Introduction to Clinical Cytogenetics: Lecture 2

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Introduction to Cytogenetics II

- Autosomal Structural Abnormalities and Nomenclature
- Translocations and Derivative Chromosomes
- Inversions and Recombinant Chromosomes
- Isochromosomes
- Hyperdiploidy/hypodiploidy
- Oncology nomenclature – stemline, sidelines, etc
- Chromosome heteromorphisms
- Sex chromosomes

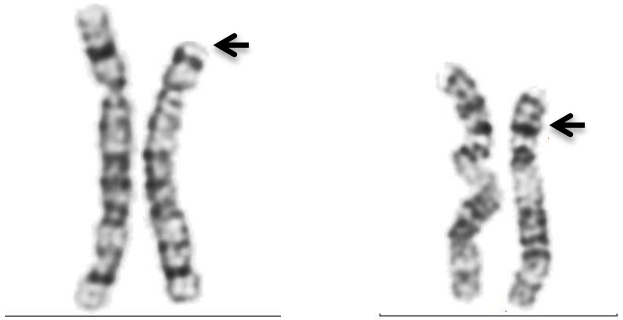
Structural Abnormalities

- Definition: Breakage and rejoining of chromosomes or chromosome segments
- May be either balanced or unbalanced
- Balanced rearrangements:
  - Breakpoints can disrupt gene expression (within a gene or regulatory element)
  - Can create gene fusions or affect gene expression (↑↓) by position effects
    - Common in cancer

Structural abnormalities

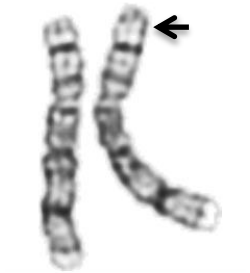
(Abnormal is on the right)

Deletions

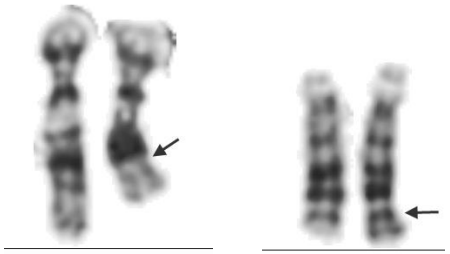


Terminal Interstitial

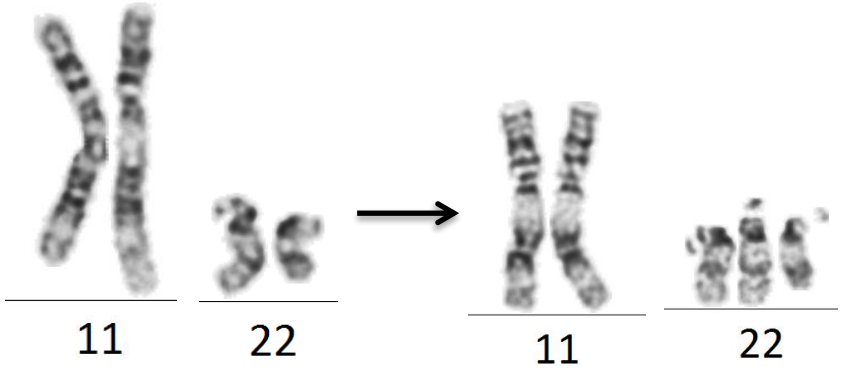
Duplications



Insertions

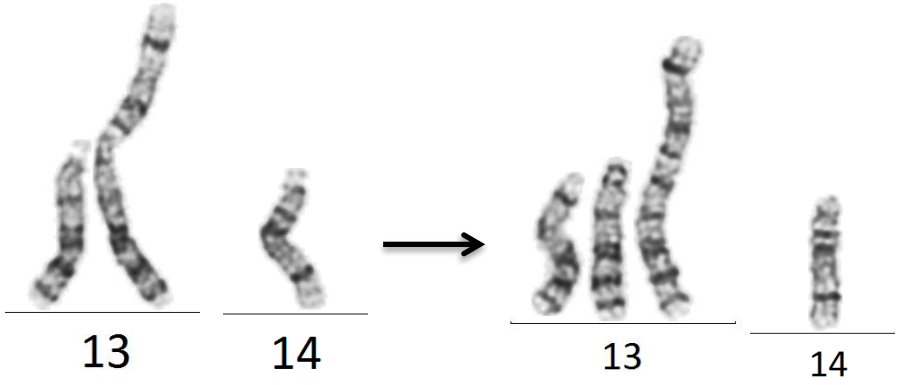


Reciprocal Translocations



Balanced Unbalanced

Robertsonian Translocations

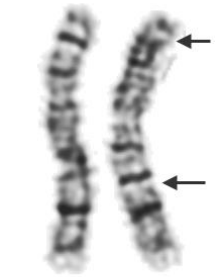


Balanced Unbalanced

Structural abnormalities

(Abnormal is on the right)

Inversions



8

Pericentric inversion

7

Paracentric inversion

Ring chromosomes

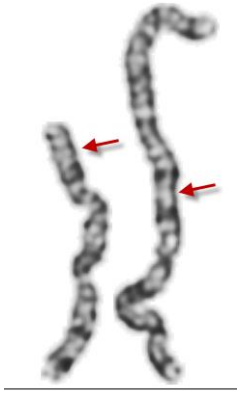
X

13

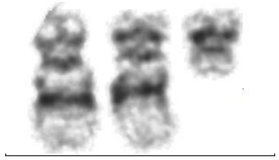
Recombinant chromosomes

8

Isochromosomes



X



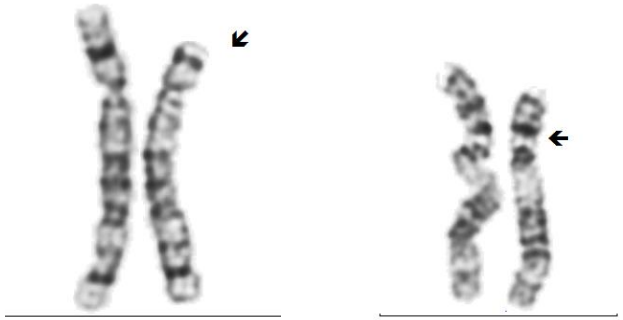
12

15

22

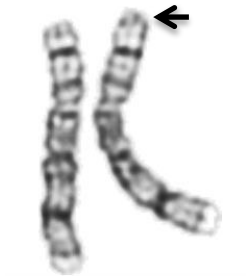
Structural abnormalities

Deletions

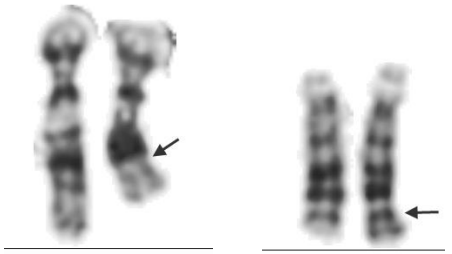


Terminal Interstitial

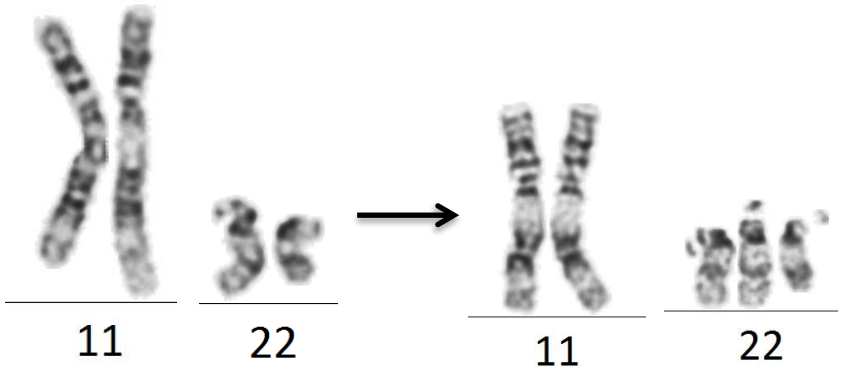
Duplications



Insertions

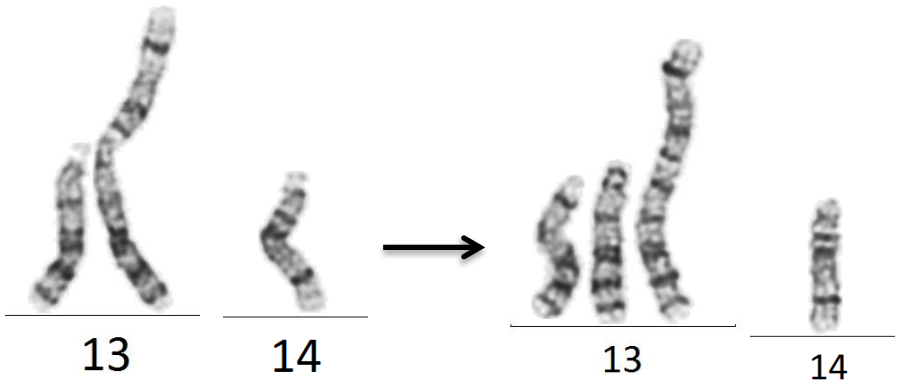


Reciprocal Translocations



Balanced Unbalanced

Robertsonian Translocations



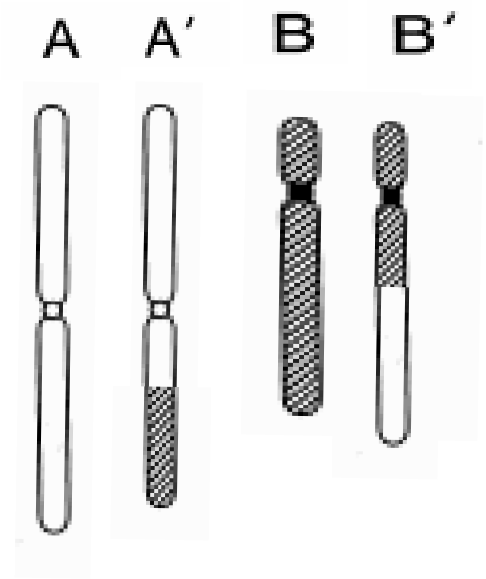
Balanced Unbalanced

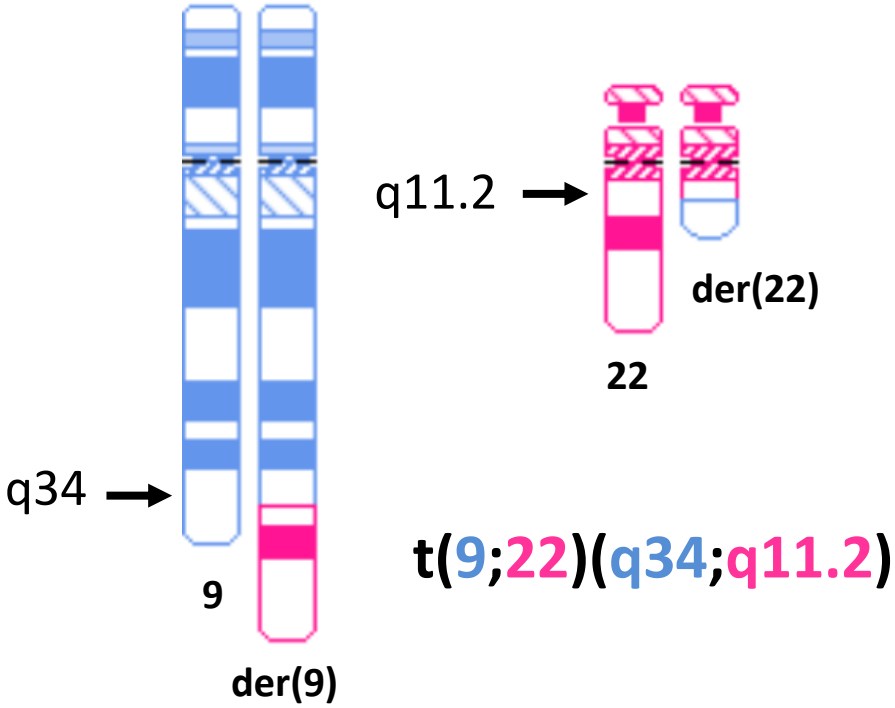
Effects of Translocations

- Can create gene fusions
  - *BCR-ABL1*, *ETV6-RUNX1*, *PML-RARA*
- May disrupt gene expression (breakpoint within a gene or regulatory element by position effect)
  - In prenatal setting and de novo, risk for expression of abnormal phenotype is ~6-9% (Warburton AJMG 1991)
- Constitutional carriers are at risk for infertility, recurrent miscarriage and/or birth of a child with a congenital anomaly syndrome
  - Most risk figures fall into the range of 0-30% for a liveborn child with an abnormality (higher end if previous child)

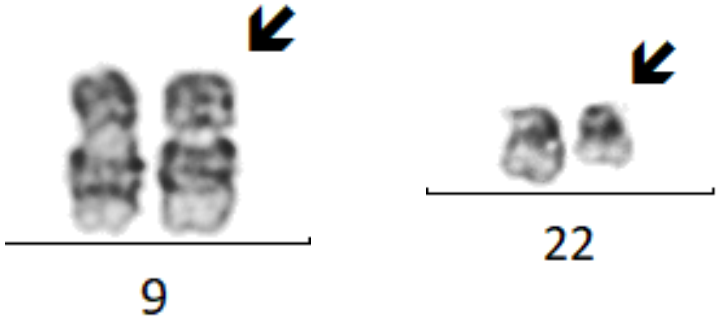
Translocation Nomenclature

A, B: Normal chromosomes
A', B': Derivative chromosomes



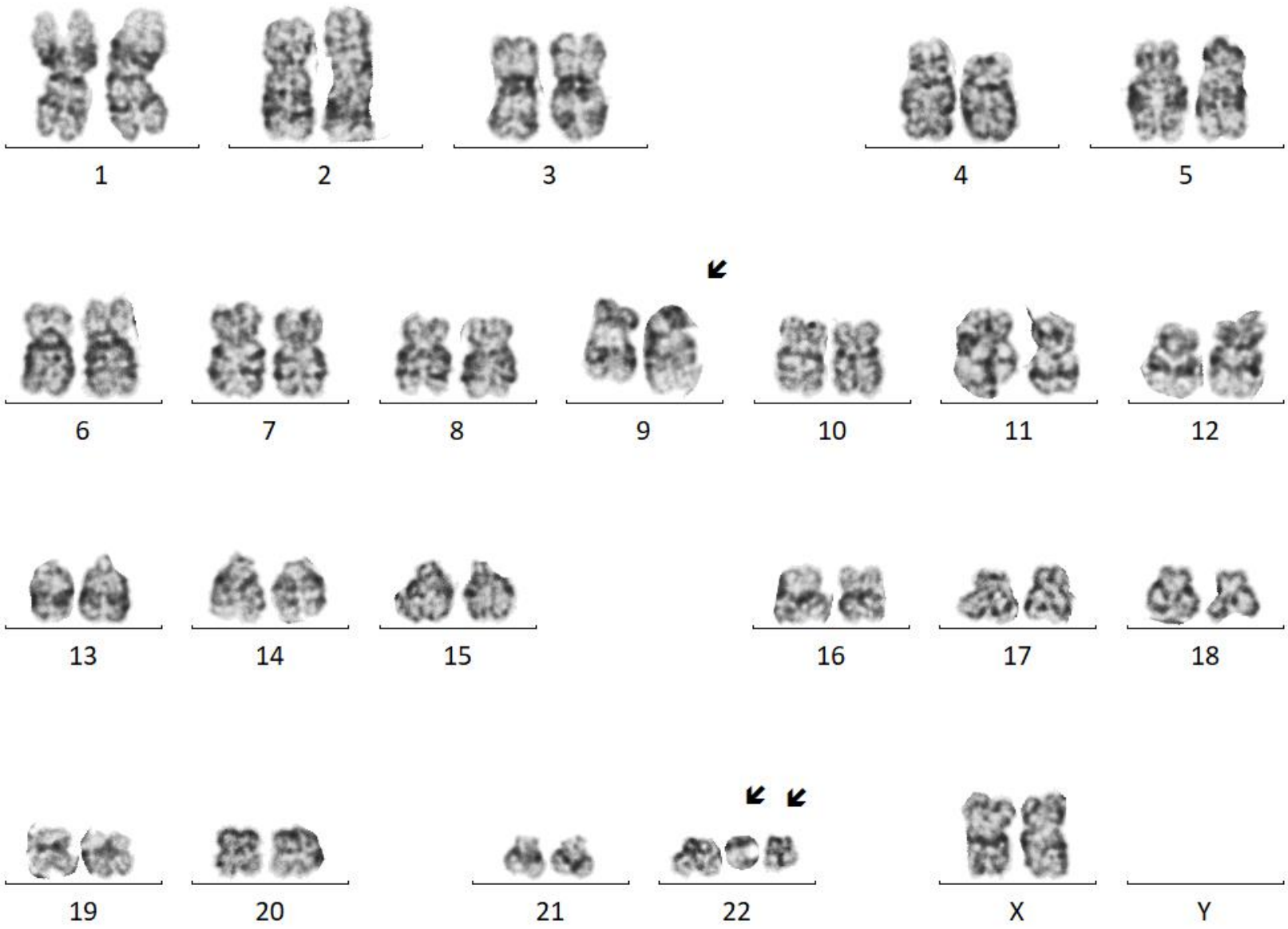


t(9;22)(q34;q11.2)



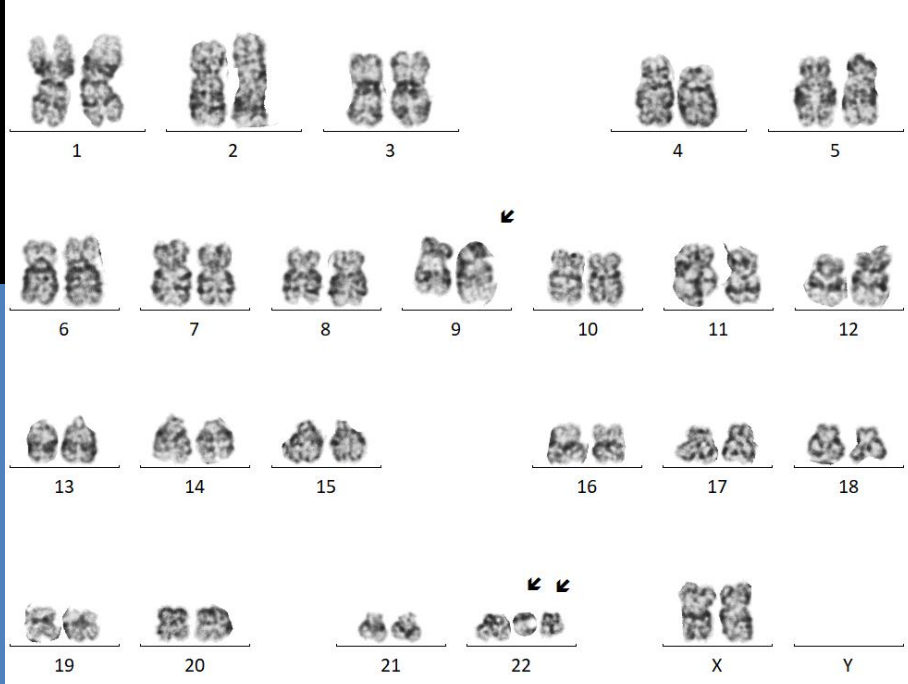
Gardner, Sutherland and Shaffer. 2012

Ph chromosome gain

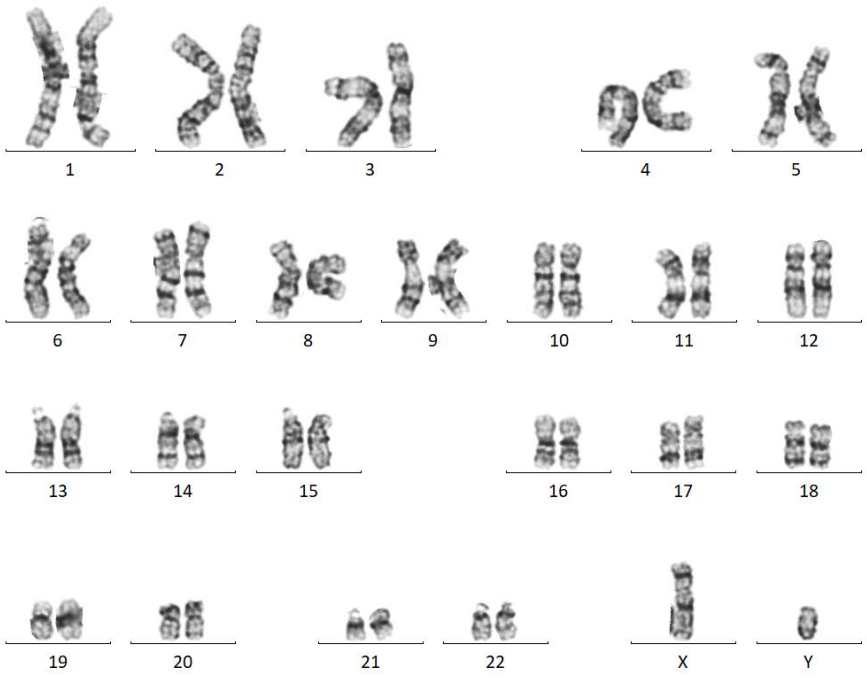


Can you tell what is going on in this case?

In 1 cell



In 19 cells

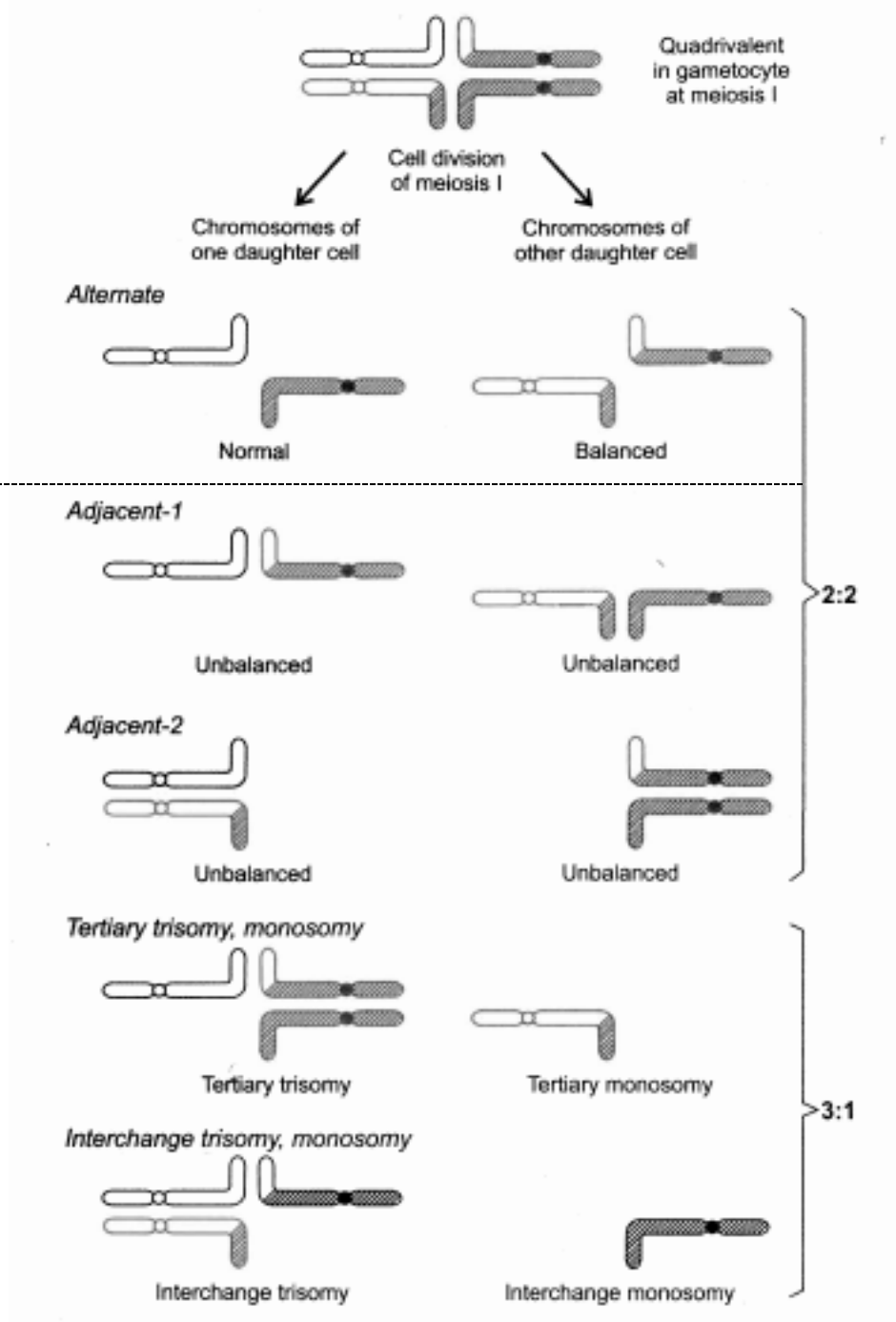


47,XX,t(9;22)(q34;q11.2),+der(22)t(9;22)[1]//46,XY[19]

Meiosis in the Balanced Translocation Carrier

Only 2:2 alternate segregation will result in normal/balanced gametes

All other modes of segregation result in unbalanced gametes



Chromosome Abnormalities and Genetic Counseling. 4th ed. Gardner, Sutherland and Shaffer. 2012

Predicting clinical outcomes for the balanced translocation carrier

Factors that influence segregation and outcomes

- Location of the breakpoints, relative to chromosome size and the centromere
- Relative size of chromosomes involved

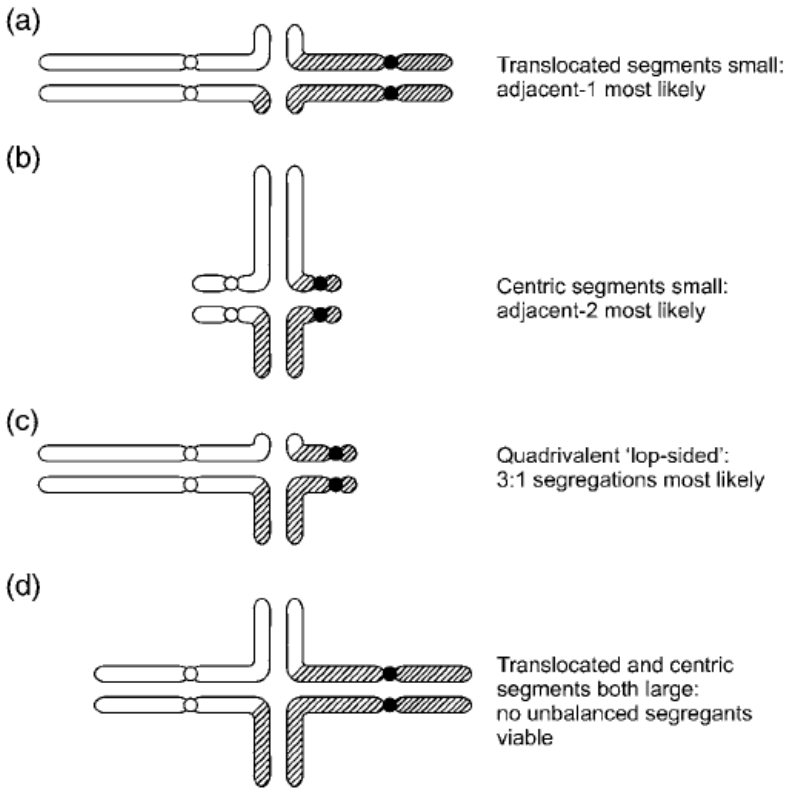


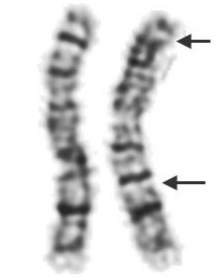
FIGURE 5–5 Prediction of likely viable segregant outcomes by pachytene diagram drawing and assessment of the configuration of the quadrivalent.

- See also Table 5-4 in Gardner, Sutherland and Shaffer 2012

Gardner, Sutherland and Shaffer. 2012

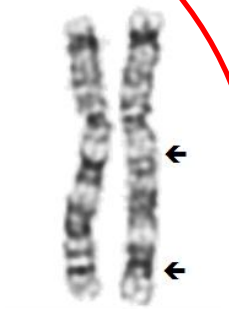
Structural abnormalities

Inversions



8

Pericentric inversion



7

Paracentric inversion

Ring chromosomes

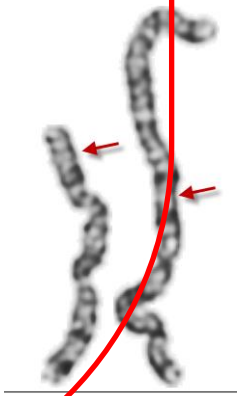
X

13

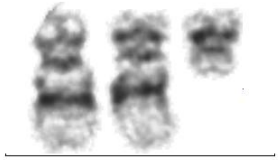
Recombinant chromosomes

8

Isochromosomes



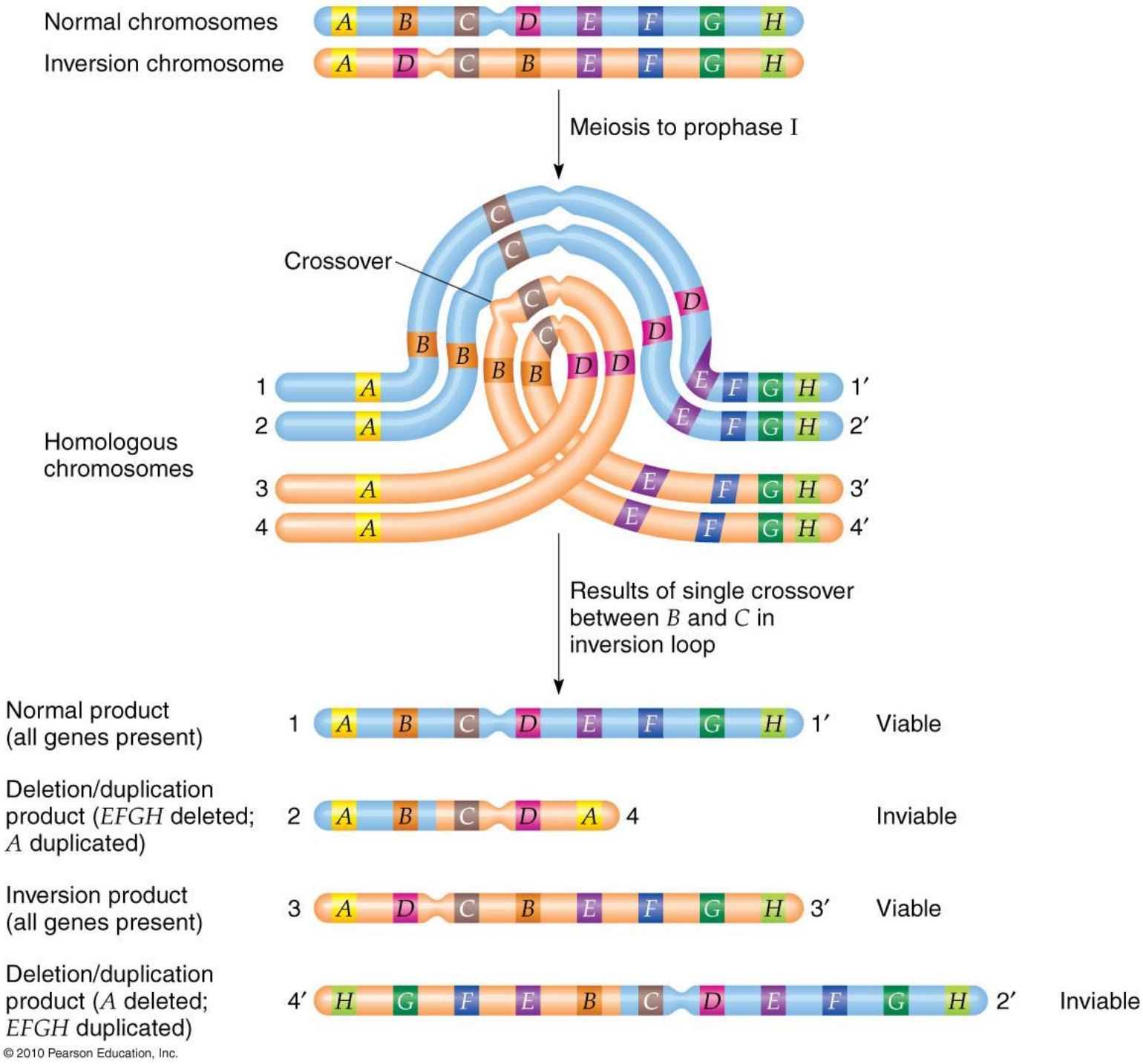
X



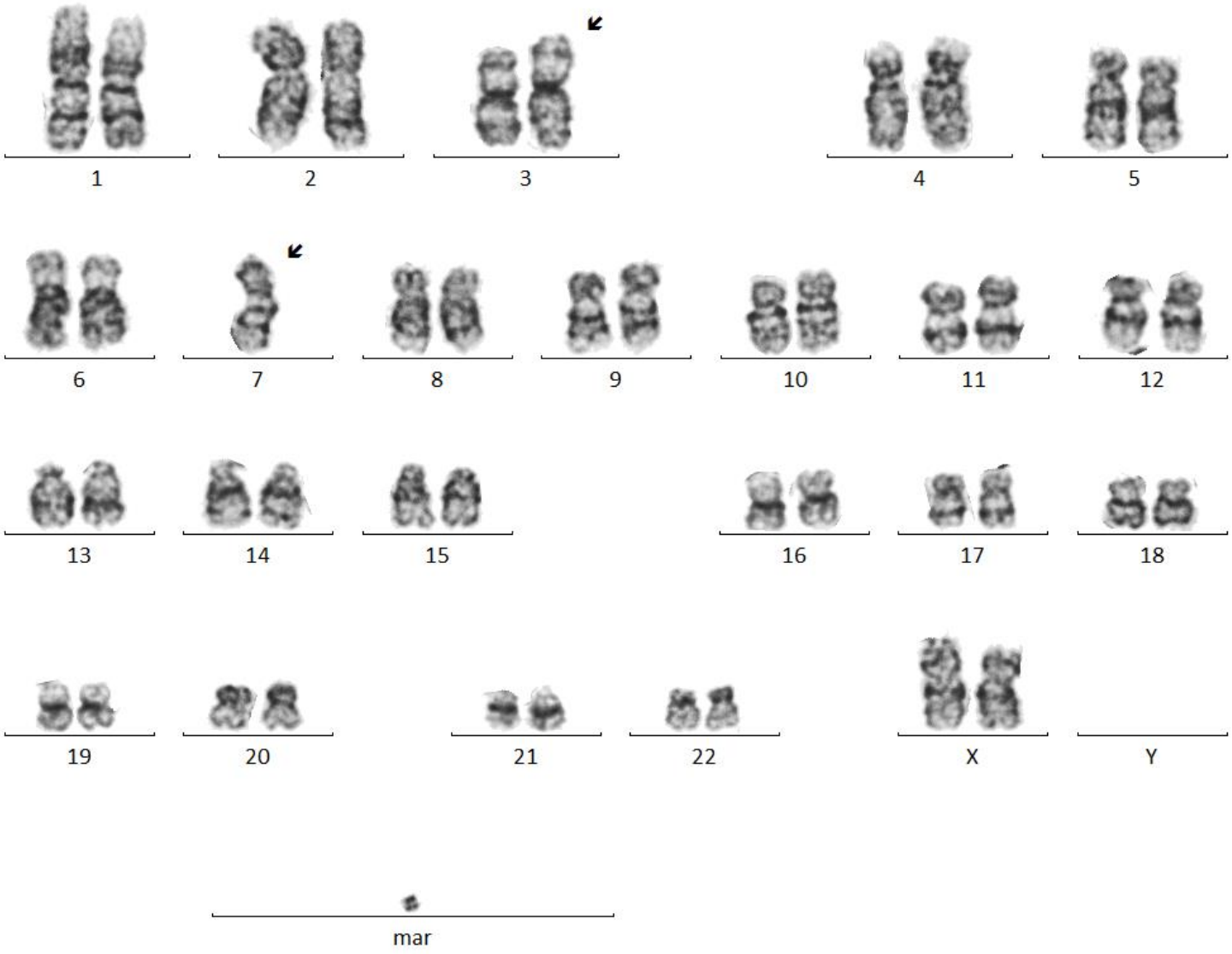
12

15

22

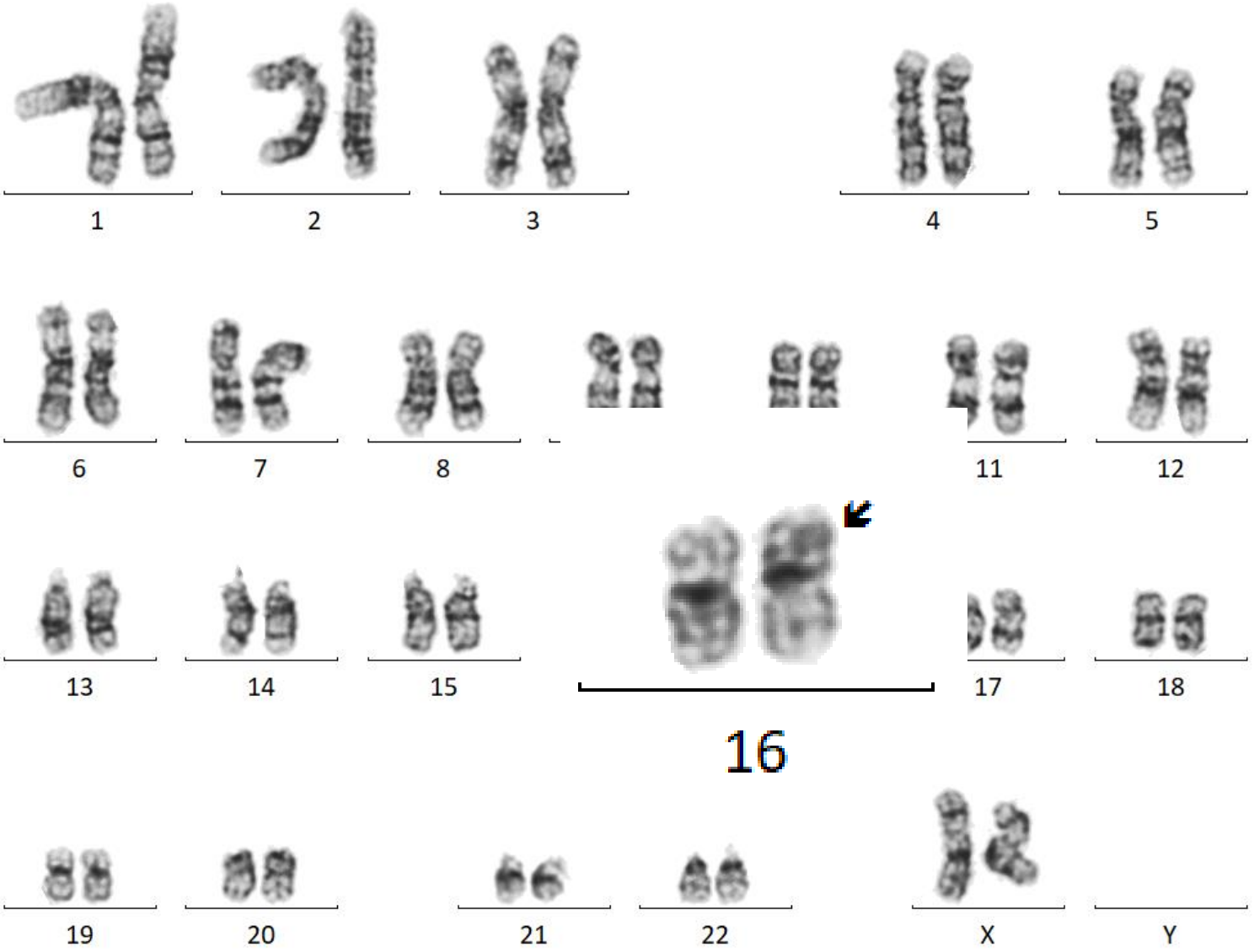


Some inversions are easy to detect by karyotype



45,XX,inv(3)(q21q26.2),-7[5]/46,sl,+1mar[15] *RPN1/MECOM*

Some inversions are hard to detect by karyotype



46,XX,inv(16)(p13.1q22)[16]/46,XX[4] *CBFB/MYH11*

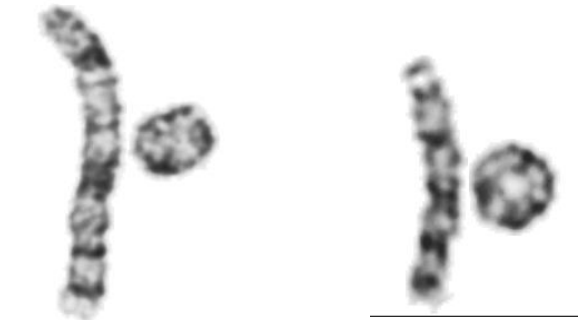
Structural abnormalities

Inversions

Pericentric inversion

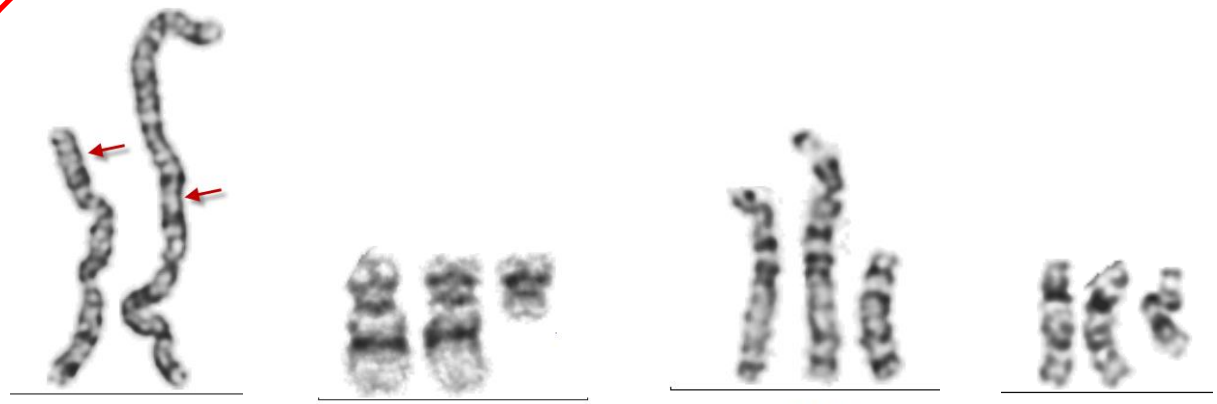
Paracentric inversion

Ring chromosomes

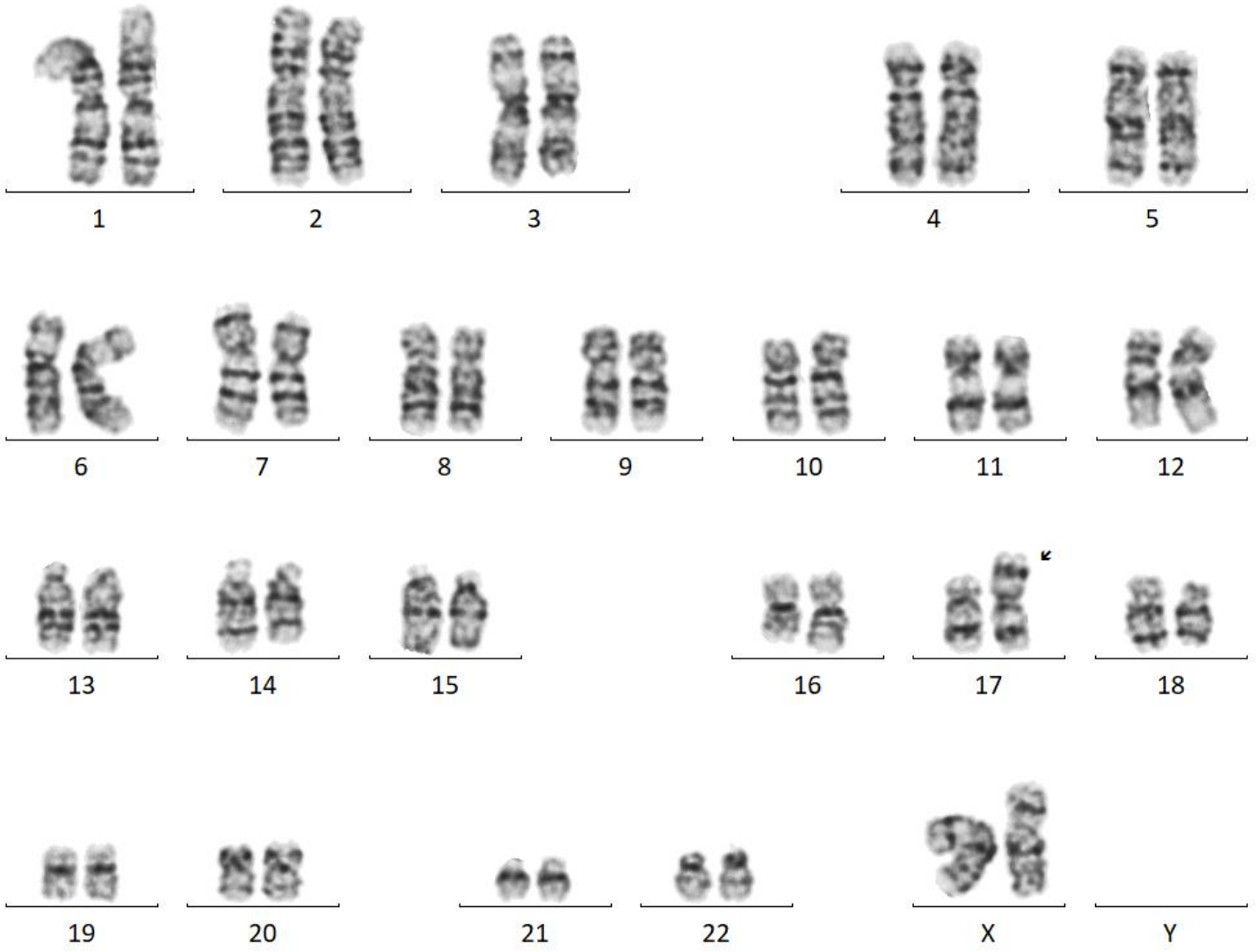


Recombinant chromosomes

Isochromosomes



Isochromosomes in hematological neoplasms



46,XX,i(17)(q10)[13]/46,XX[7]

Oncology nomenclature: Stemlines, sidelines and more

- **Stemline (sl):** the most basic clone of a tumor cell population. Listed first.
- **Sideline (sdl):** additional deviating subclones from the stemline. Listed after stemline. If ≥1 sdl, these can be listed as sdl1, sdl2, sdl3, etc
- **Idem (idem):** refers to the karyotype listed first. In tumors with subclones, idem can be used followed by the additional changes in relation to the stemline.

sl and sdl usage example:

46,XX,t(9;22)(q34;q11.2)[3]/47,sl,+8[17]/48,sdl1,+9[3]/49,sdl2,+11[12]

46,XX,t(9;22)(q34;q11.2)[3]/
47,sl,+8[17]/
48,sdl1,+9[3]/
49,sdl2,+11[12]

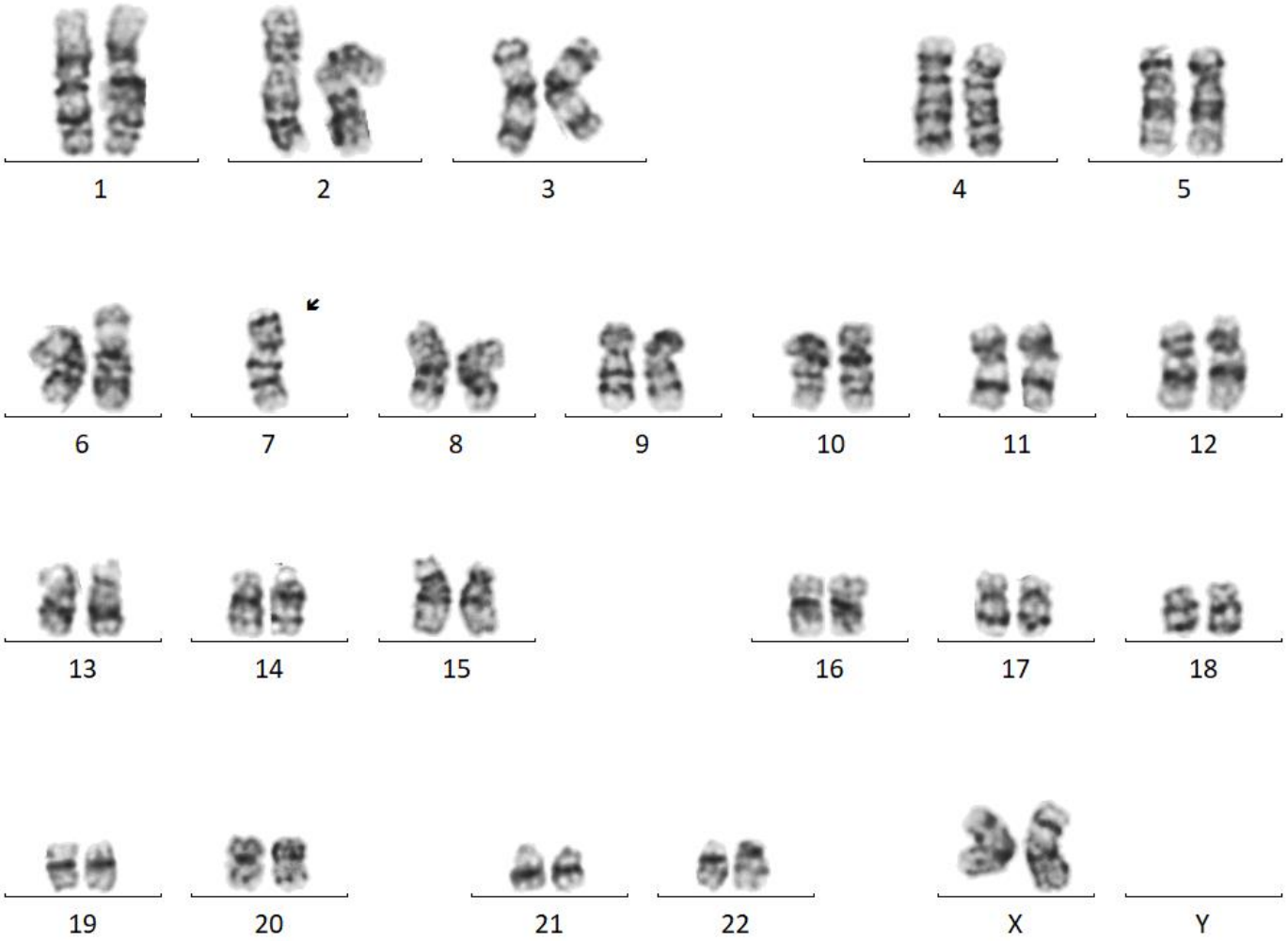
Pro-tip! *idem or sl and × can indicate polyploidy*
26,X,+4,+6,+21[3]/52,idem×2
26,X,+4,+6,+21[3]/52,sl×2

idem usage example:

46,XX,t(9;22)(q34;q11.2)[3]/47,idem,+8[17]/48,idem,+8,+9[3]/49,idem, +8,+9,+11[12]

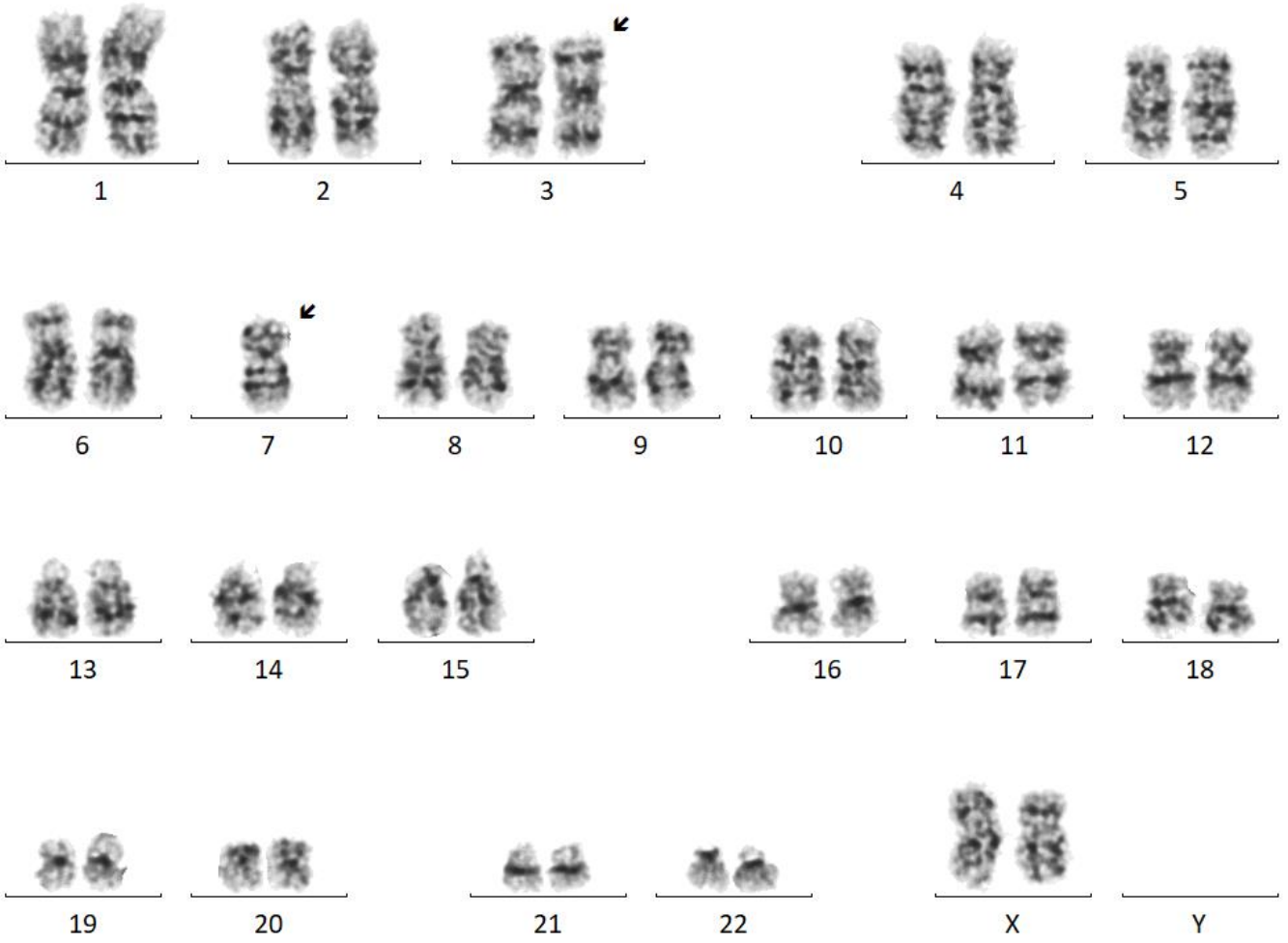
46,XX,t(9;22)(q34;q11.2)[3]/
47,idem,+8[17]/
48,idem,+8,+9[3]/
49,idem, +8,+9,+11[12]

Stemlines, sidelines and more



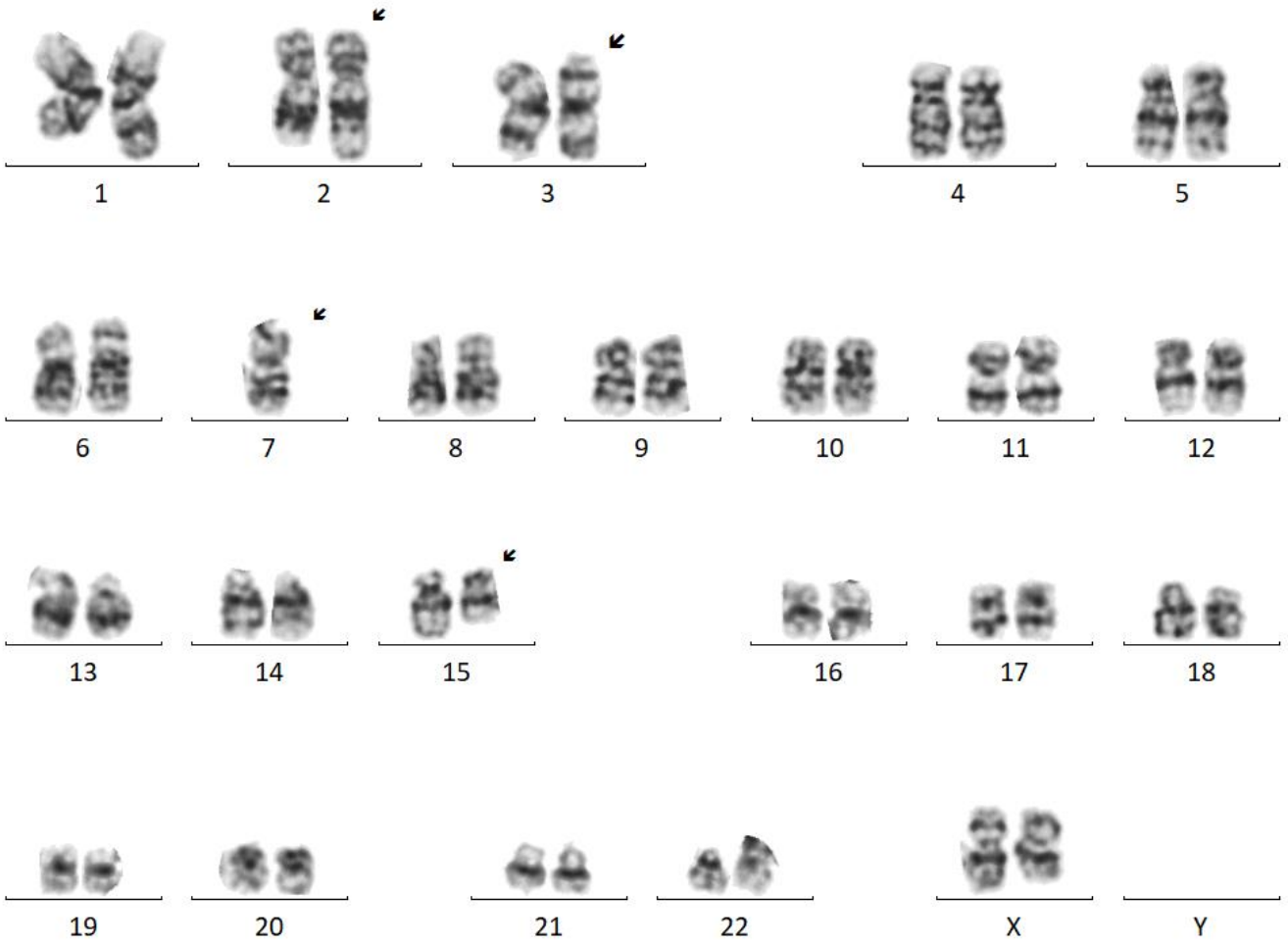
45,XX,-7[7]/

Stemlines, sidelines and more



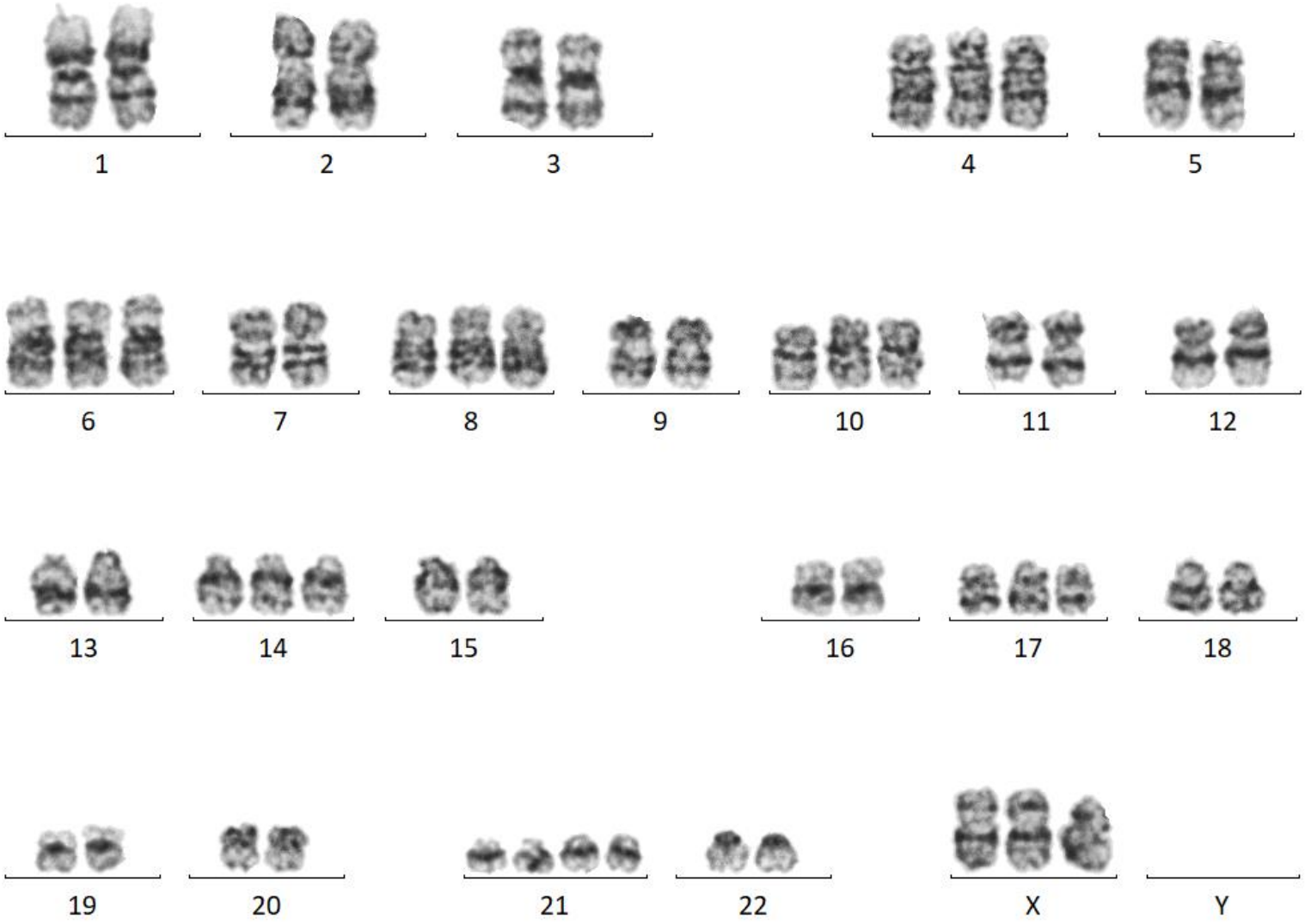
45,XX,-7[7]/
45,sl,add(3)(q26.2)[9]/

Stemlines, sidelines and more



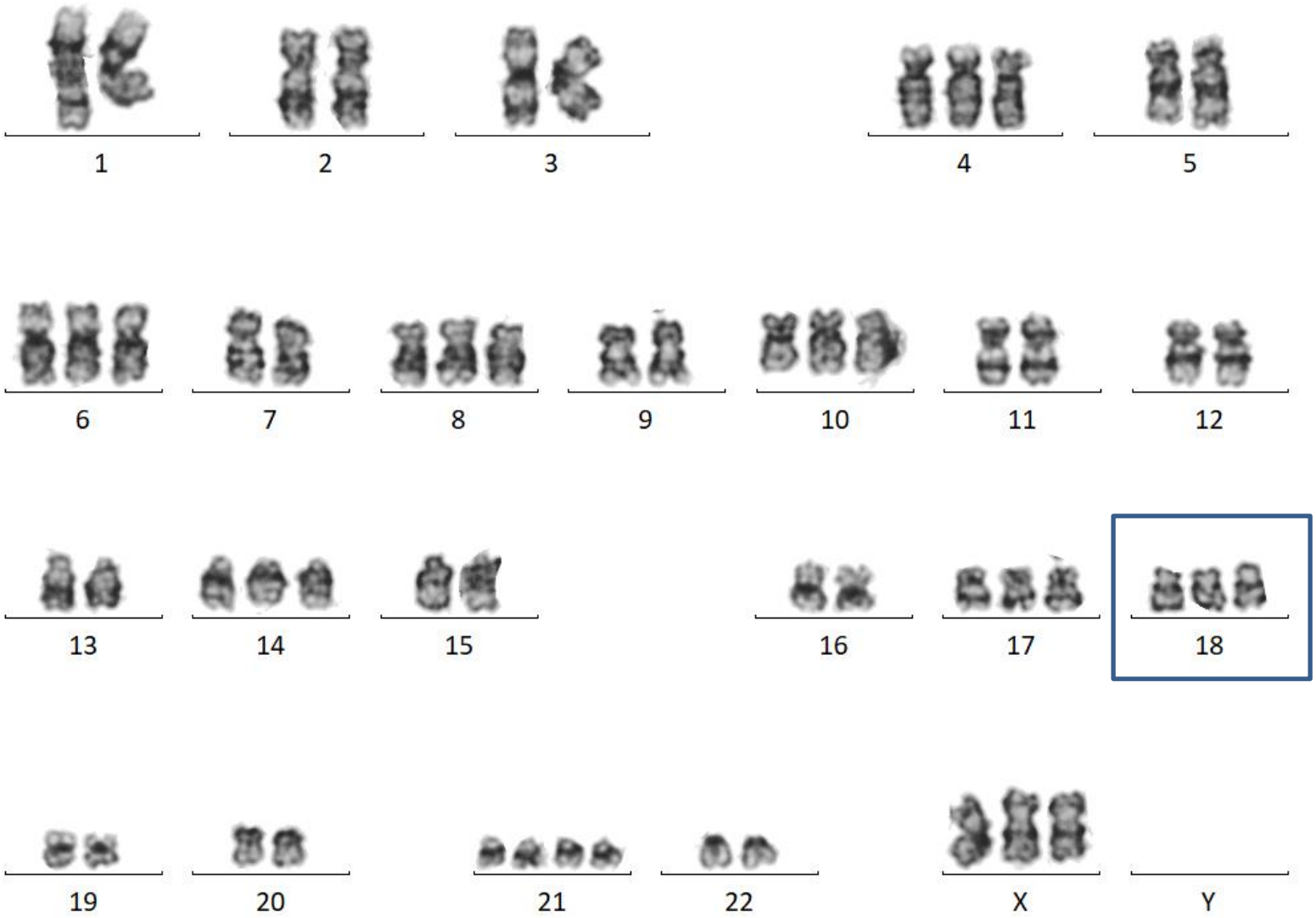
45,XX,-7[7]/
45,sl,add(3)(q26.2)[9]/
45,sdl1,t(2;15)(q33;q15)[2]/
46,XX[2]

B-ALL hyperdiploidy



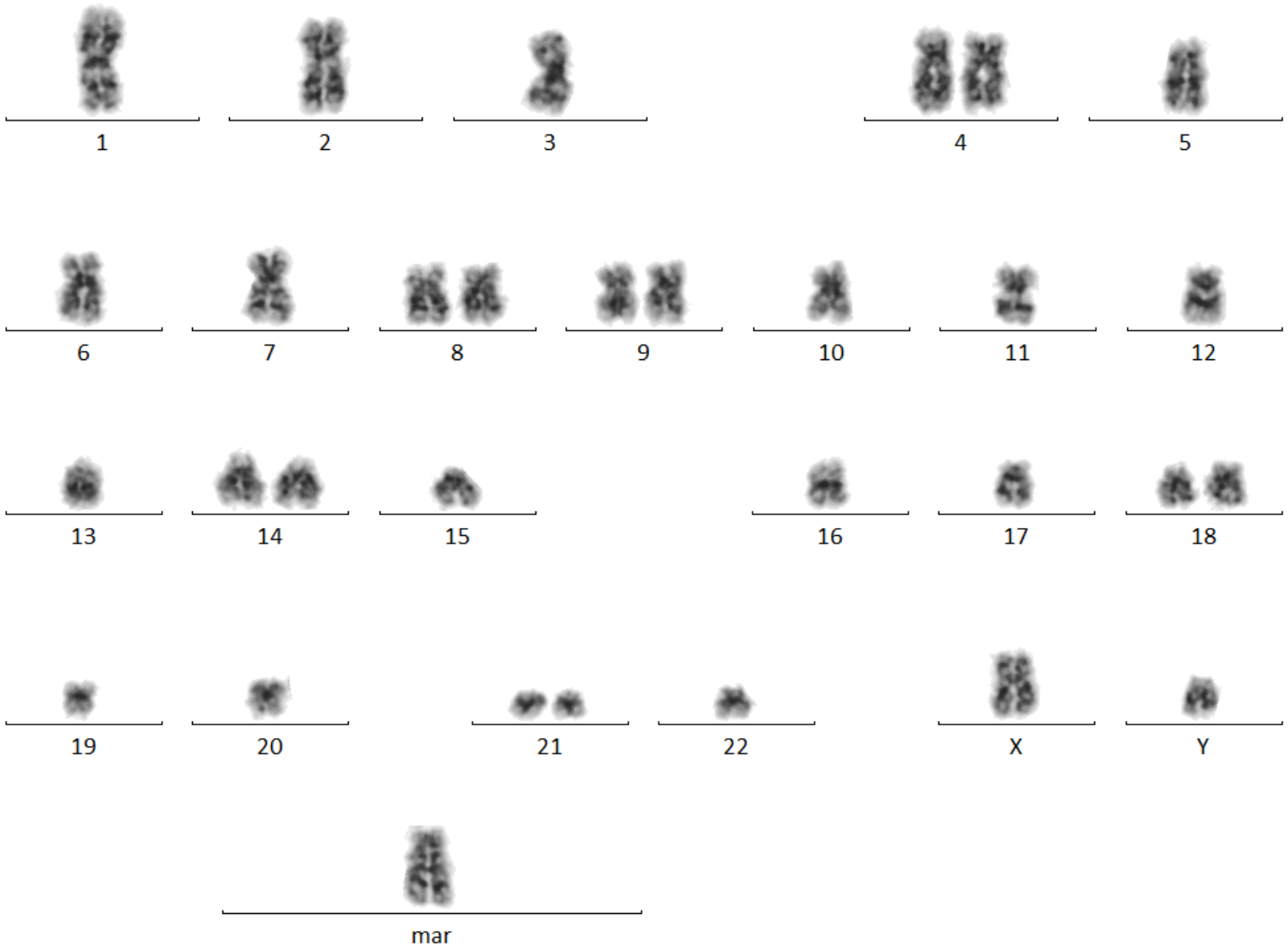
55-56,XX,+X,+4,+6,+8,+10,+14,+17,+18,+21,+21[cp11]/46,XX[9]

B-ALL hyperdiploidy



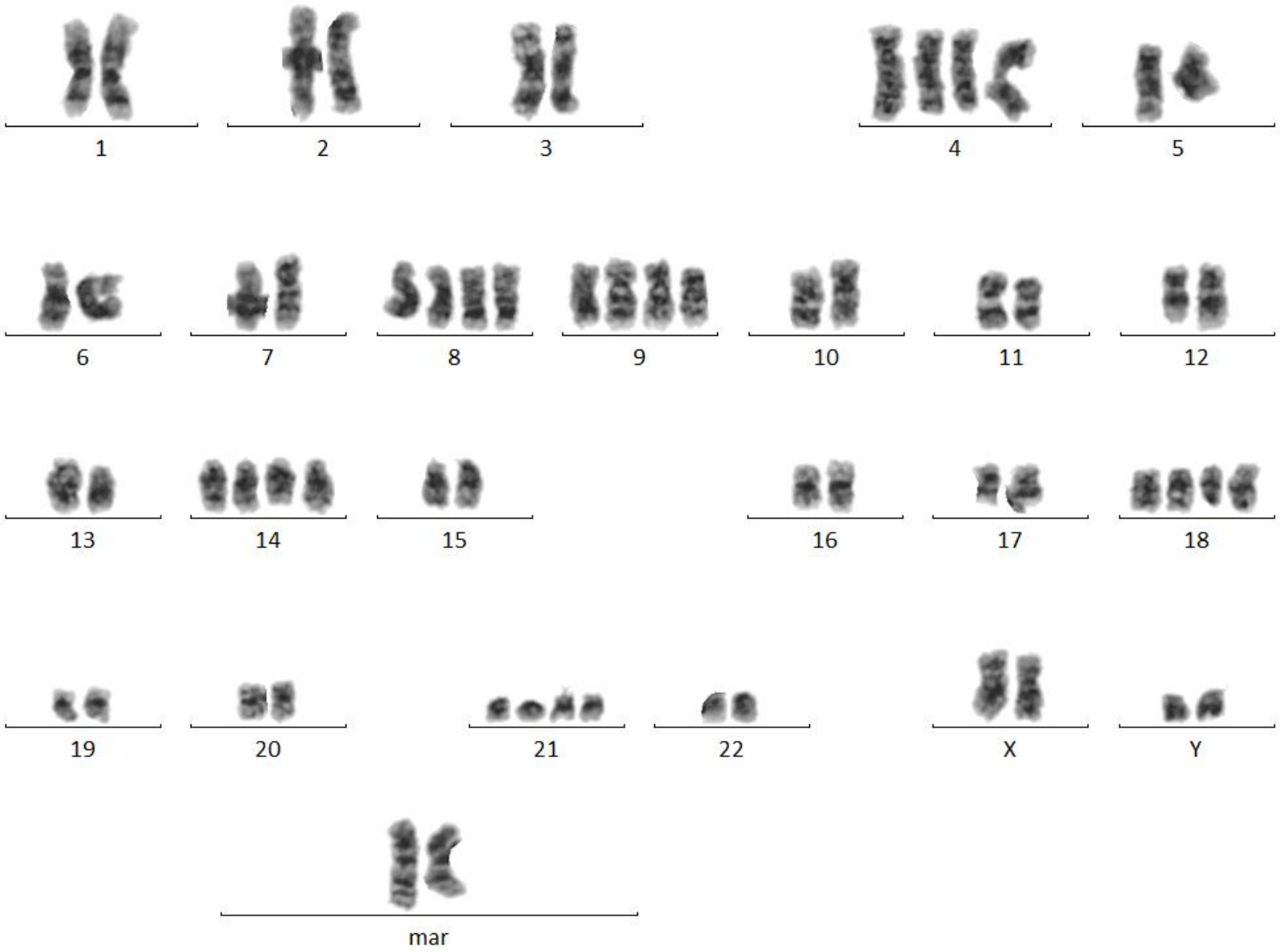
55-56,XX,+X,+4,+6,+8,+10,+14,+17,+18,+21,+21[cp11]/46,XX[9]

B-ALL near-haploidy



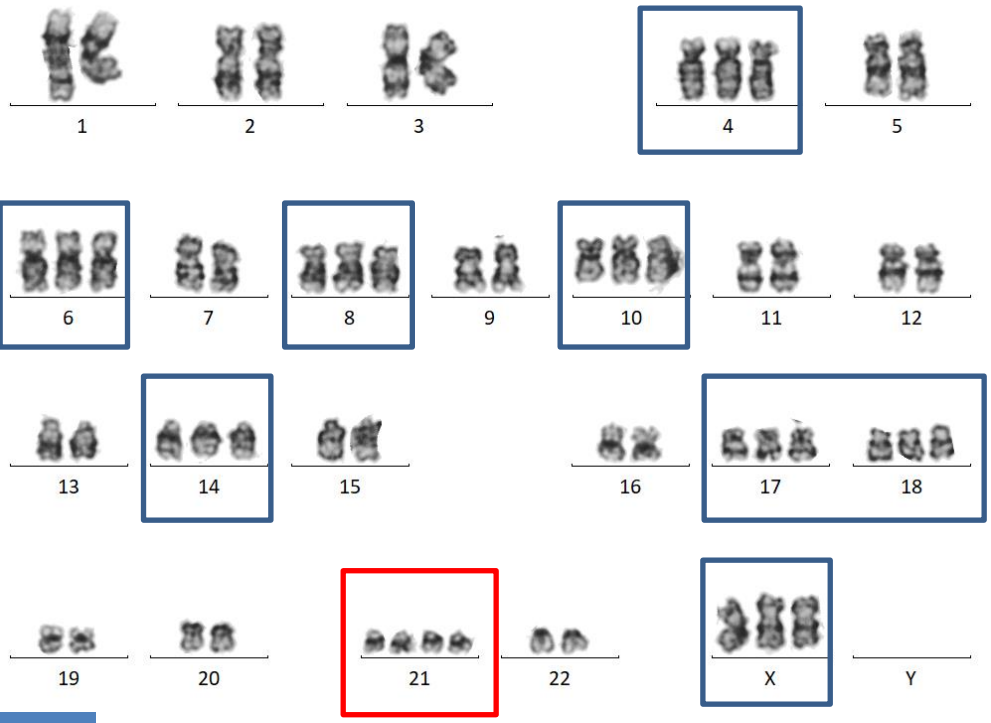
31,XY,add(1)(q21),+4,+8,+9,+14,+18,+21,+mar[cp6]

B-ALL masked near-haploidy



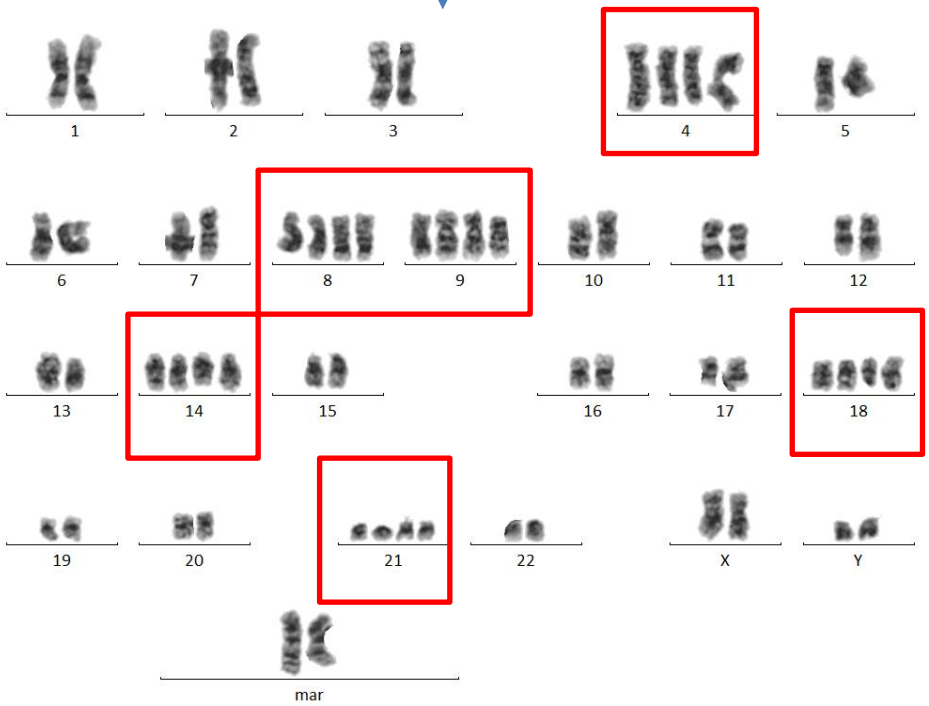
31,XY,add(1)(q21),+4,+8,+9,+14,+18,+21,+mar[cp6]/62,slx2[cp5]/46,XY[9]

B-ALL near-haplo/hypodiploidy vs hyperdiploidy



Hyperdiploid

Masked near-haploid



Near-haploidy ≤34

- Hypohaploidy <23
- Hyperhaploidy 24-34

Near-diploidy 35-57

- Hypodiploidy 35-45
- Hyperdiploidy 47-57

Structural Abnormalities Description
(Illustrated by Examples)

- Terminal vs interstitial
  - add(11)(q23)
  - del(4)(p16.3)
  - dup(17)(p13p11.2)
- Interchromosomal vs intrachromosomal
  - t(9;22)(q34;q11.2)
  - inv(3)(q21q26.2)
  - ins(2)(p13q21q31)
- Whole chromosome arm rearrangements
  - i(12)(p10)
  - der(1;7)(q10;p10)
  - rob(13;14)(q10;q10)
- Combination of abnormalities
  - 47,XY,+8,t(8;14)(q24;q32)
  - der(7)del(7)(p11.2)del(7)(q22)
  - mos 45,X[12]/46,X,idic(X)(p11.22)[8]

Normal variable chromosomal features/ Heteromorphisms

(NOTE: generally, these are not included in the karyotype)

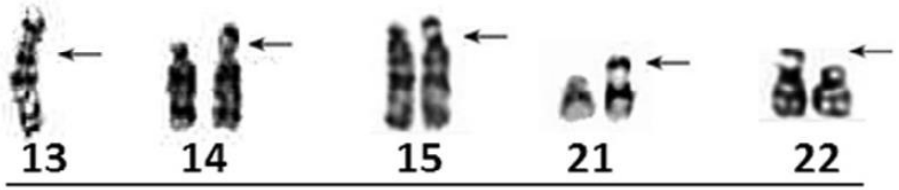
Variation in length (+ or -)

- Yqh+
- 1qh+
- 9qh+
- 16qh+
- 13ps+
- 21pstk+

Variation in position

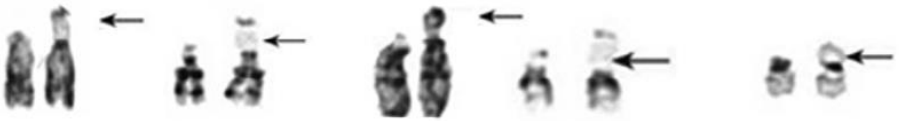
- inv(2)(p11.2q13)
- inv(9)(p12q13)
- Yqs

qh+



pss/ps+

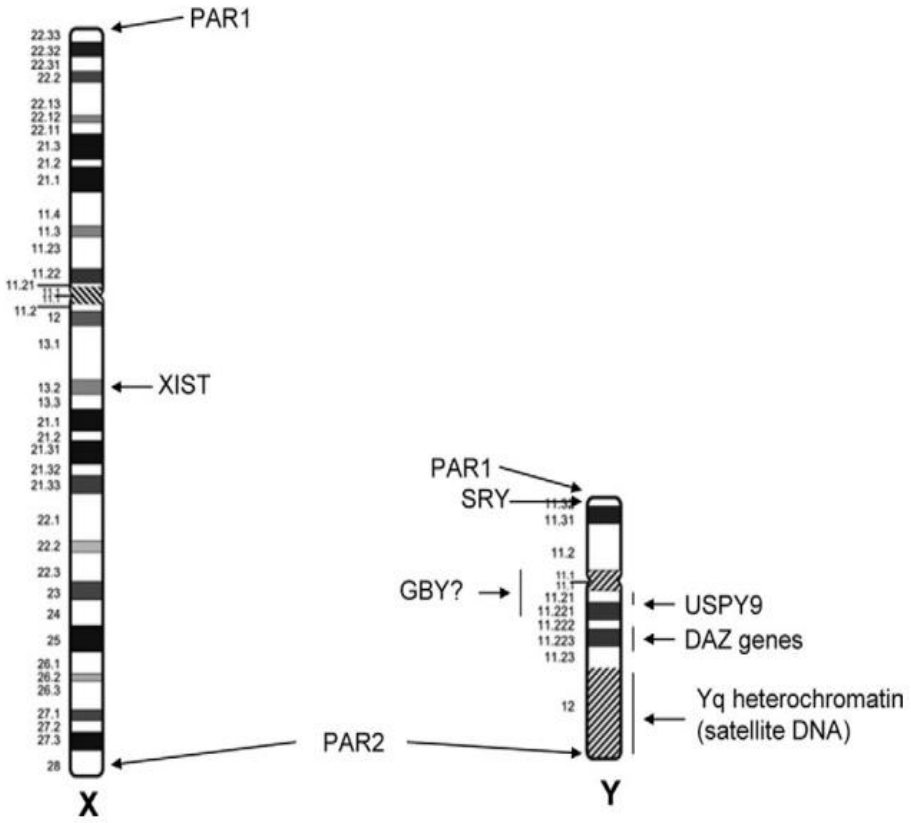
inv



pstk+

Sex Chromosomes

- X chromosome: 1000's of genes, one X is inactive in females
  - XIST: dosage compensation
- Y chromosome: main function is in male sexual development
  - *SRY* determines male phenotype
  - Other genes regulate sexual development
  - Yqh is inactive
- Pseudoautosomal (PAR) regions are required for pairing and recombination between the X and Y in males
  - Errors in XY pairing lead to increased incidence of XY nondisjunction, higher rates of sex chromosome aneuploidy



Li, Clin Lab Med 31 (2011)

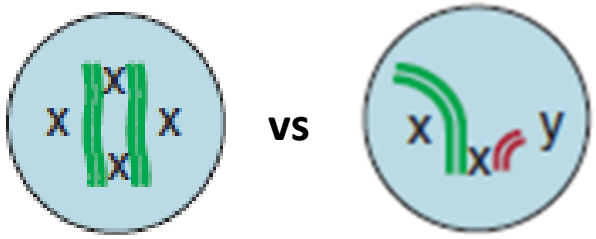
Common sex chromosome aneuploidies

Sex Chromosome Aneuploidy	Syndrome	Incidence in newborns	Characteristics
45,X and variants	Turner	1 in 3500 females*	Female: growth delay, short stature, neck webbing and edema, CHD (coarctation of aorta), renal anomalies, amenorrhea, ovarian failure, infertility
47,XXX	(Triple X)	1 in 1000 females	Female: normal appearance, risk for developmental delays and psychiatric impairment, normal fertility
47,XXY	Klinefelter	1 in 500-1000 males	Male: normal appearance, hypogonadism, speech delay, learning disability, infertility
47,XYY		1 in 1000 males	Male: normal appearance, tall stature, risk for developmental delay, learning disabilities, normal fertility

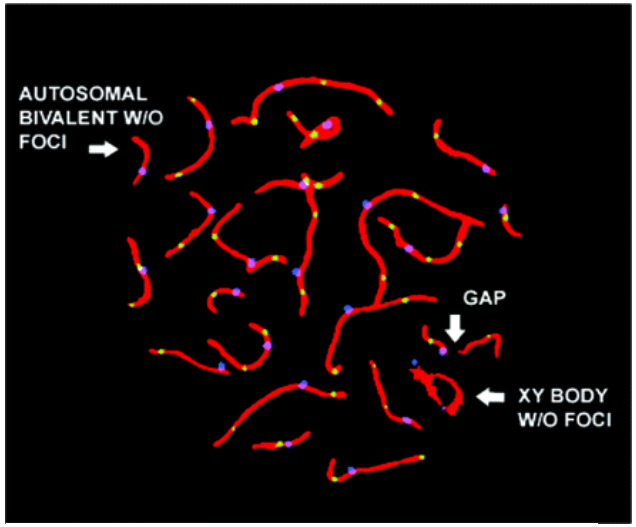
* 99% of 45,X conceptuses result in spontaneous abortion

Sex Chromosomes and Meiotic Behavior

- In female meiosis I, X homologs pair like the autosomes
- In male meiosis I, X and Y pair only in the pseudoautosomal regions (PAR), an obligatory recombination event occurs in Xp/Yp (PAR1)
- Heterochromatic DNA (present on Yq) replicates late in the cell cycle (asynchrony)
- The timing of separation of sex chromosome sister chromatids in meiosis II may be uncoupled from the autosomes



Spermatocyte at MI Prophase

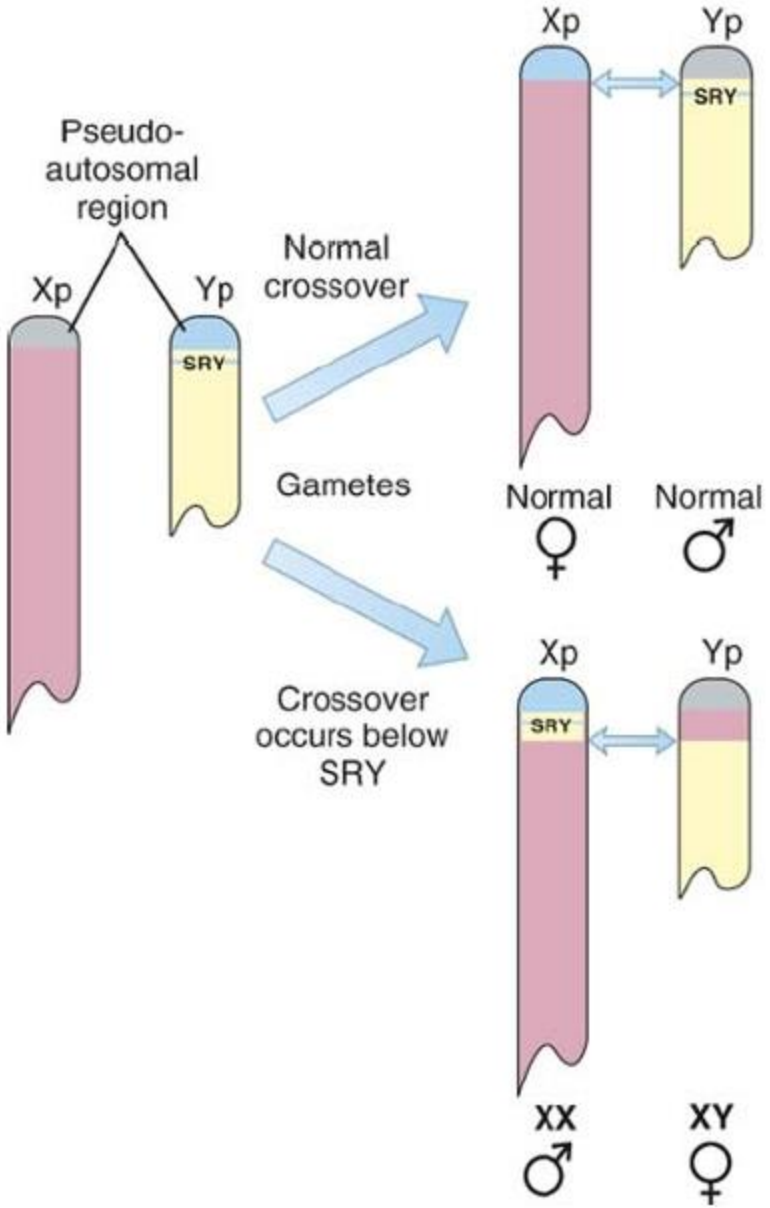


Red = chromosomes (2n,4c)
Blue = centromeres
Yellow = Synaptonemal complexes

Ma *et al.*, 2005

Translocation (X;Y)

PAR1 aberrant crossover leads to 46,XX male and 46,XY female



Jorde, Carey and Bamshad. 2016, Fig 6-13