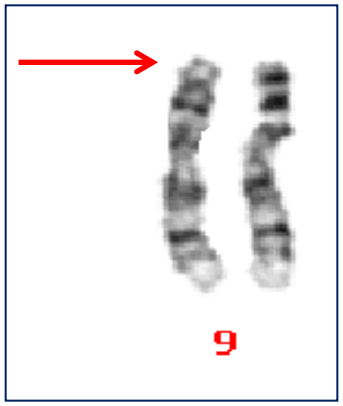
- Only clinically relevant or informative results need to be in the karyotype, control probes don't need to be mentioned

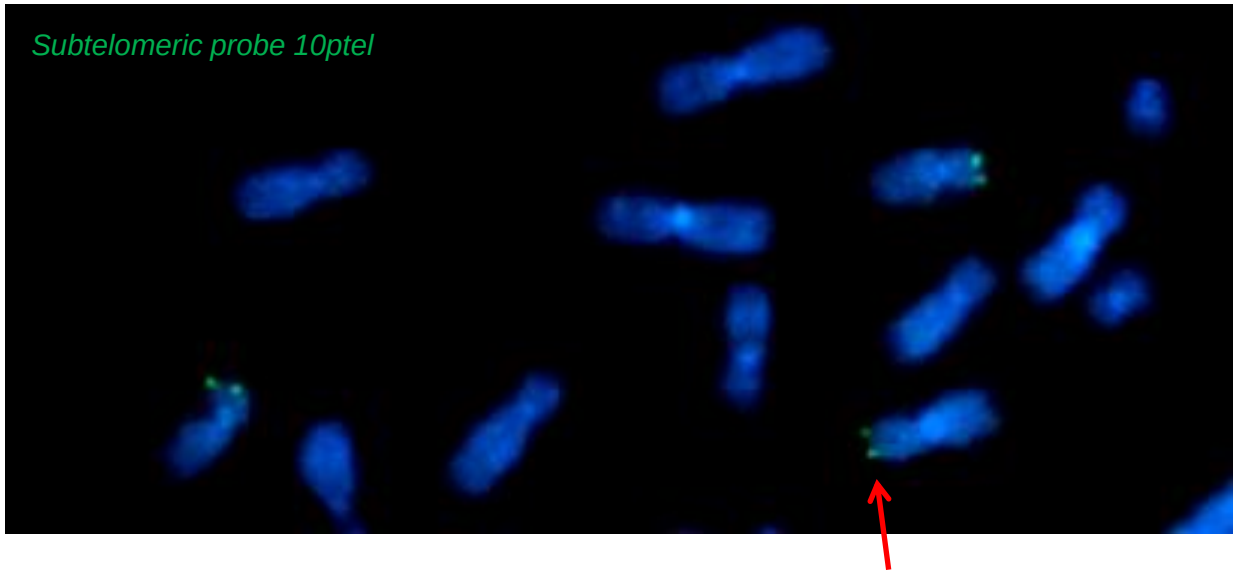
Example methaphase FISH

46,XY,add(9)(p23).ish add(9)(wcp9-,9ptel-)

wcp = whole chromosome paint
ptel = telomere of p-arm

Based on chromosomes → 10p?





46,XY,add(9)(p23).ish der(9)t(9;10)(p2?2;p12.?2)(9ptel-,10ptel+)

Based on 250K SNP array analysis:
46,XY,der(9)t(9;10)(p23;p13) [10Mb loss of 9p, 16Mb gain of 10p]

In situ Hybridisation_interphase

- **nuc ish** interphase / nuclear in situ hybridisation
  - number of cells scored is placed in square brackets [ ].
  - x number of signals
    - short: nuc ish(locusxnumber of signals)
    - detailed: nuc ish 9q34(locusxnumber of signals)

      nuc ish(TP53x2)[400]
      nuc ish 17p13.1(TP53x2)[400]

    - If probes for ≥ 2 loci → (1st locus,2nd locus)xnumber of signals

      nuc ish(ABL1,BCR)x2[400]

- When both normal and abnormal cells are found, the number of abnormal cells is listed over the total number of cells scored for each abnormal locus, i.e. [130/400]

  nuc ish 17p13.1(TP53x1)[100/200]
  nuc ish(ATMx1)[100/200],(D12Z1x3)[50/200],(D13S319,TP53)x2[200]

In situ Hybridisation_metaphase and interphase

- If metaphase and interphase FISH are both performed, each is reported within the string, separated by a period.

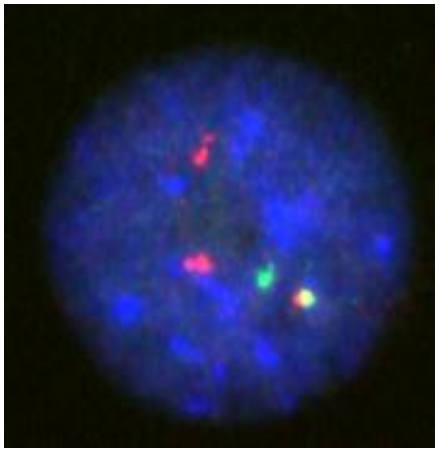
46,XY[20].ish 9q34(ABL1x2),22q11.2(BCRx2)[20].nuc ish(TP53x2)[400]

Interphase In situ Hybridisation_translocation_amp

- **Translocation detection (fusion genes)**
  - Description of FISH results depends on type of probes used
    - single fusion probes
    - single fusion probes with extra signals
    - dual fusion probes
    - break apart probes

    - con connected signals
    - sep separated signals

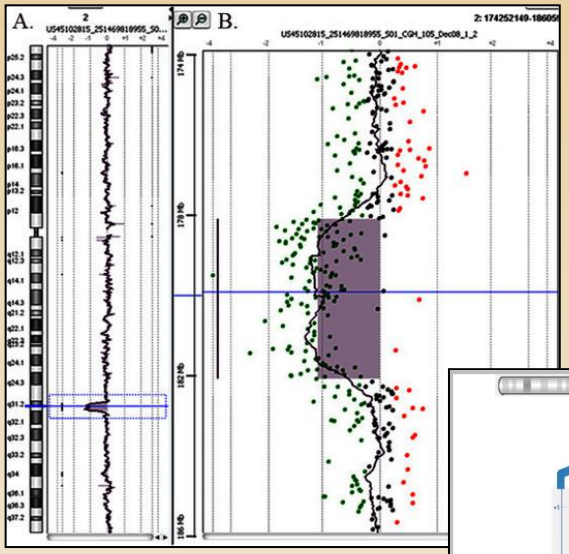
  ➔ various examples given in ISCN 2013

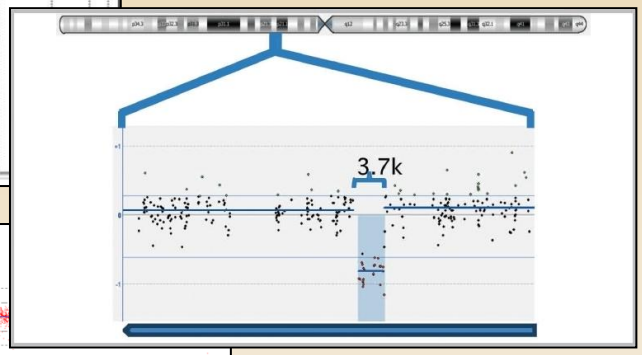


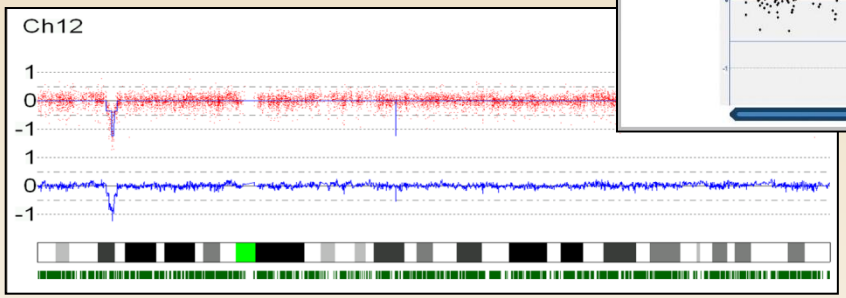
- **amp** amplification:
  - position of “amp” (changed compared to ISCN 2009)

    ➔ various examples in ISCN 2013

Genome wide Microarray







Microarrays_Copy Number Detection_1

- **arr** array
  - detects a relative gain or loss of DNA (compared to diploidy (2n))

- Two systems:
  - Short description that includes only the abnormal nucleotides (most used)
  - Detailed description: includes the abnormal nucleotides as well as the bordering normal nucleotides

- Genome build
  - optional, but recommended to include in nomenclature

arr 15q12q26.3(…-…)x1 or arr[hg19] 15q12q26.3(…-…)x1

- Platform information should be placed in description/interpretation of the report

Microarrays_Copy Number Detection_2

- **normal results**:
  - sex chromosomes separated from the autosomes, which are listed first

arr(1-22,X)x2	normal female
arr(1-22)x2,(XY)x1	normal male

- **abnormal results:**
  - whole chromosome abnormalities

arr(X)x1	Turner (45,X)
arr Xp22.3q28(1-247,249,719)x1	Turner (45,X)
arr(X)x2,(Y)x1	Klinefelter (47,XXY)
arr(1-22,X)x3	Triploidy (69,XXX)
arr(21)x3	Down (+21)
arr(8)x3,(21)x3	(acquired) trisomy 8 and trisomy 21
arr(8)x3,(21)x3 c	Down patient with acquired trisomy 8

- Note: genome build not necessary

Microarrays_Copy Number Detection_3

- **abnormal results**:
  - list only the aberrations, sex chromosomes first, followed by the lowest chromosome number
  - only the band designations of the abnormal probes are shown
  - the aberrant probe positions are listed from pter → qter

arr[hg19] 6q22q24(…-…)x1,(21)x3	loss of 6q22q24 and trisomy 21
arr[hg19] Xq28 or Yq12(…-… or …-…)x1	loss of PAR2 region

- **Highly complex array results**:
  - It is allowed to display results using ISCN nomenclature in a table instead of in a string.

Microarrays_SNP array (regions of homozygosity)

- **hmz** region of homozygosity (CNLOH)
  (htz region of heterozygosity)

  arr[hg19] 15q12q26.3(…-…)x2 hmz

- Multiple regions (e.g. consanguinity), may be combined

  arr[hg19](15q12q26.3(…-…),16p13.3q23.1(…-…),21q21.2q22(…-…))x2 hmz

  arr[hg19](15q12q26.3(…-…),16p13.3q23.1(…-…))x2 hmz,18p11.32p11.2(…-…)x1,21q21.2q22(…-…)x2 hmz

  arr[hg19] 15q12q26.3(…-…)x2 hmz,16p13.3q23.1(…-…)x3,(18p11.32p11.2(…-…),21q21.2q22(…-…))x2 hmz

- In neoplasms, constitutional and acquired

  arr[hg19] 15q12q26.3(…-…)x2 hmz c,16p13.3q23.1(…-…)x2 hmz

Microarrays_Complex Array Results

- **cx** complex genome wide
  - is used for multiple complex rearrangements across the entire genome

arr(1-22,X)cx	female complex genomic aberrations, too many to describe
arr(1-22)cx	unknown sex, complex genomic aberrations, too many to describe

Note: should NOT be used to describe chromotripsis of individual chromosomes

Microarrays_Chromothripsis

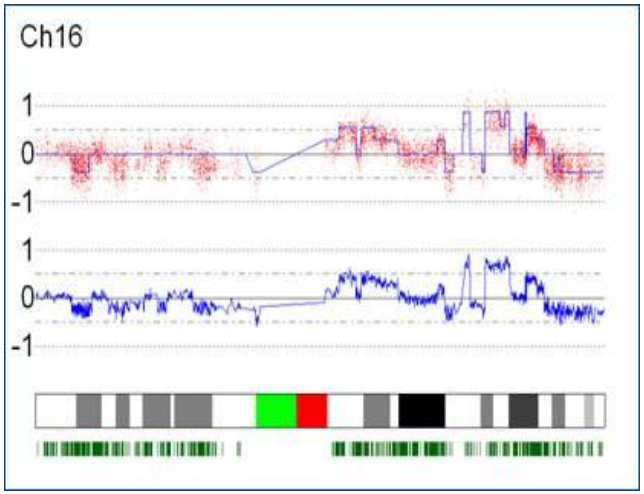
- **cth** chromothripsis
  - refers to complex patterns of alternating copy number changes (normal, gain, or loss) along a chromosome or chromosomal segment

arr(1)cth

arr(1,13)cth

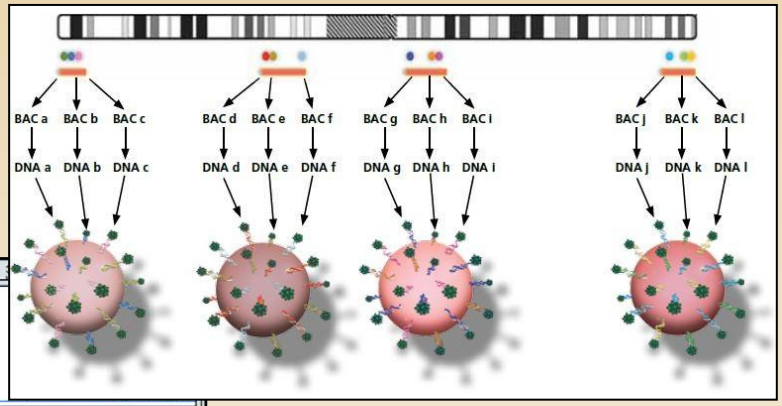
arr(1)(p36p36)cth

arr[hg19] 1p36.3q44(…-…)cth,15q12q26.3(…-…)x1,16p13.3q23.1(…-…)cth



Region specific assays

(e.g. MLPA, QF-PCR, bead based assays)



Targeted/region specific molecular assays_1

- MLPA, Q(F)-PCR, BOB, etc… ➔ generic name

- **rsa** region specific assay (including targeted microarrays!)

  - aneuploid kits:

    rsa(13,18,21,X)x2 female, normal for 13,18,21 and X

    rsa(13,18,21)x2,(X,Y)x1 male, normal for 13,18,21,X and Y

  - multiplex kits:

    rsa(assay)x2

    assay can be any type of tested target(s):

    - range of probes (separated by commas, no spaces)
    - names of oligos (separated by commas, no spaces)
    - names of genes (separated by commas, no spaces)
    - names of commercial kits (separated by commas, no spaces)

Note: explanation in clinical reports!

Targeted/region specific molecular assays_2

- **rsa** for targeted translocations or fusion genes (via e.g. t-CGH arrays)
  - also use rsa
  - pos (positive) and neg (negative)

rsa(assay)neg or rsa(assay)pos

rsa(BCR::ABL1)neg
rsa(BCR::ABL1)pos

arr[hg19] 9q34(…-…)x1.rsa(BCR::ABL1)pos,(CBFB::MYH11)neg


That's all Folks!