Introduction to Cytogenetics
Part 2

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Introduction to Cytogenetics II

- Structural Chromosome Abnormalities
  - Underlying Mechanisms
  - Nomenclature
  - Deletions and Duplications
  - Translocations and Segregation Mechanisms
  - X-chromosome Abnormalities
  - Inversions and Recombinant Chromosomes
- Cytogenetics in Cancer
  - Hematologic malignancies overview
  - Cytogenetic abnormalities and nomenclature
  - Genetic basis of cancer: oncogenes, tumor suppressors

Structural Abnormalities

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

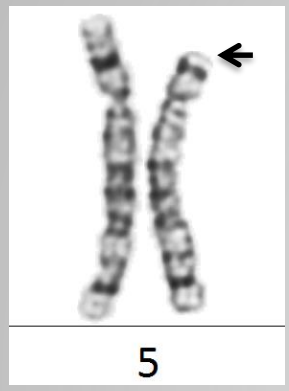
Mechanisms Underlying Structural Rearrangements- Errors in…

- Recombination: exchanges between homologous, non-allelic sequences via non-allelic homologous recombination (NAHR)
- Repair: double-stranded breaks that are repaired incorrectly by non-homologous end-joining (NHEJ)
- Replication: discontinuous replication of the lagging strand leads to invasion into other replication forks: fork stalling and template switching (FoSTes)

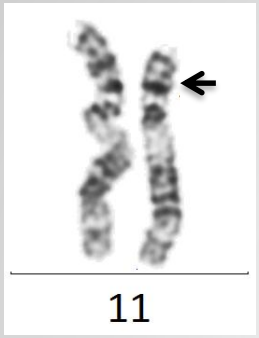
Structural abnormalities

(Abnormal is on the right)

Deletions



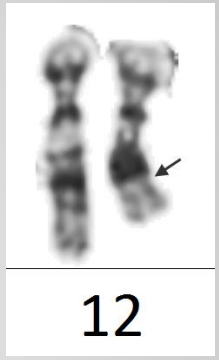
Terminal

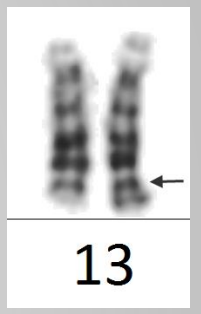


Interstitial

Duplications

Insertions



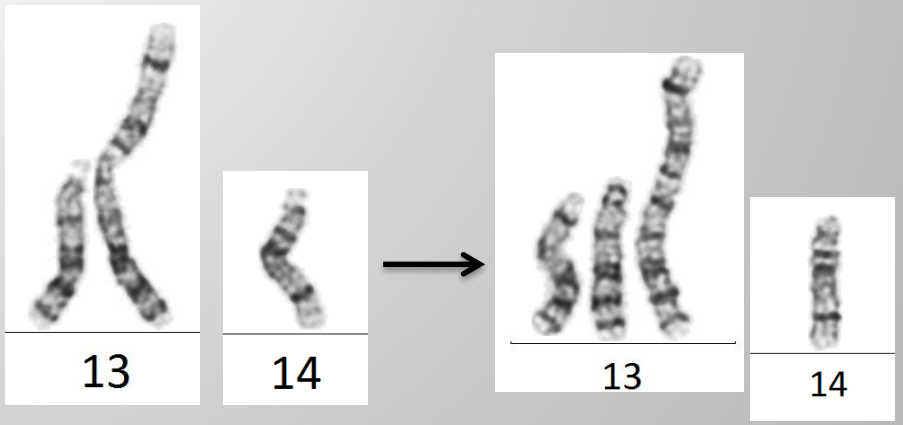


Reciprocal Translocations

Balanced

Unbalanced

Robertsonian Translocations



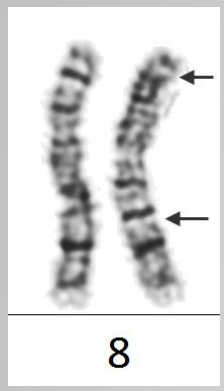
Balanced

Unbalanced

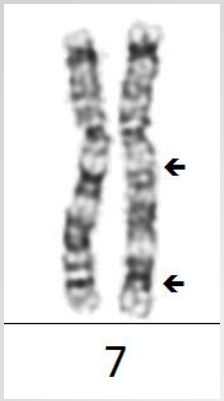
Structural abnormalities

(Abnormal is on the right)

Inversions

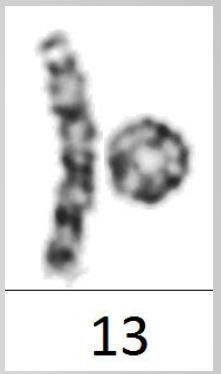


Pericentric inversion

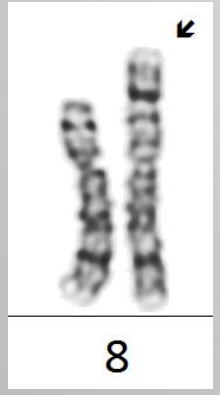


Paracentric inversion

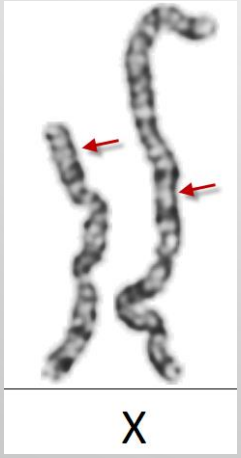
Ring chromosomes

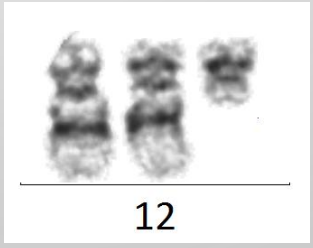


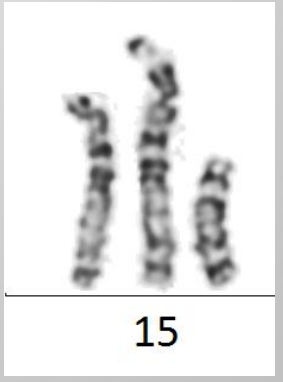
Recombinant chromosomes



Isochromosomes







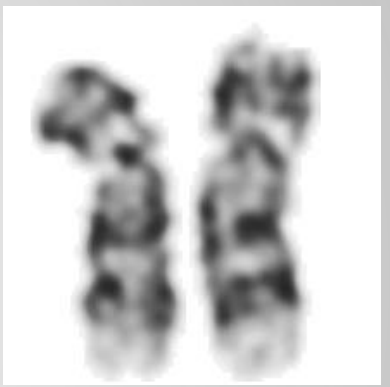
Normal variable chromosomal features/ Heteromorphisms

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

Variation in length (+ or -)

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

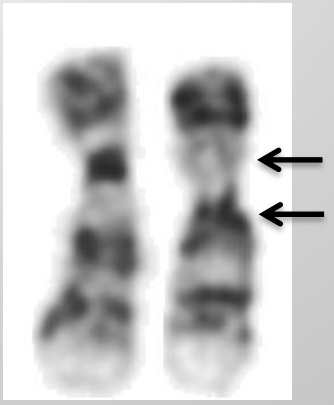
Normal 9's



Variation in position

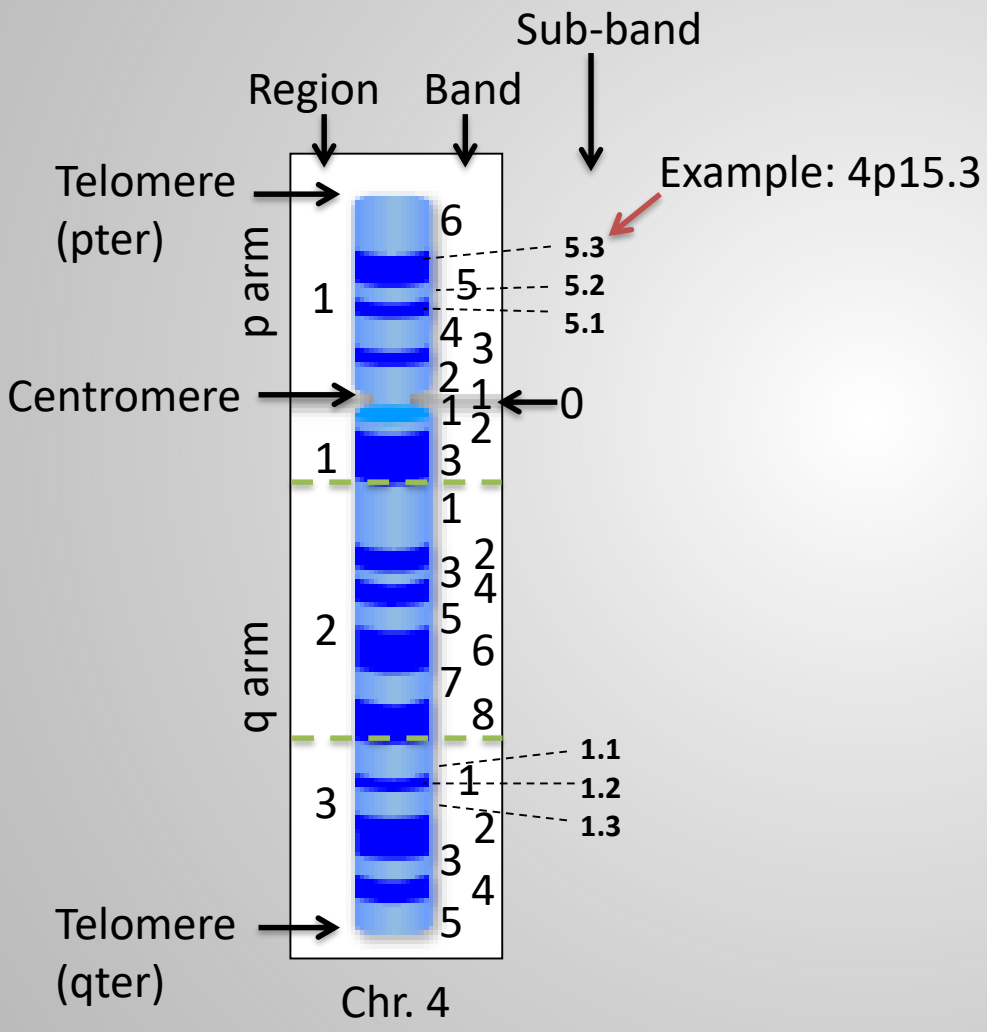
- inv(2)(p11.2q13)
- inv(9)(p12q13)
- Yqs

inv(9)(p12q13)

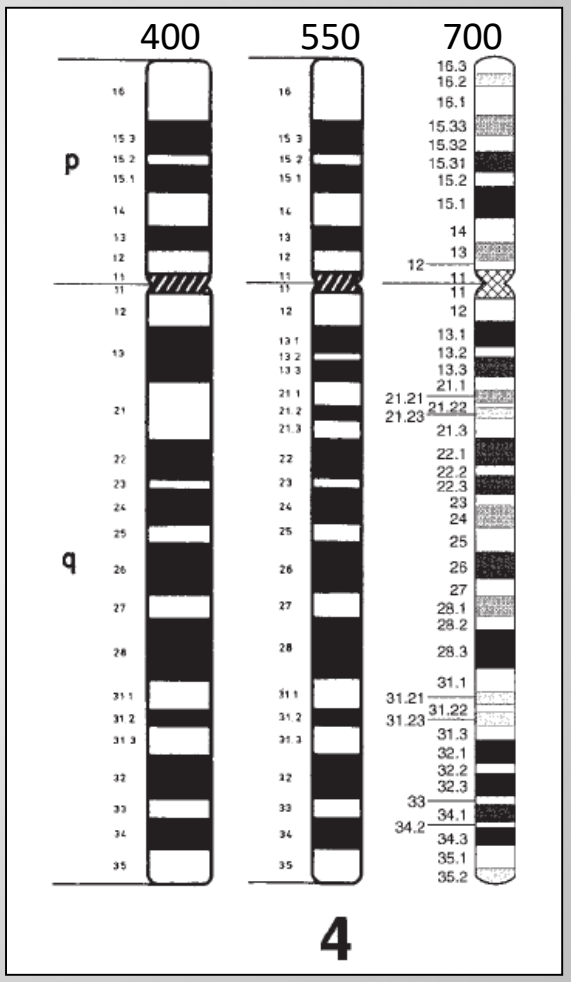


9qh-

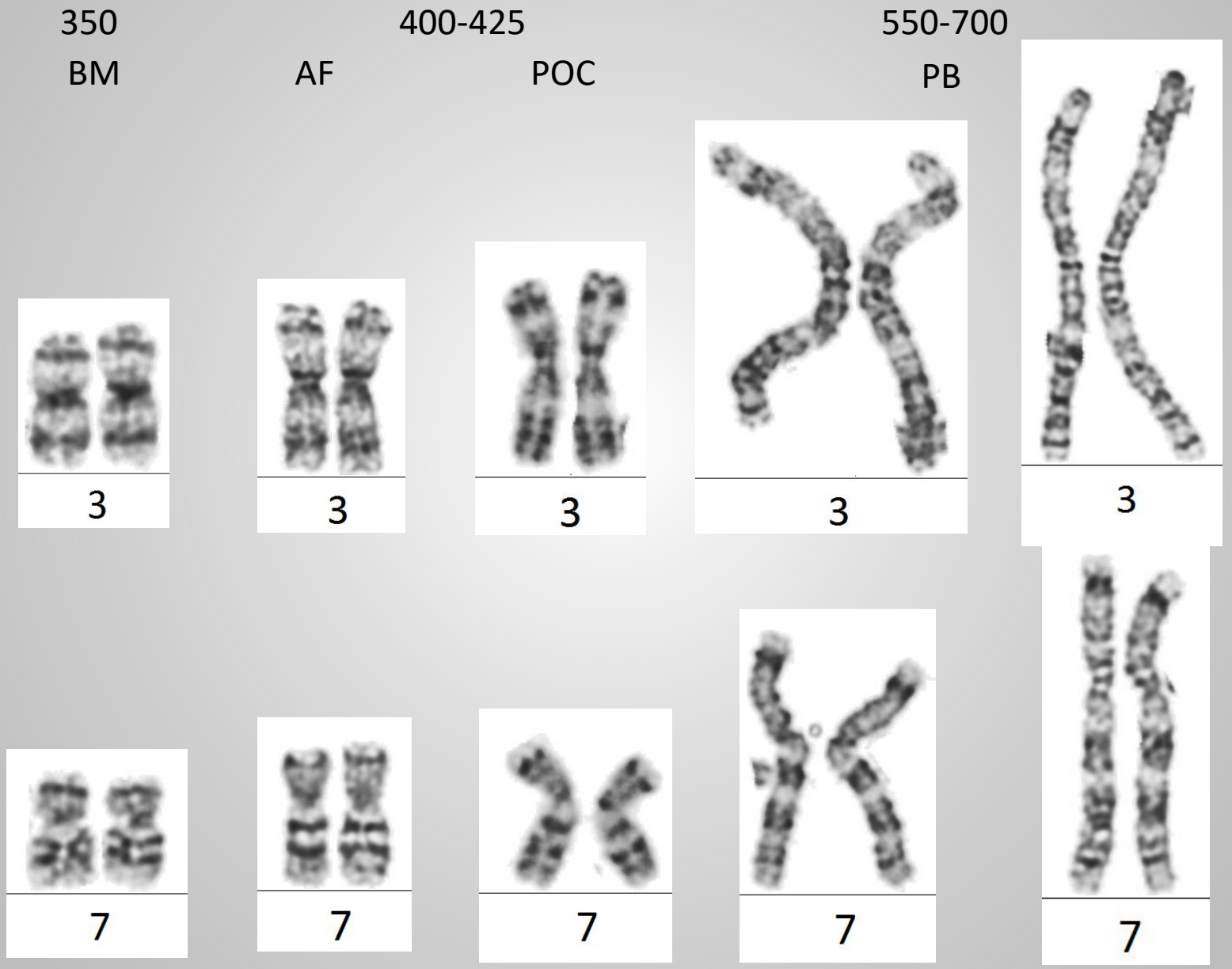
Designation of Regions, Bands, Sub-bands



Idiogram



Differences in level of resolution by sample type



Standard Nomenclature for Karyotype Designation

General designation includes:

- Chromosome number (count)-based on #centromeres
  - Expressed relative to the ploidy level
- Sex chromosome constitution
  - Use +/- for acquired sex chromosome aneuploidy only
- List of abnormalities present
  - Ordered by chromosome number (sex chromosomes, then autosomes 1-22) and abnormality type (numerical abnormalities/aneuploidies, then structural abnormalities, listed alphabetically and by arm/band, low to high)
- Multiple cell lines
  - Mosaicism: List abnormal clone(s) first, list multiple abnormal clones from largest to smallest in size
  - Chimerism: List recipient (individual's karyotype) first

Common symbols and abbreviated terms (constitutional studies)

+	additional normal or abnormal chromosome (trisomy)
-	loss of a chromosome (monosomy)
add	added material of unknown origin, typically resulting in a loss of material distal to breakpoint
del	deletion
der	derivative chromosome, due to structural rearrangement(s)
dic	dicentric chromosome
dup	duplication
dn	de novo (not inherited)
i	isochromosome (composed of two identical chromosome arms)
idic	isodicentric chromosome (isochromosome w/ two centromeres)
ins	insertion
inv	inversion
mar	marker chromosome, unknown origin
mat	maternal origin
mos	mosaic (multiple cell lines/clones present)
pat	paternal origin
r	ring chromosome
rob	Robertsonian translocation, a whole arm translocation between acrocentric chromosomes
t	translocation
/	separates clones (for mosaic karyotypes)
//	separates clones (for chimeric karyotypes)
[ ]	indicate number of cells (for mosaic or chimeric karyotypes)

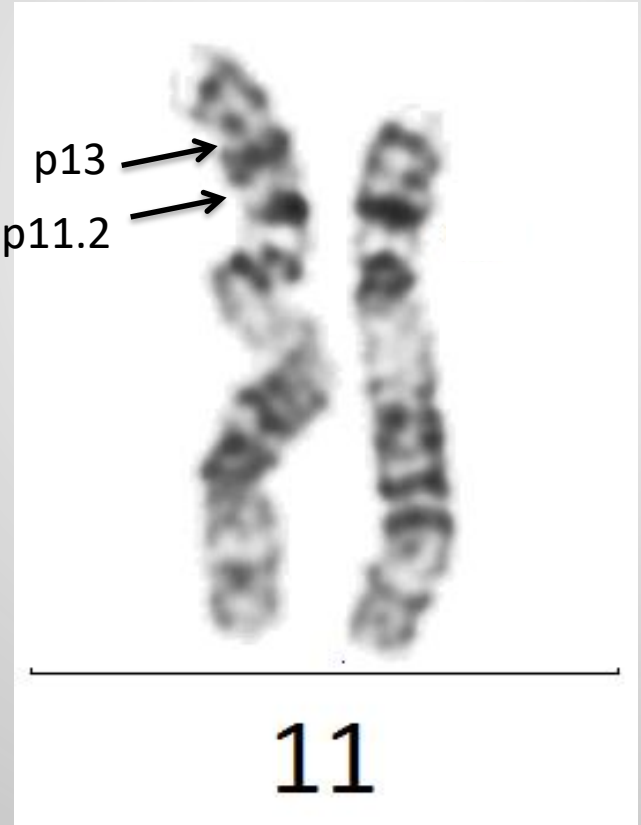
Structural Abnormalities Description (Illustrated by Examples)

- Terminal vs interstitial
  - add(11)(q23)
  - del(4)(p16.3)
  - dup(17)(p11.2p13)
- Interchromosomal vs intrachromosomal
  - t(9;22)(q34;q11.2)
  - inv(3)(q21q26.2)
  - ins(2)(q13p11.2p14)
- 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]

Nomenclature Practice:
Structural Abnormalities

Abnormal, constitutional

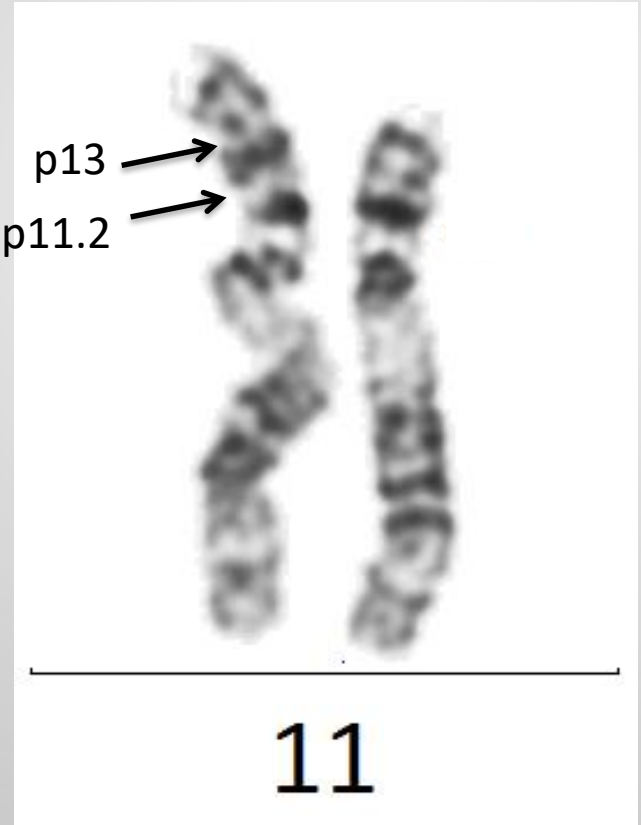
Female



Abnormal, constitutional

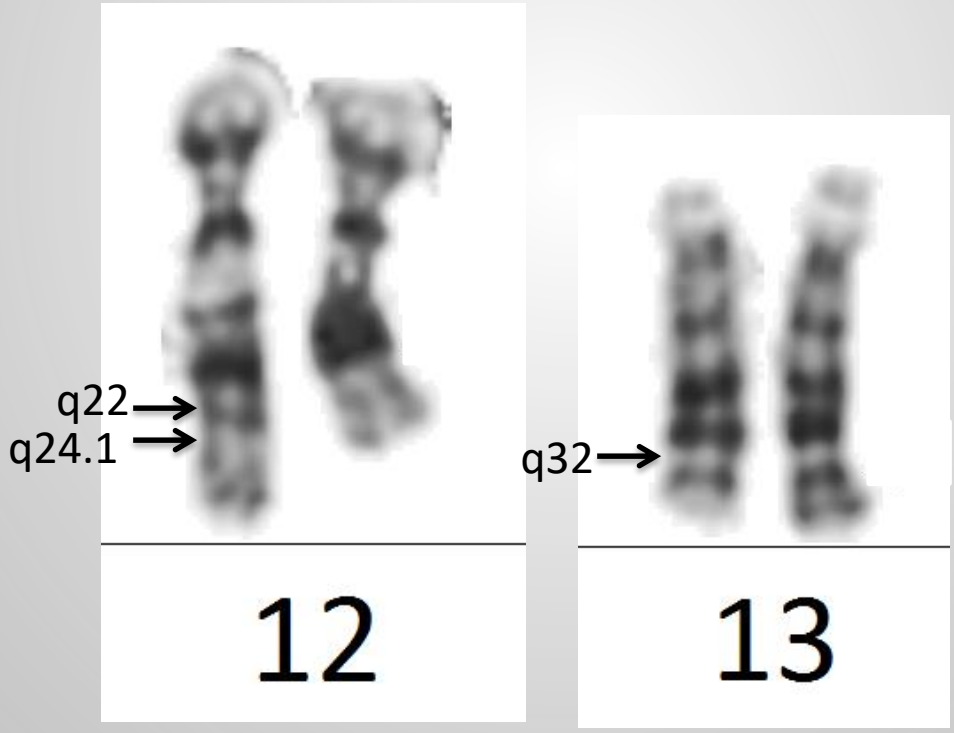
46,XX,del(11)(p11.2p13)

Female



Abnormal, constitutional

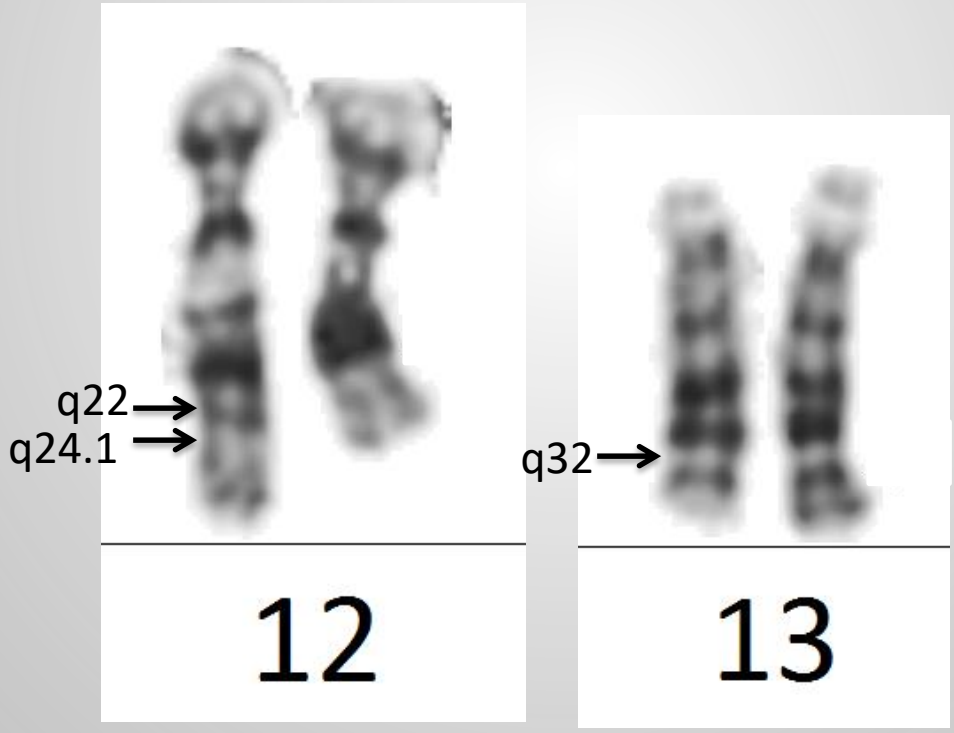
Male with Klinefelter syndrome



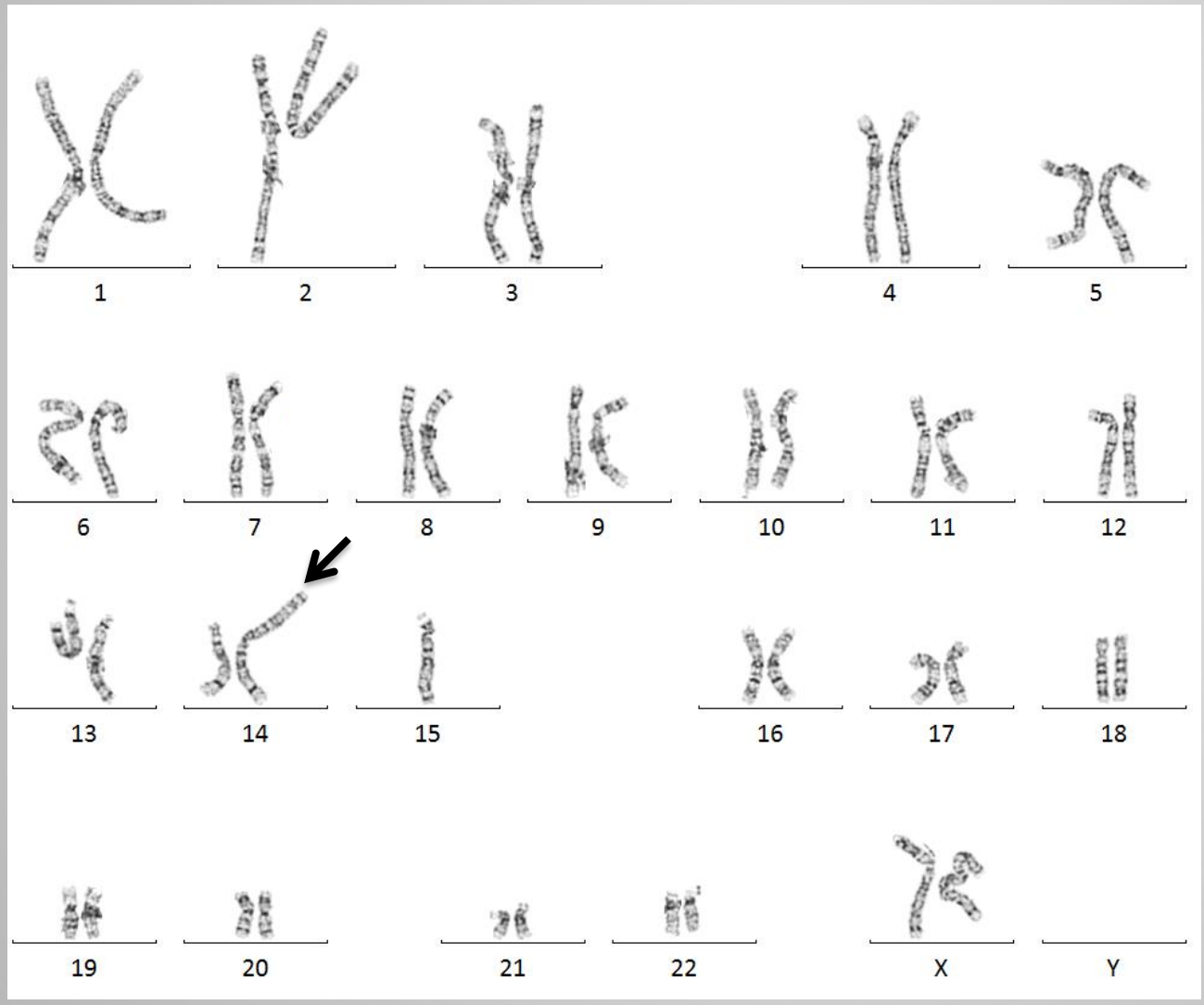
Abnormal, constitutional

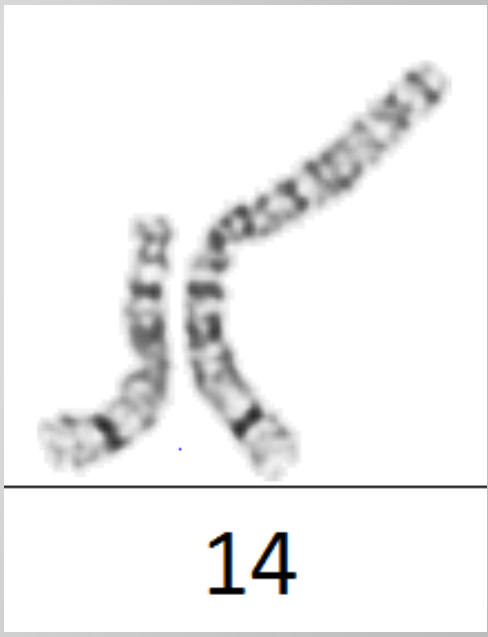
47,XXY,ins(13;12)(q32;q22q24.1)

Male with Klinefelter syndrome



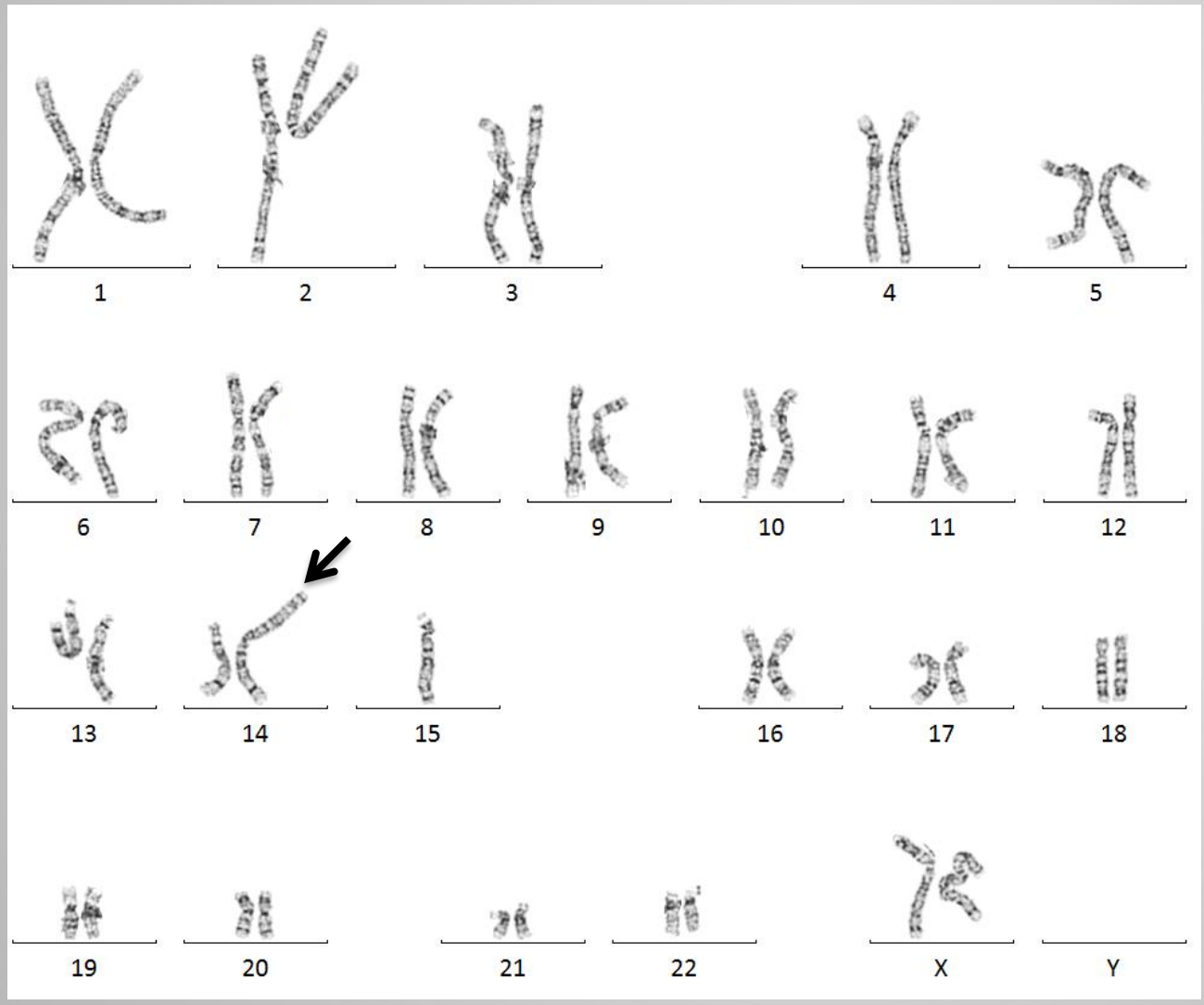
Abnormal, constitutional

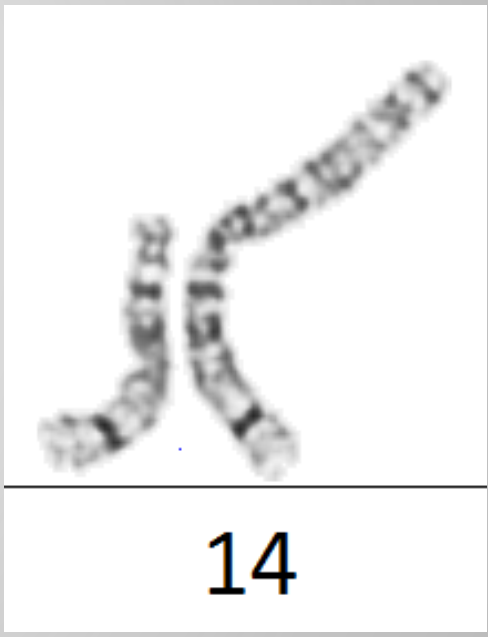




Abnormal, constitutional

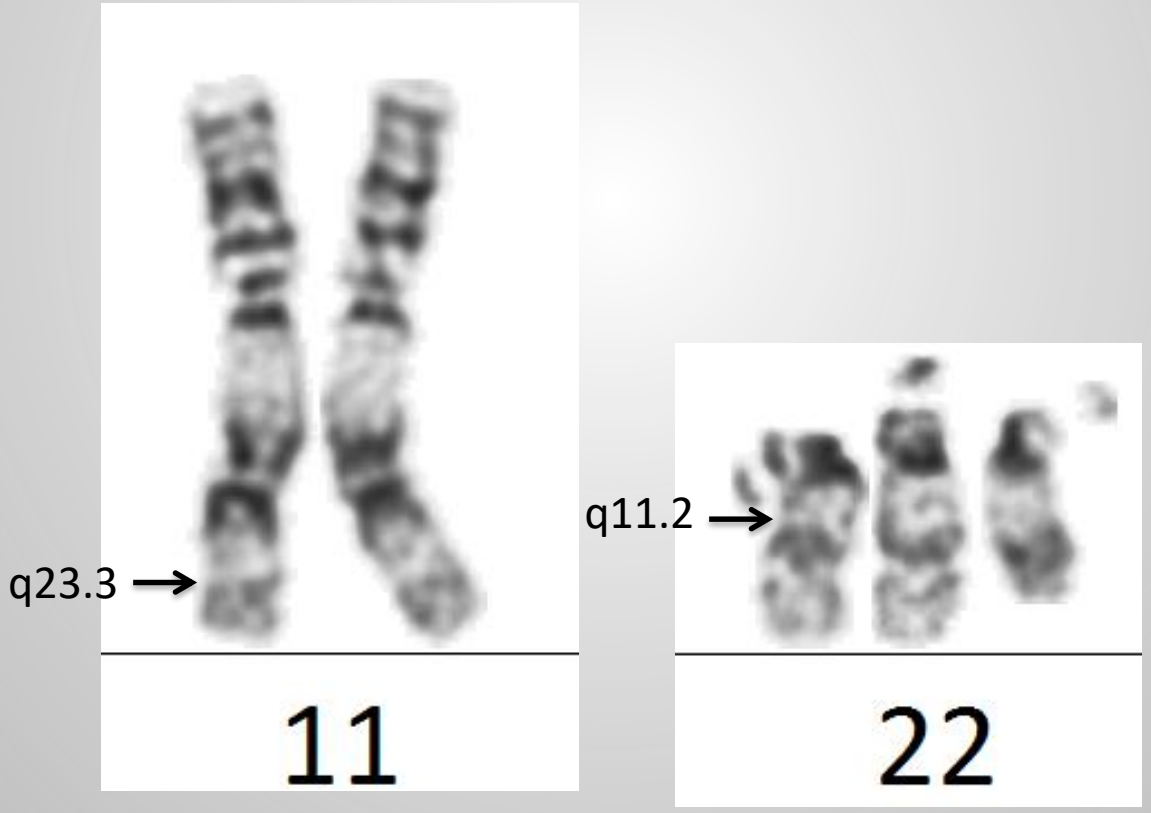
45,XX,rob(14;15)(q10;q10)





Abnormal, constitutional

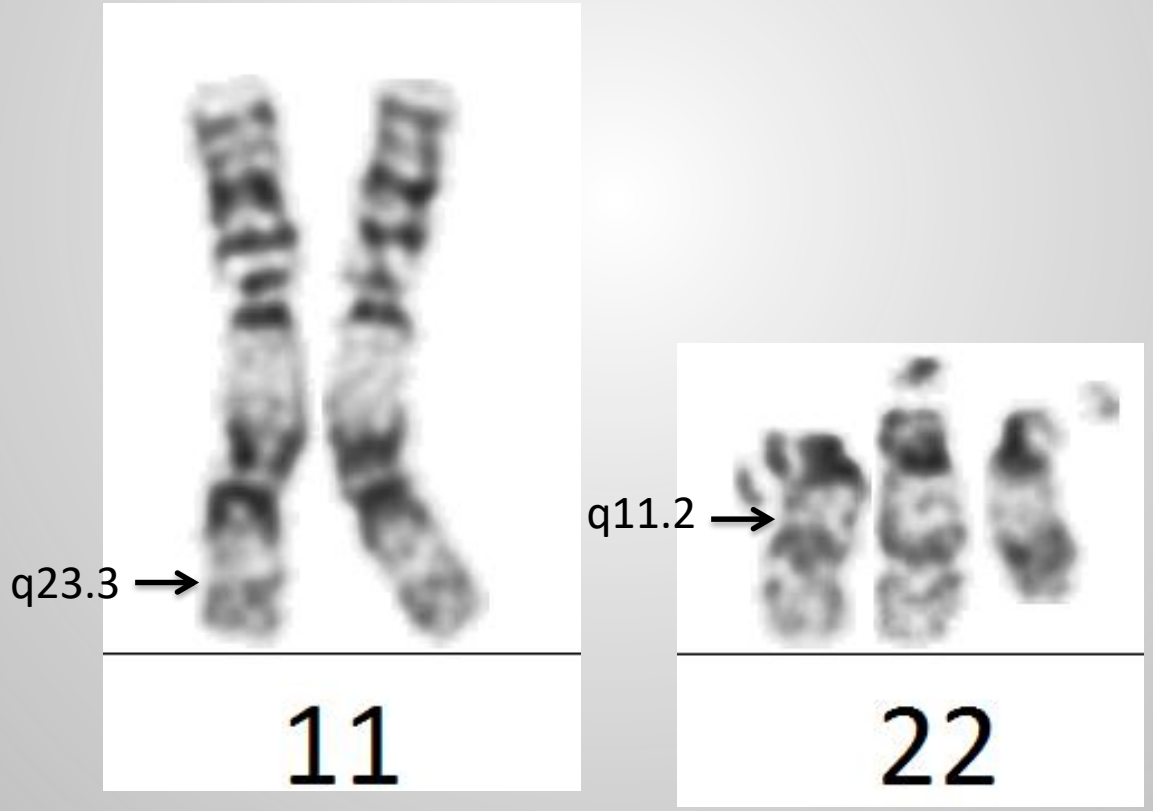
Female



Abnormal, constitutional

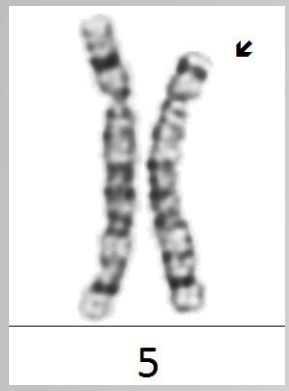
47,XX,+der(22)t(11;22)(q23.3;q11.2)

Female

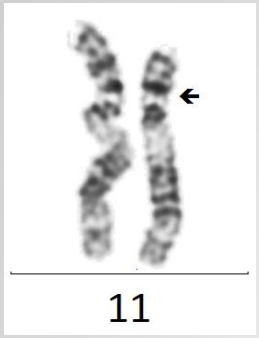


Structural abnormalities

Deletions



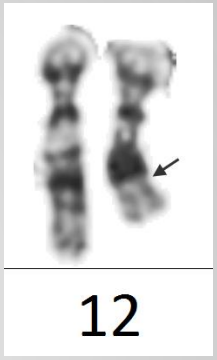
Terminal

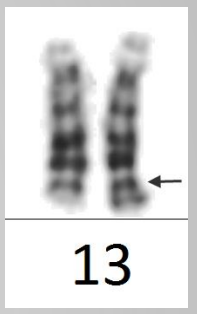


Interstitial

Duplications

Insertions



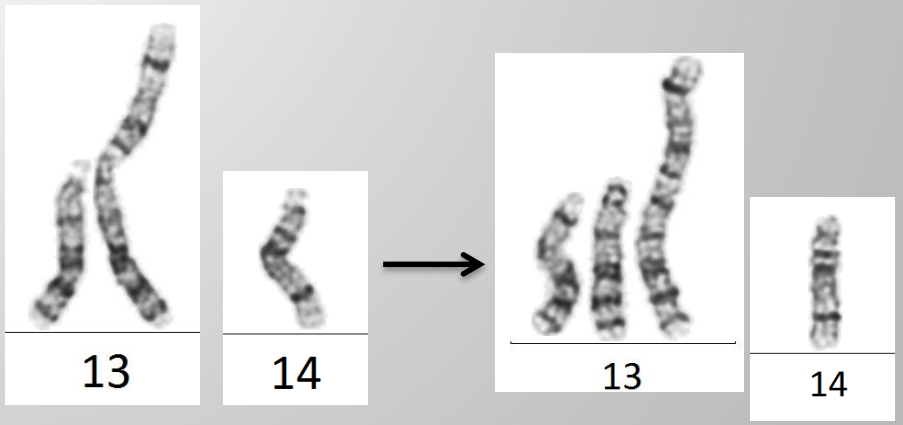


Reciprocal Translocations

Balanced

Unbalanced

Robertsonian Translocations



Balanced

Unbalanced

Some recurrent deletions and duplications

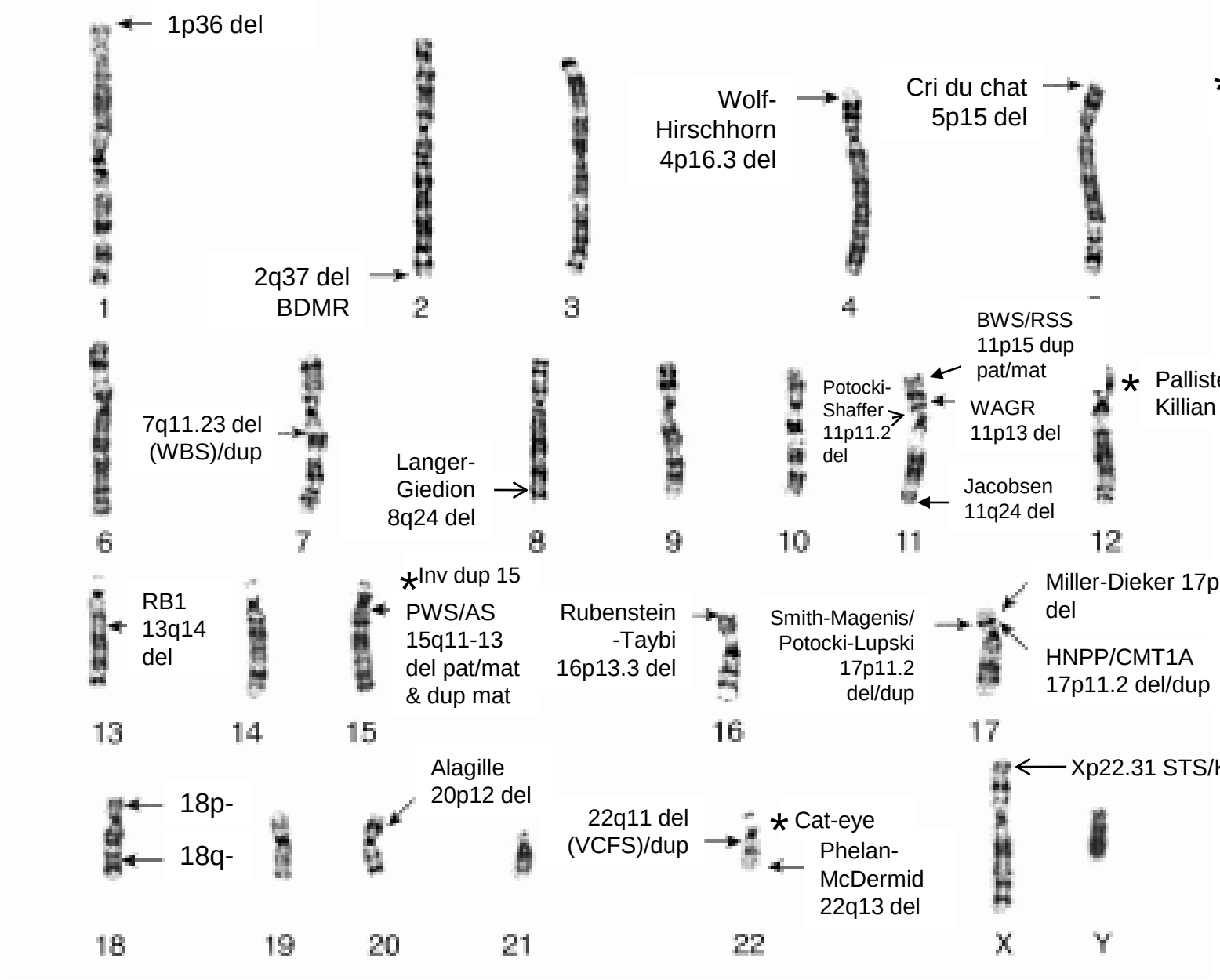
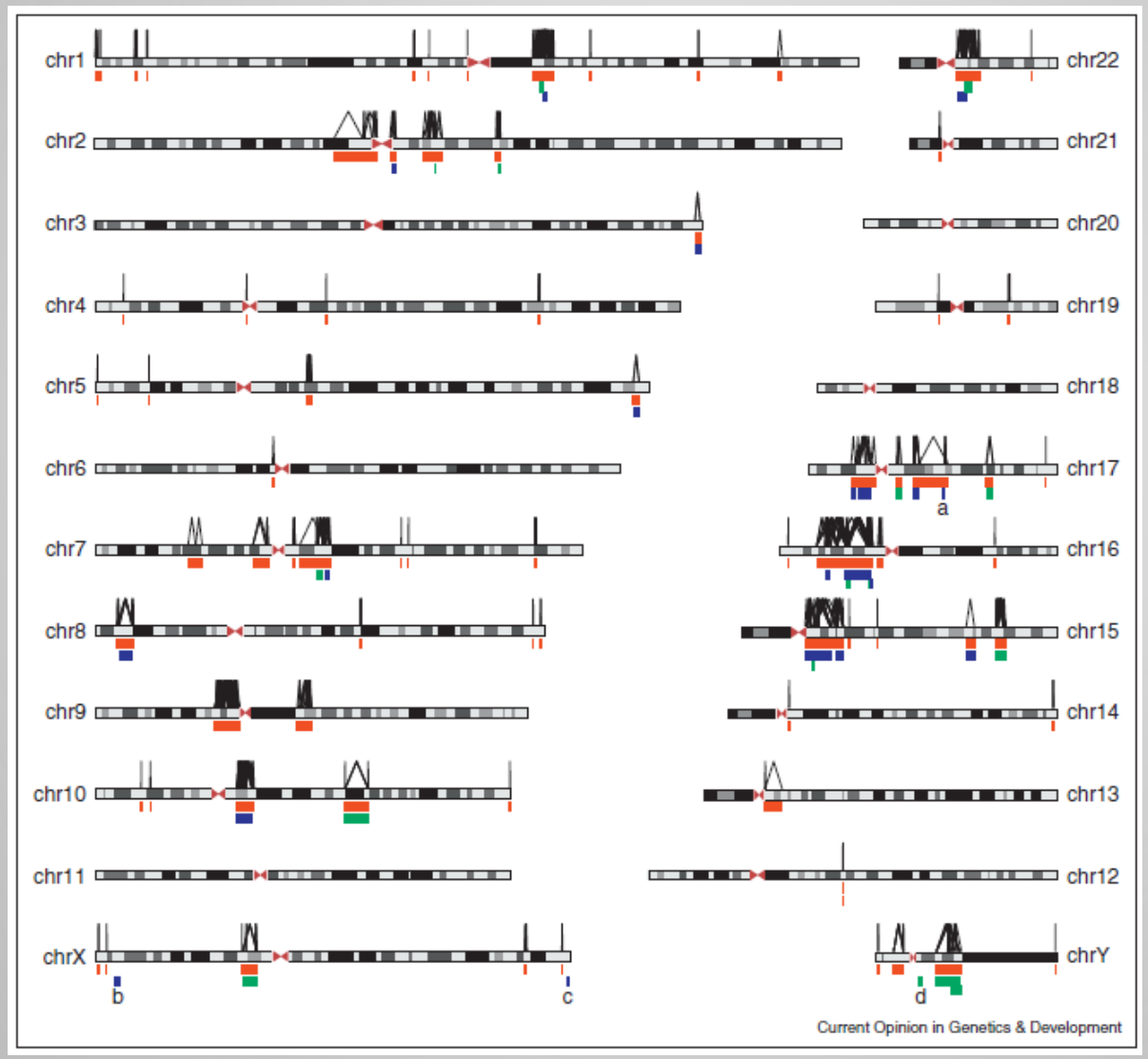


Image modified from Gardner, Sutherland and Shaffer Chromosome Abnormalities and Genetic Counseling 4th ed (2011)

Incidence of Recurrent Deletion and Duplication Syndromes

Syndrome	Incidence	Cause
1p36 deletion	1:7500	Terminal deletion
1q21.1 deletion (distal)	1:500	Interstitial deletion (SD)
4p-/Wolf-Hirschhorn	1:50,000	Terminal deletion
5p-/Cri du chat	1:50,000	Terminal deletion
7q11.23/Williams	1:7500	Interstitial deletion (SD)
15q11q13/Prader willi	1:20,000	Interstitial deletion (pat)/mUPD/Me defect/mutation
22q11.2/DiGeorge/VCFS	1:5000	Interstitial deletion (SD)

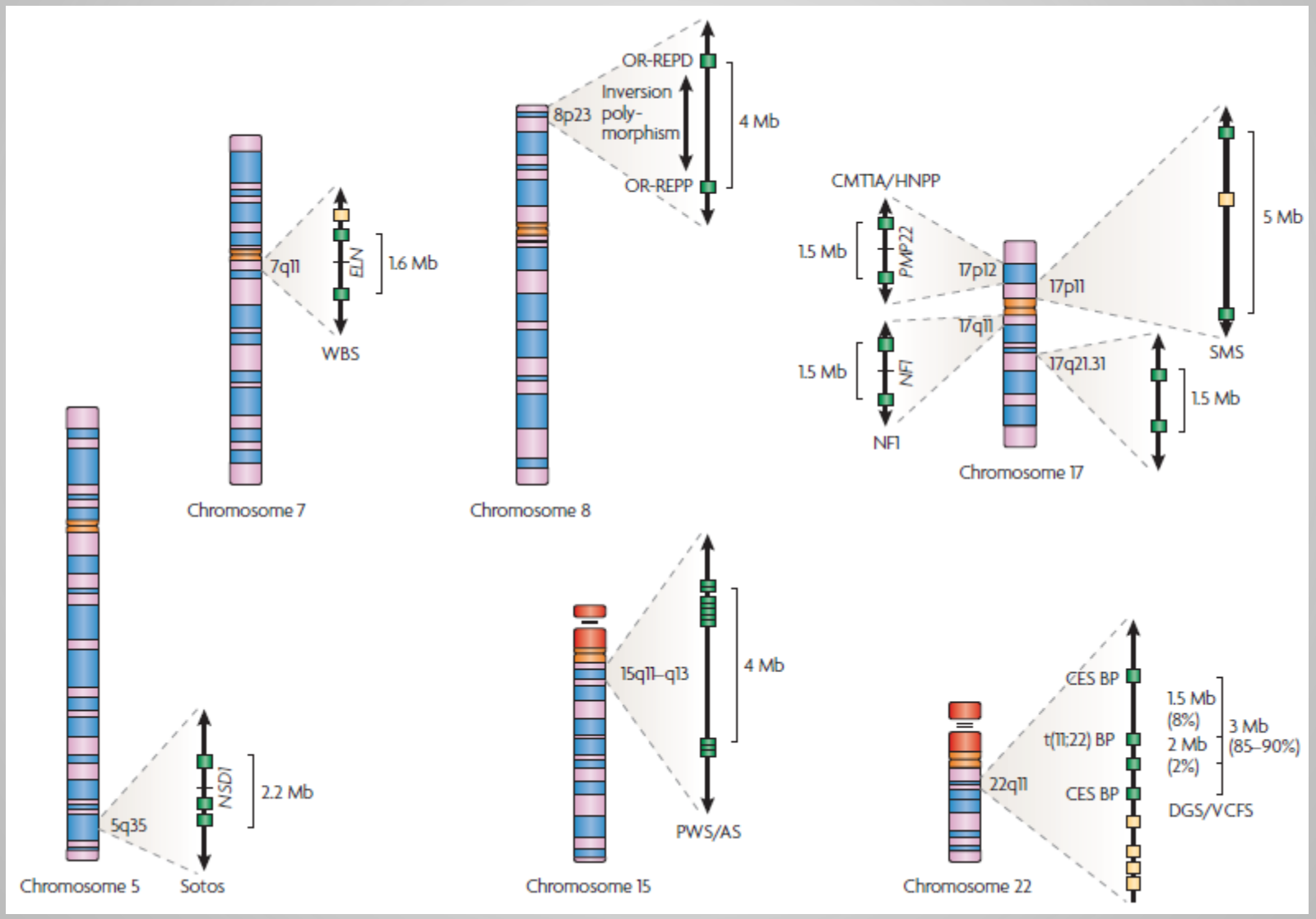
Low copy repeats (LCRs) mediate many recurrent genomic rearrangements via NAHR



Key
NAHR-prone regions
Deletion disorders
Del/dup disorders

Liu et al, 2012

Segmental duplication (low-copy repeat, LCR) architecture mediates recurrent CNVs/rearrangements



Emanuel and Saitta, Nat Rev Genet 2007

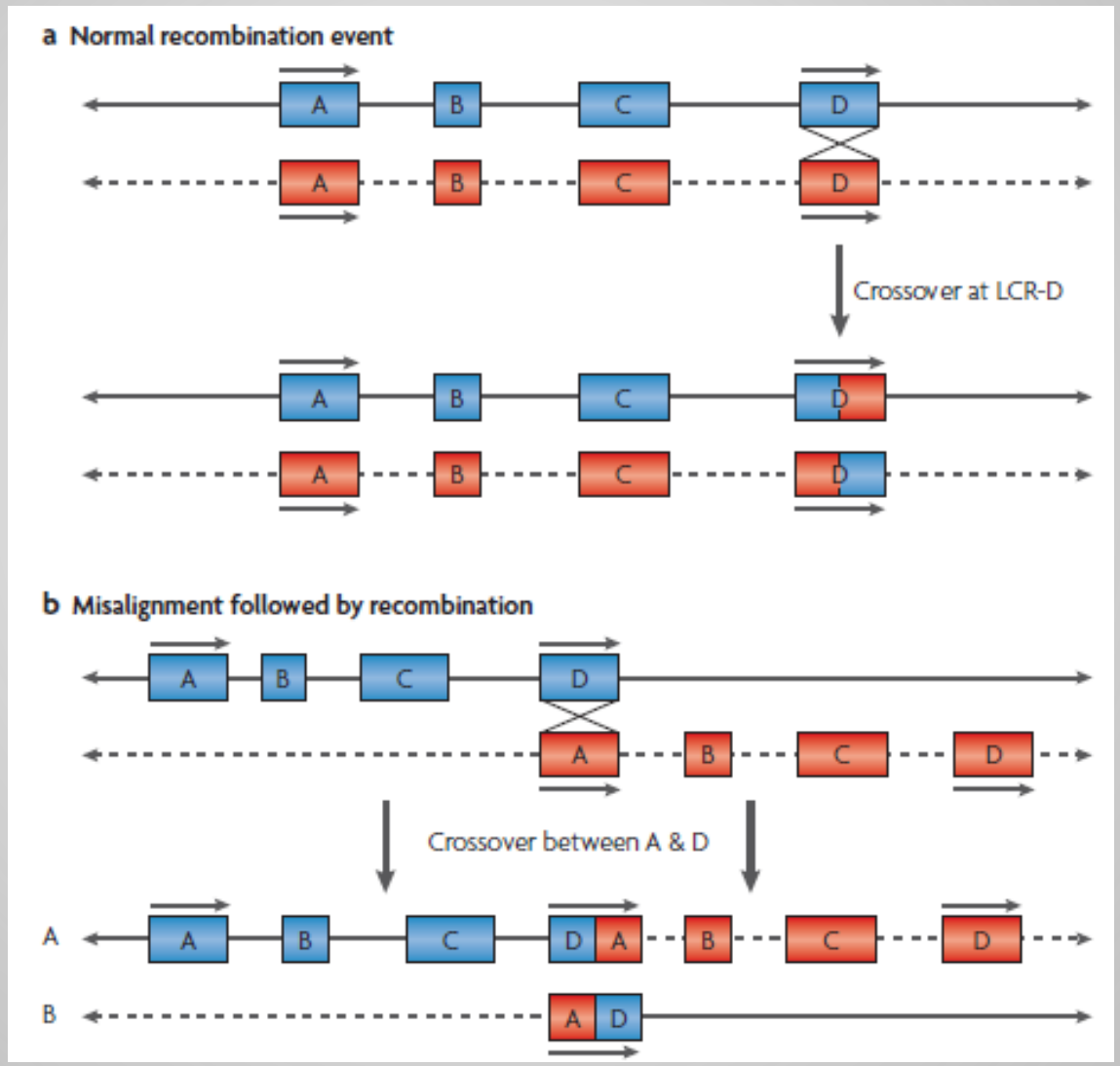
NAHR: misalignment and exchange occurs between non-allelic homologous sequences (LCRs)

DxD=allelic HR

Balanced recombinants

DxA=non-allelic HR

Unbalanced recombinants

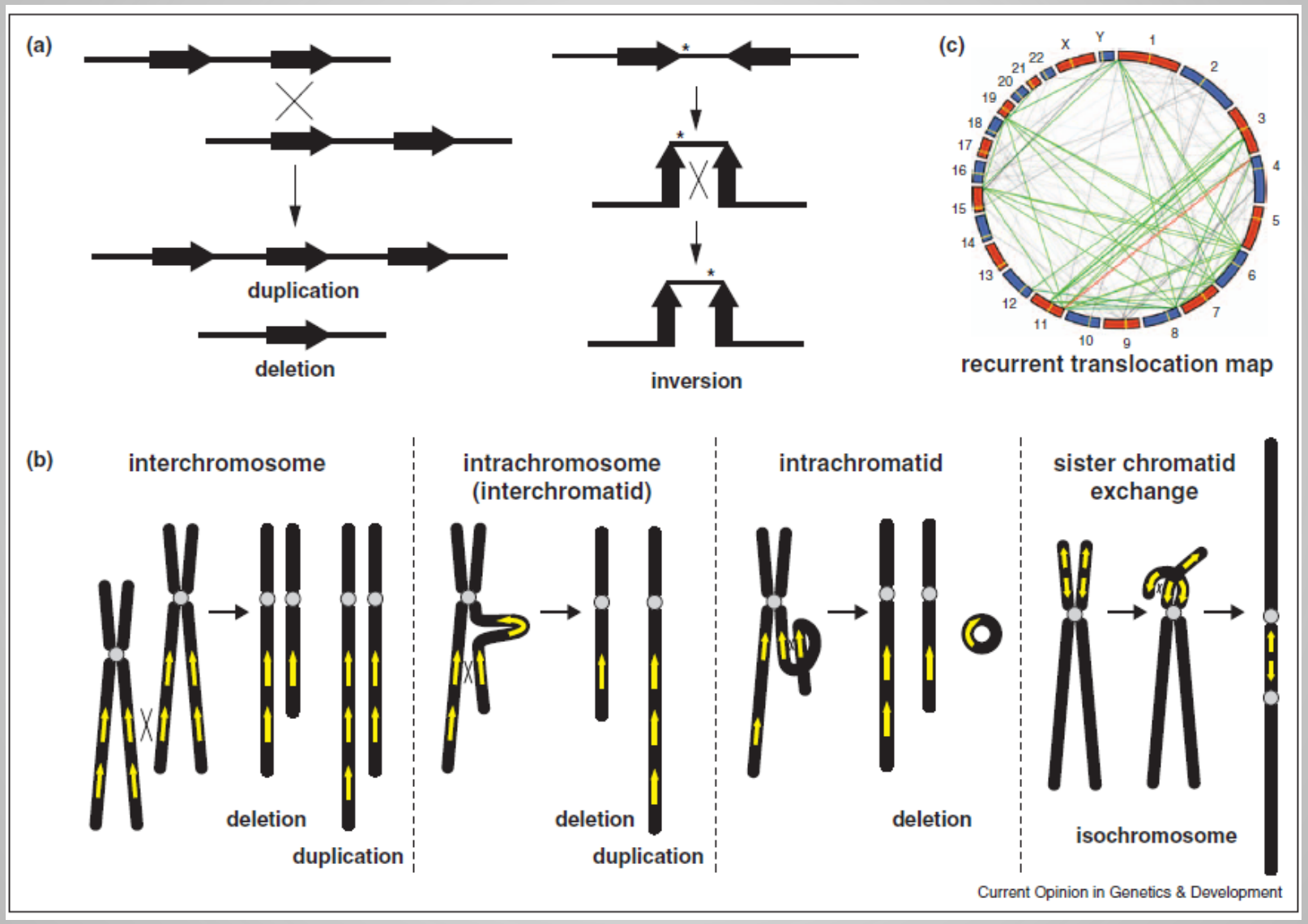


Duplicated

Deleted

Emanuel and Saitta, Nat Rev Genet 2007

NAHR underlies many recurrent genomic rearrangements



Liu et al., 2012

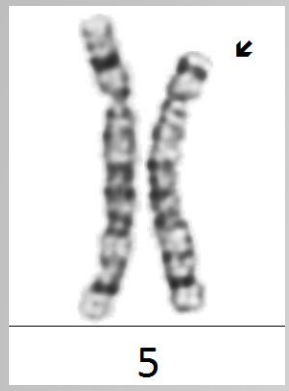
Multiple techniques are employed for the detection of different cytogenetic abnormalities

Technique	Resolution	Sensitivity (mosaicism)	Culturing required?	Global?	Unbalanced abs?	Balanced abs? Structural info?
G-banded chromosomes	3-5 Mb (550 bands)	10-15%	Yes	Yes	Yes	Yes
Metaphase FISH	100's kb	n/a	Yes	No	Yes	Yes
Interphase FISH	100's kb	1-5%	No	No	Yes	Yes
GMA	10-100's kb	10-20%	No	Yes	Yes	No

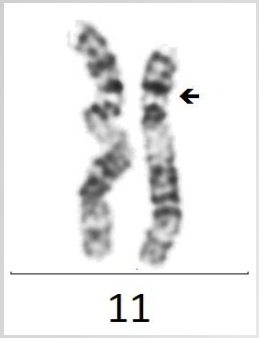
- Sizes: kb=$1x10^3$, Mb=$1x10^6$

Structural abnormalities

Deletions



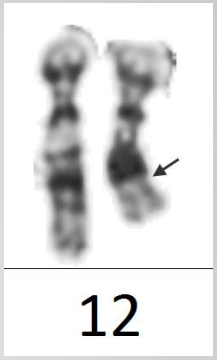
Terminal

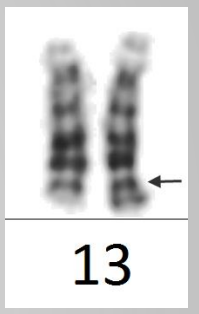


Interstitial

Duplications

Insertions



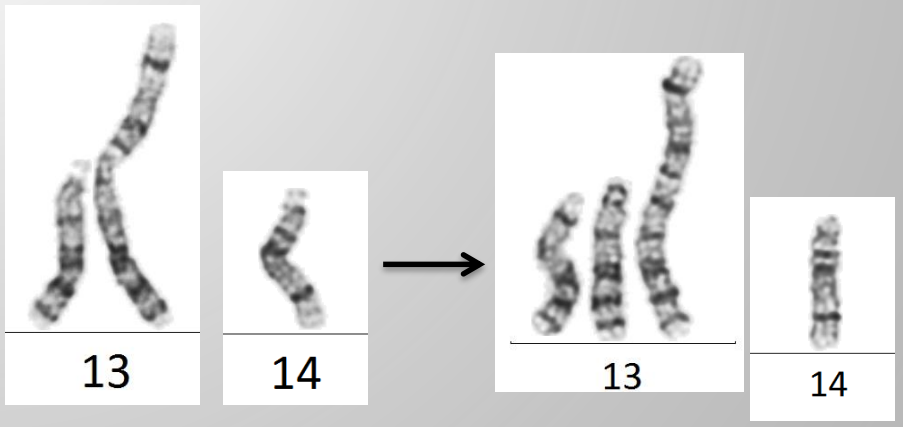


Reciprocal Translocations

Balanced

Unbalanced

Robertsonian Translocations



Balanced

Unbalanced

Incidence of chromosome abnormalities detected in newborns

Abnormality	Rate/1000	Rate (1/n)
Autosomal Trisomy	**1.62**	**617**
Sex Chromosome Aneuploidies (All)	**2.70**	**375**
Balanced Structural Rearrangements	**2.04**	**490**
Translocations, insertions	0.97	1,028
Inversions	0.16	6,331
Robertsonians	0.91	1,099
Unbalanced Structural Rearrangements	**0.63**	**1,587**
Translocations, insertions, inversions	0.09	10,935
Robertsonians	0.07	13,366
Deletions, rings	0.06	17,184
+Markers (e.g. isochromosomes)	0.41	2,455

Data from: Milunsky and Milunsky, Genetic Disorders of the Fetus, 6th Ed. (2010). Benn, Chp. 6

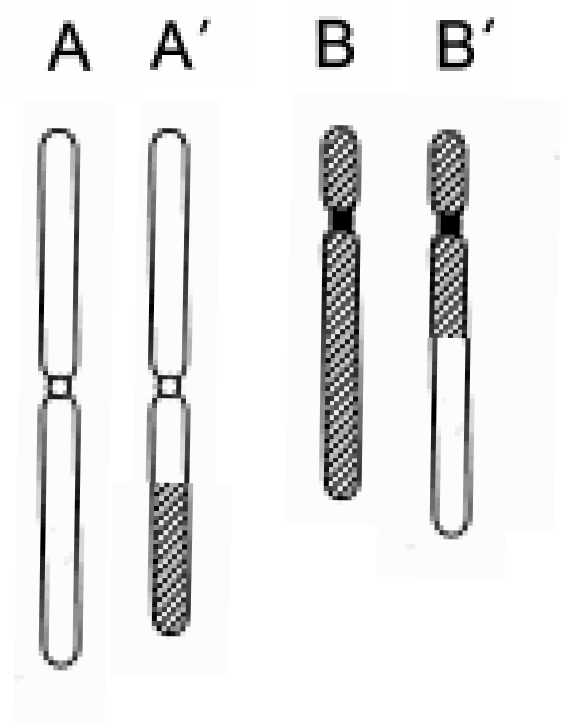
- ~1/500 is a carrier of a balanced rearrangement

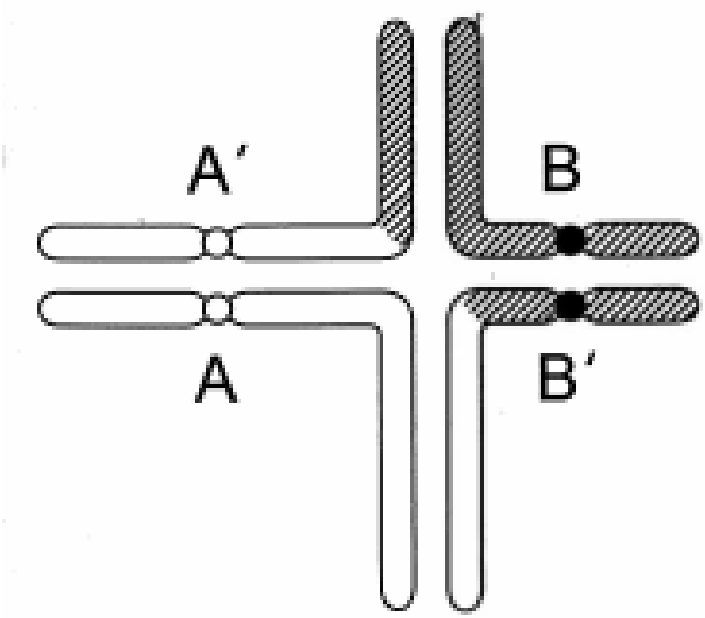
Effects of Translocations

- 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)
- May disrupt gene expression (breakpoint within a gene or regulatory element by position effect)
  - In prenatal setting and de novo, risk ~6% (Warburton '91)
- Create gene fusions and affect gene expression by position effect
  - Esp. in cancer ex. t(9;22) BCR-ABL1 chimeric transcript or t(11;14) CCND1 upregulation by translocation near the IGH locus regulatory region

Pachytene configuration (quadrivalent) in the balanced translocation carrier/translocation heterozygote

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



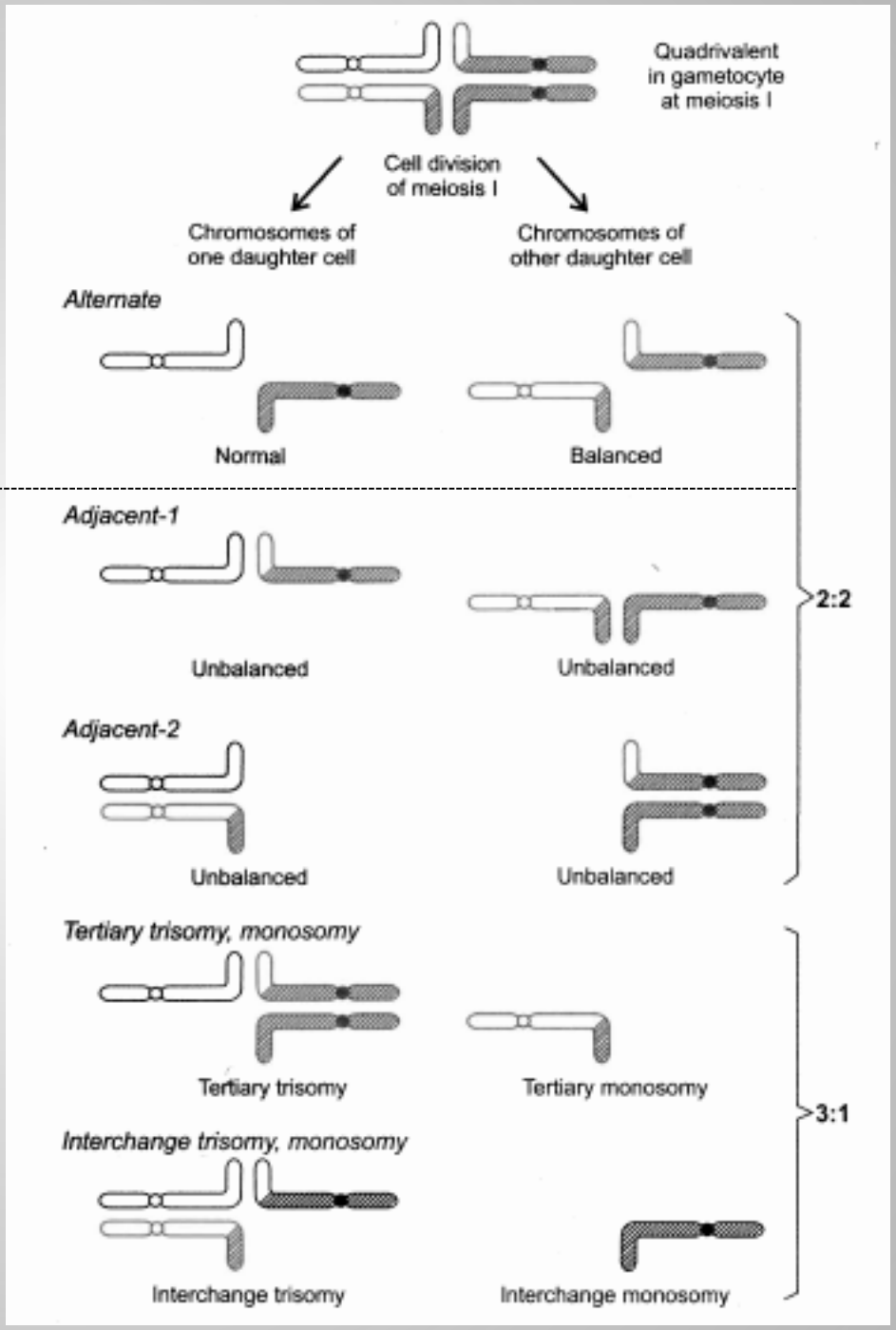


Gardner, Sutherland and Shaffer. 2012

Modes of Segregation During Gametogenesis 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

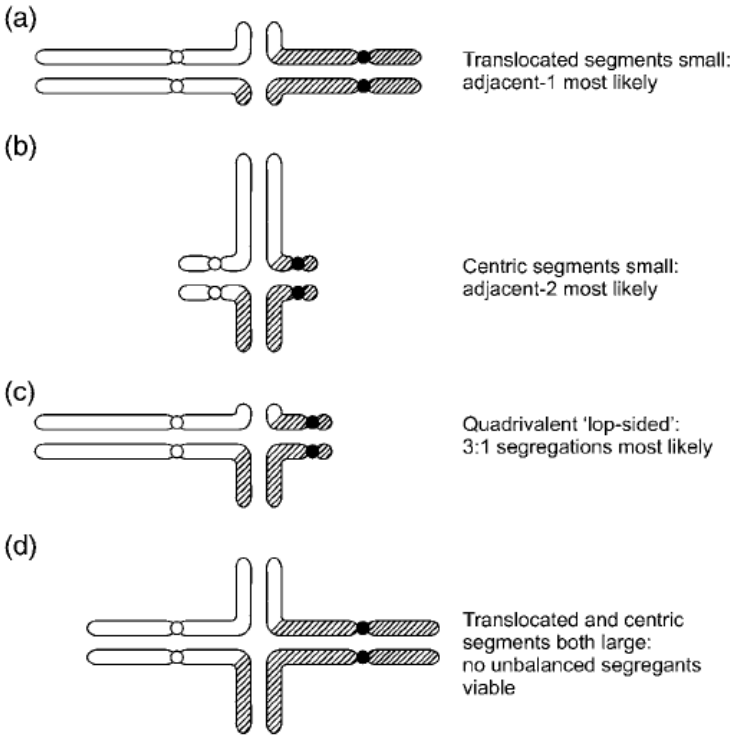


FIGURE 5–5 Prediction of likely viable segregant outcomes by pachytene diagram drawing and assessment of the configuration of the quadrivalent.

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

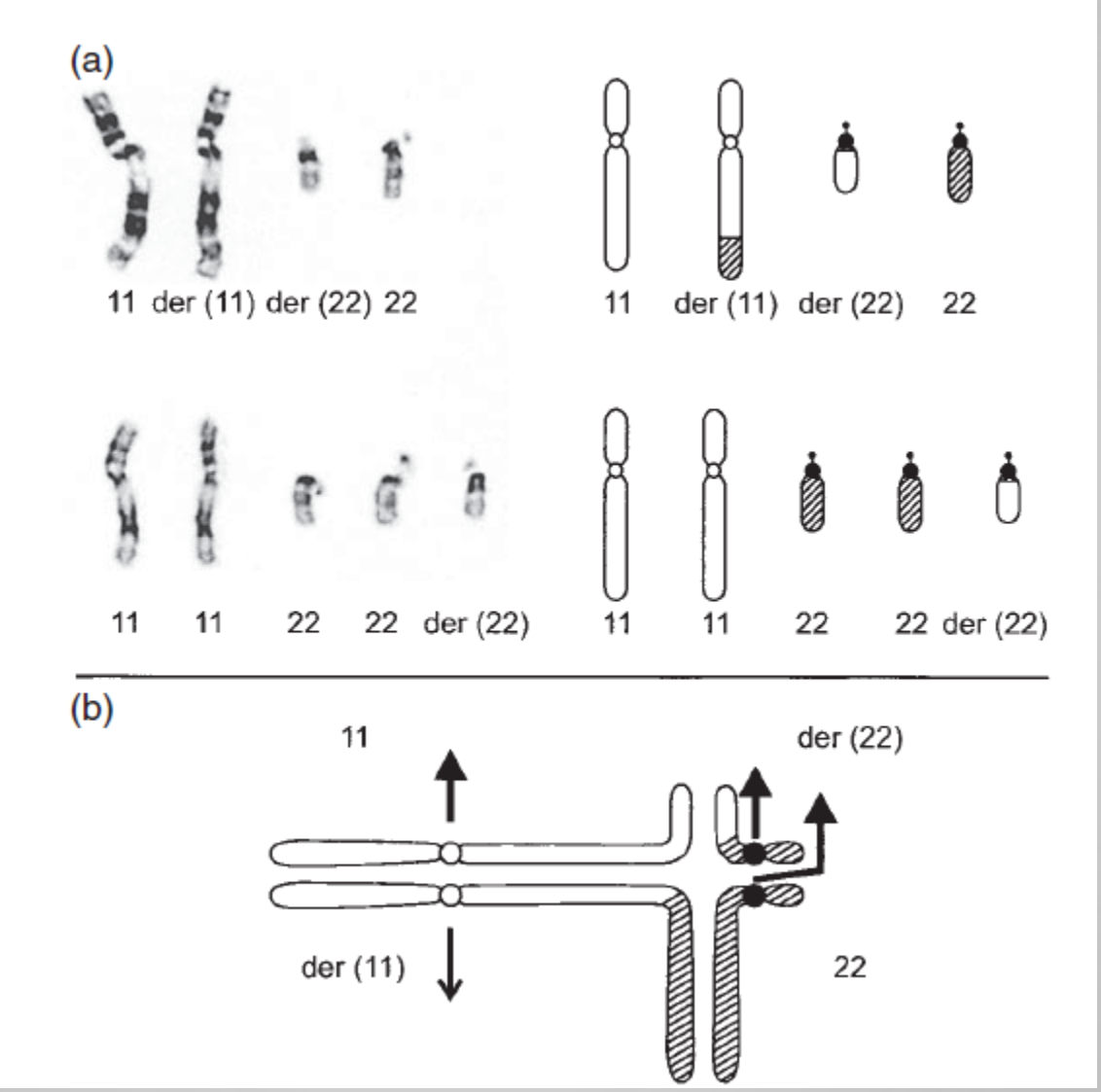
Gardner, Sutherland and Shaffer. 2012

Tertiary trisomy in the t(11;22)(q23;q11) carrier

46,t(11;22)

47,+der(22),t(11;22)
(Emanuel syndrome)

Tertiary trisomy
3:1 segregation



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
- Biological consequence of associated monosomy/trisomy
  - Least imbalanced, least monosomic is most likely to produce a viable conceptus

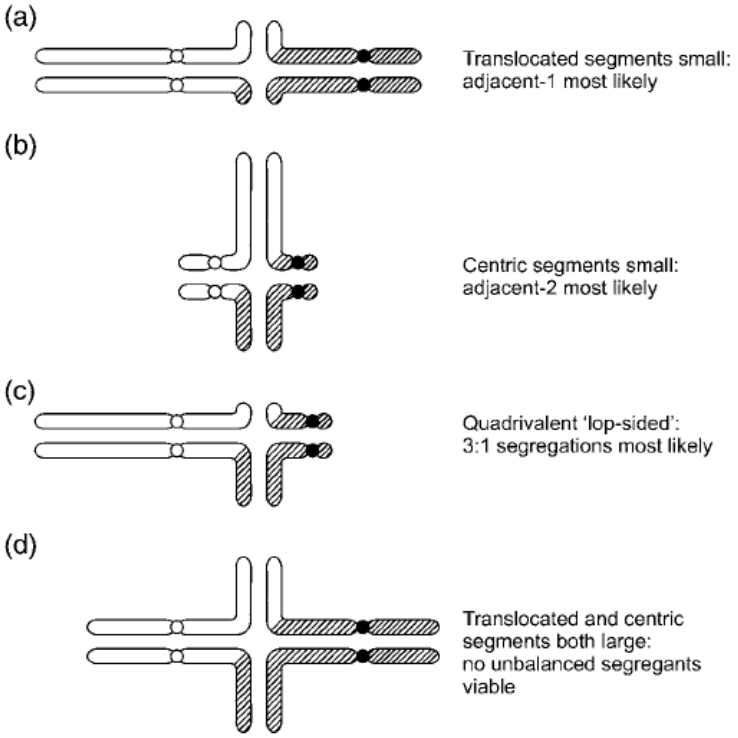


FIGURE 5–5 Prediction of likely viable segregant outcomes by pachytene diagram drawing and assessment of the configuration of the quadrivalent.

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

Gardner, Sutherland and Shaffer. 2012

Pedigree of a family carrying a translocation with a large centric segment

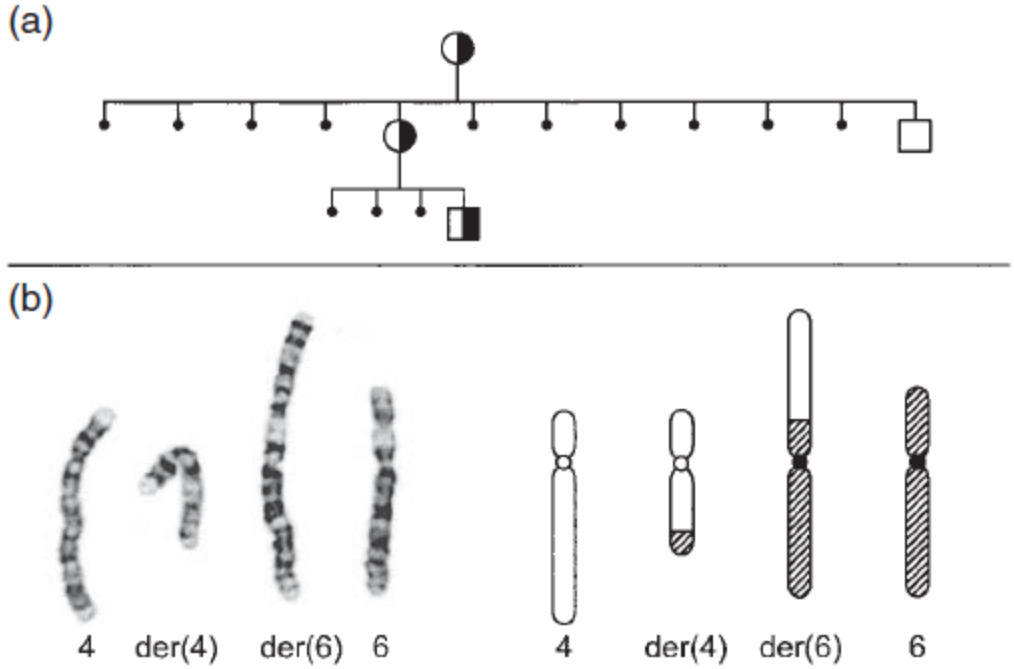
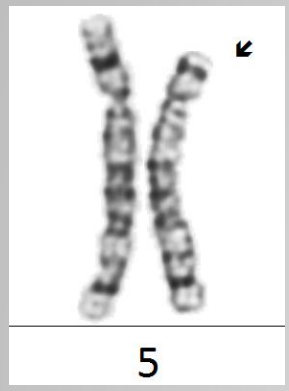


FIGURE 5–16 No unbalanced product viable. (*a*) Pedigree of a kindred in which mother and daughter have had multiple miscarriages, each having (*b*) the karyotype 46,XX,t(4;6)(q25;p23). (Case of A. J. Watt.) The presumed pachytene configuration during gametogenesis in the heterozygote would be as in Figure 5–5d (chromosome 4 chromatin, open; chromosome 6 chromatin, crosshatched) and, with large centric and translocated segments, the translocation has none of the features that enable viability of any unbalanced segregant combination.

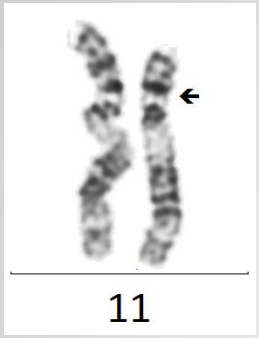
Gardner, Sutherland and Shaffer. 2012

Structural abnormalities

Deletions



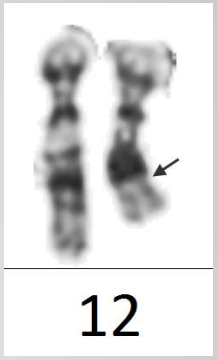
Terminal

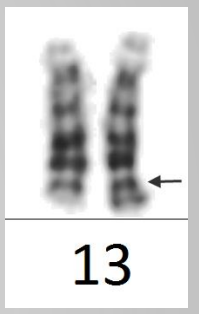


Interstitial

Duplications

Insertions



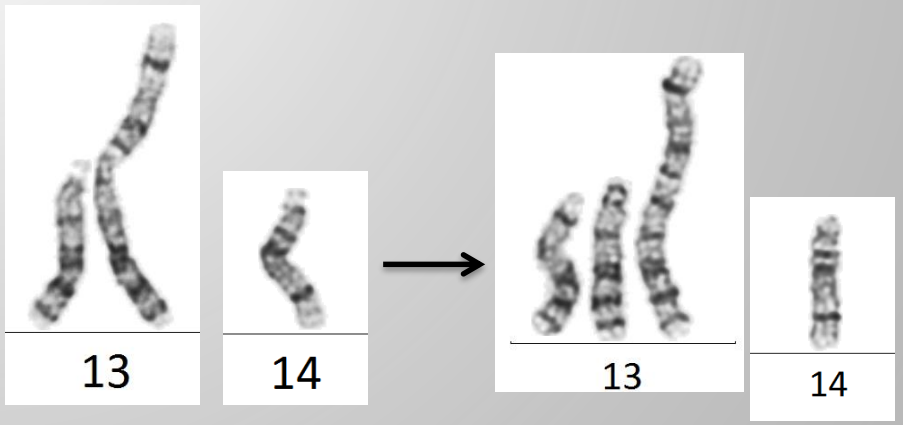


Reciprocal Translocations

Balanced

Unbalanced

Robertsonian Translocations



Balanced

Unbalanced

Robertsonian translocations

- Frequency ~1/1000, 95% are nonhomologous
  - rob(13;14) is most common (1:1300)
- Homology and orientation of sequences in p-arm stalks of chrs 13, 14 and 21 likely explain relative prevalence of rob(13;14) and rob(14;21) amongst carriers (via NAHR)

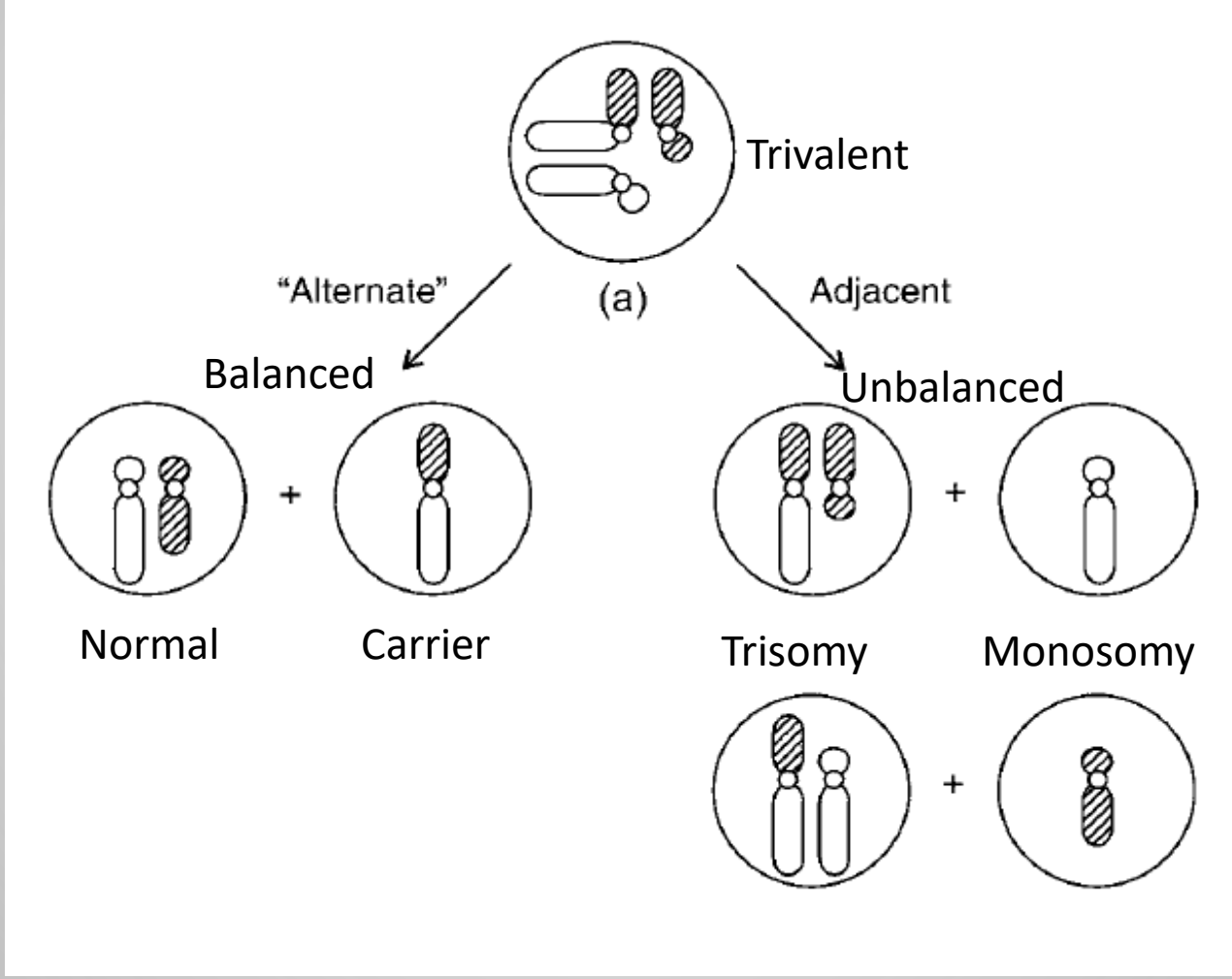
Table 7–1. The Frequency of Robertsonian Translocations

TRANSLOCATION	LITERATURE REVIEW	UNBIASED ASCERTAINMENT
13q13q	3%	2%
13q14q	33%	74%
13q15q	2%	2%
13q21q	2%	1%
13q22q	1%	2%
14q14q	½%	–
14q15q	2%	5%
14q21q	30%	8%
14q22q	1%	2%
15q15q	2%	–
15q21q	3%	½%
15q22q	½%	1%
21q21q*	17%	3%
21q22q	2%	½%
22q22q	1%	–

Gardner, Sutherland and Shaffer. 2012

Robertsonian translocations: Meiotic segregation

Gametes



Modified from Gardner, Sutherland and Shaffer. 2012

Imprinted chromosomes and human disease due to uniparental disomy (UPD)

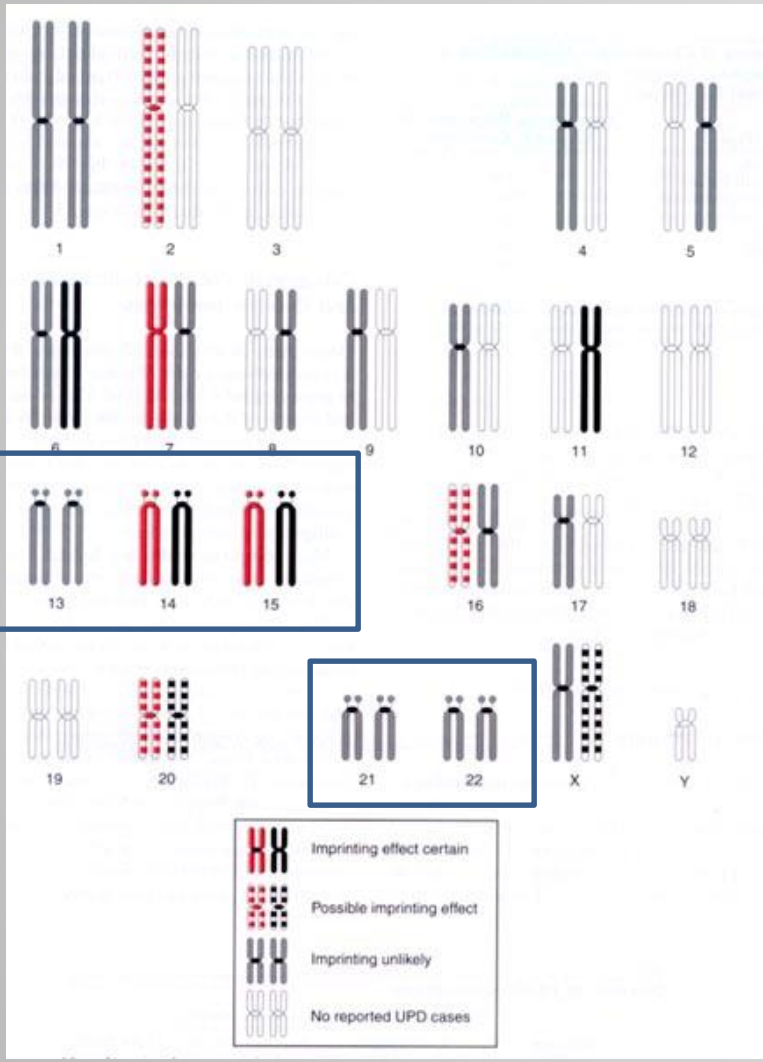


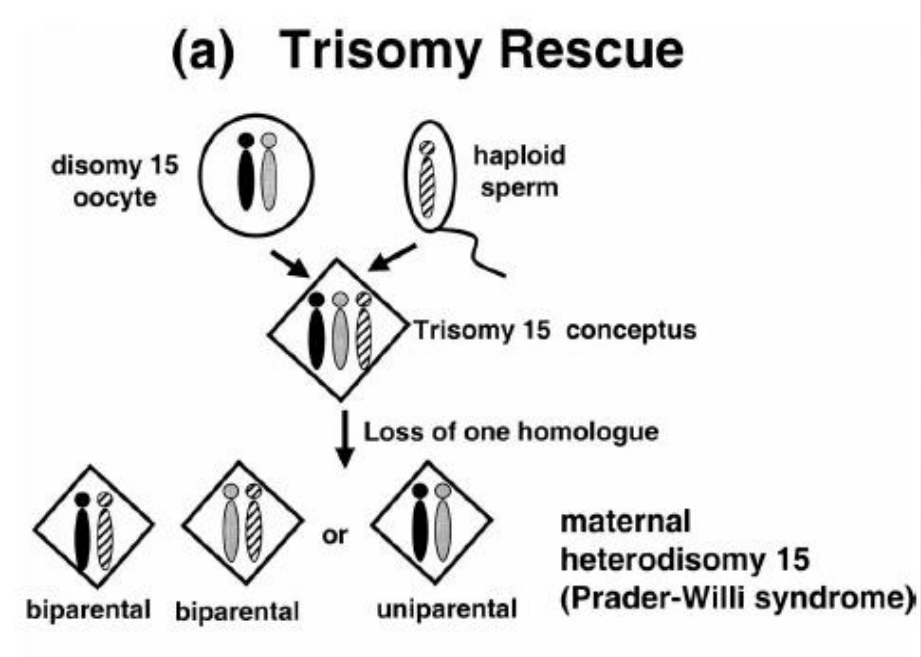
Image from: http://carolguze.com/text/442-10-nontraditional_inheritance.shtml

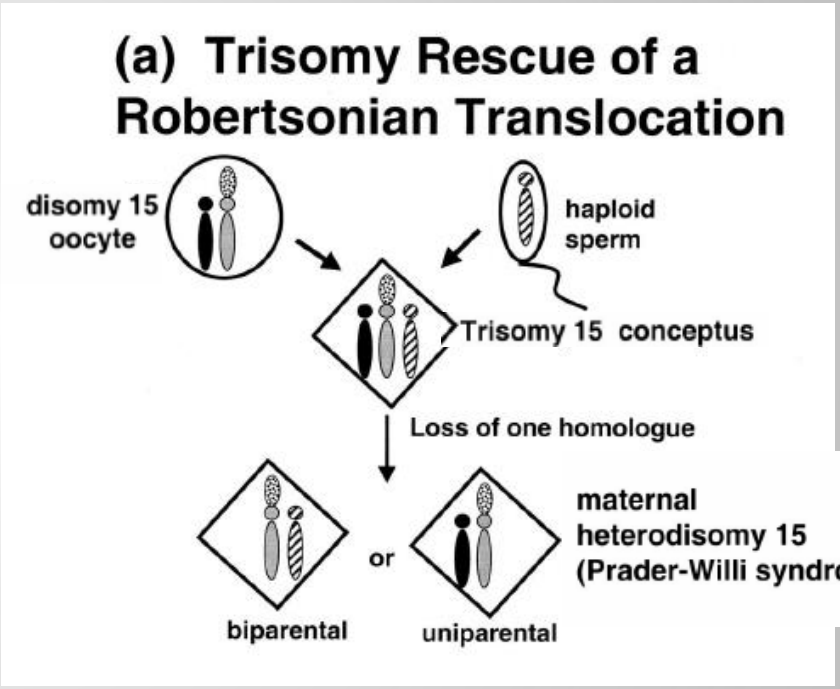
Chromosome UPD and Inheritance	Associated Genetic Disease or Abnormalities
Paternal UPD 6	Transient neonatal diabetes mellitus
Maternal UPD 7	Silver-Russell syndrome
Paternal UPD 11	Beckwith-Wiedemann syndrome
Maternal UPD 14	Hypotonia, motor development delay, mild dysmorphic facial features, low birth weight, growth abnormalities
Paternal UPD 14	Severe mental and muscoskeletal abnormalities
Maternal UPD 15	Prader-Willi syndrome
Paternal UPD 15	Angelman syndrome
Maternal UPD 16	Intrauterine growth retardation
Maternal UPD 20	Intrauterine growth retardation and/or postnatal growth retardation

Velissariou, Balkan J Med Gen

Risk for uniparental disomy (UPD)

- Risk for expression of clinical phenotype if rob chromosome contains imprinting genes (differentially expressed genes based on parent of origin) (chrs. 14 and 15)



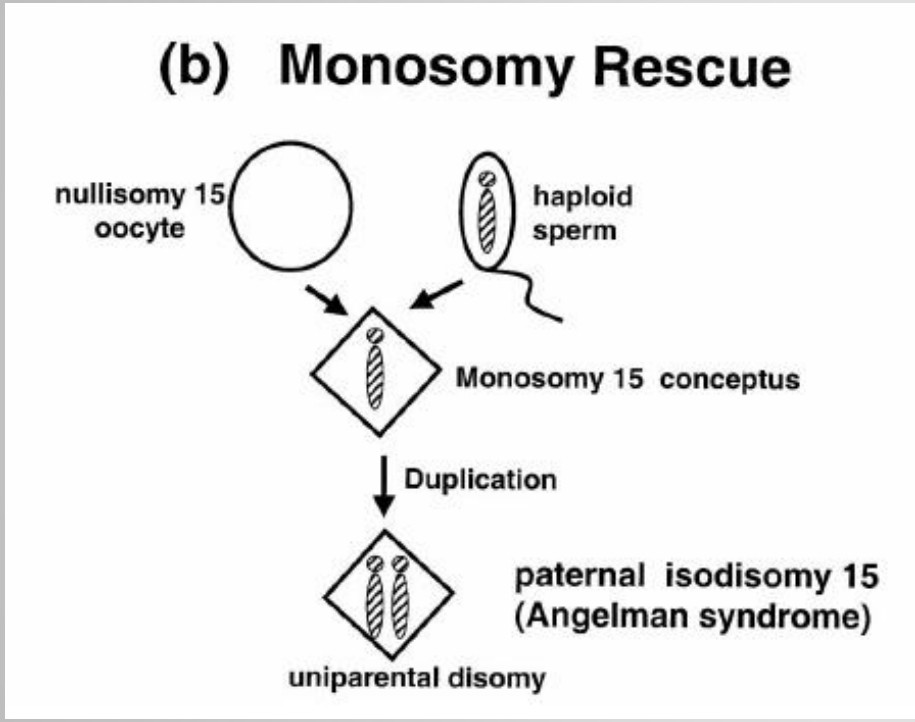


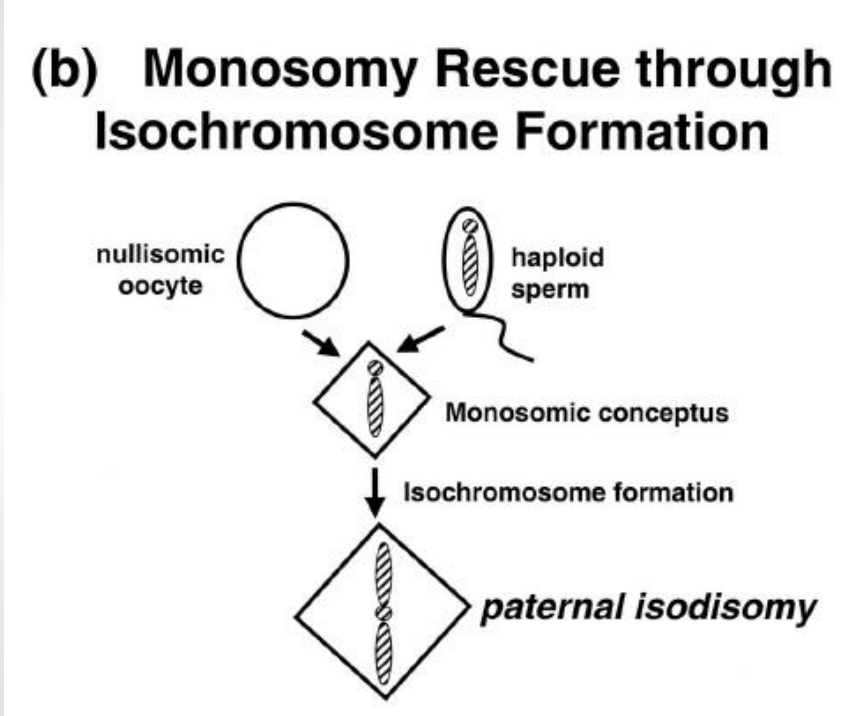
Images modified from from Shaffer et al., 2001, Genetics in Medicine

- Heterodisomy: two homologous copies or segments from the same parent

Risk for uniparental disomy (UPD)

- Risk for expression of clinical phenotype if rob chromosome contains imprinting genes (differentially expressed genes based on parent of origin) (chrs. 14 and 15)





Images from Shaffer et al., 2001, Genetics in Medicine

- Isodisomy: two identical copies or segments from the same parent
  - Risk for expression of two recessive alleles with isodisomy

Empiric risk estimates for offspring of Robertsonian translocation carrier

- Risk to have unbalanced is greater for females
  - 10-15% for chromosomes 21
- Risk for UPD is the same
- The risk to homologous rob carriers is ~100%
  - Very rare instances of post-zygotic correction are reported

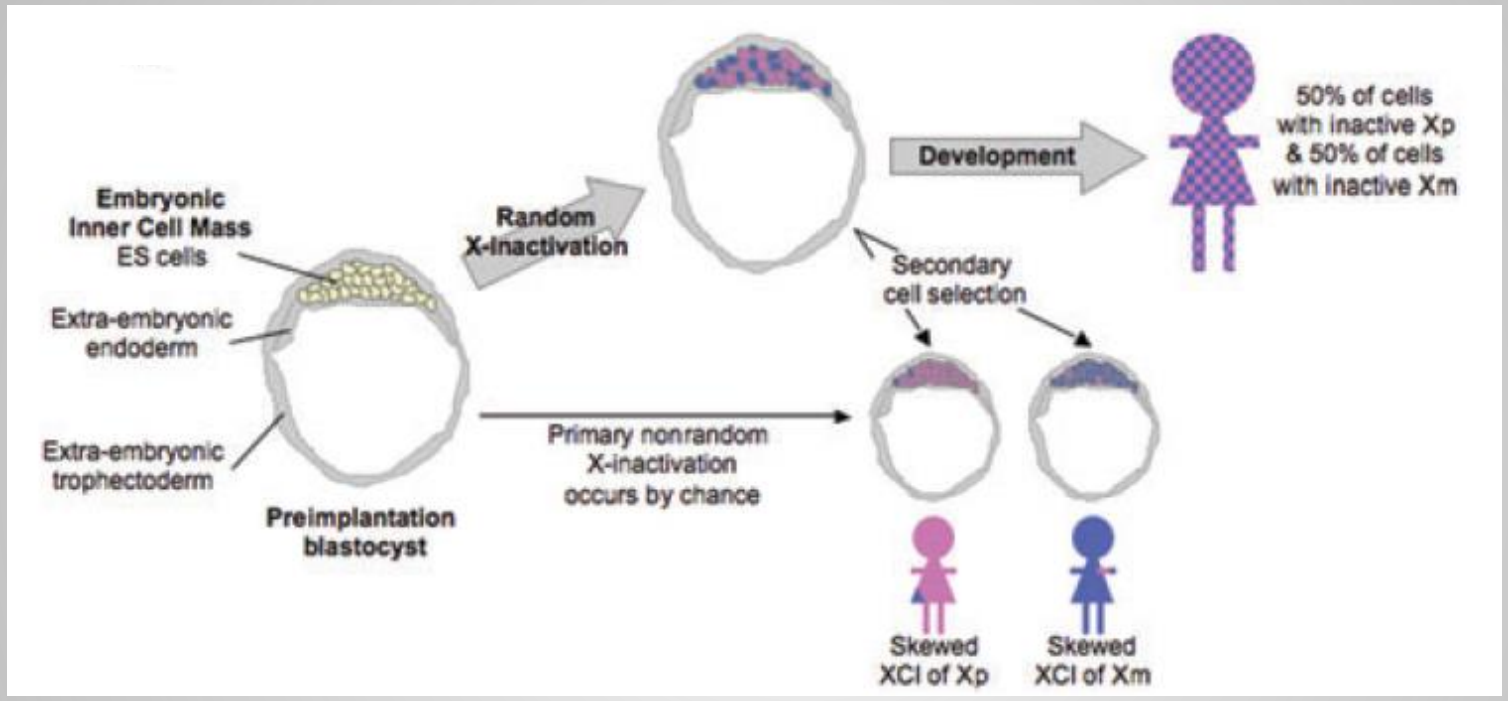
Table 7–2. Estimates of Risks to Have a Child with Aneuploidy or with a Uniparental Disomy Syndrome, for the Heterologous rob Carrier

	CARRIER PARENT			
	MOTHER		FATHER	
rob	UNBAL.	UPD*	UNBAL.	UPD*
13q14q	1%	<½%	<1%	<½%
13q15q	1%	<½%	<1%	<½%
13q21q	10%–15%	–	<1%	–
13q22q	1%	–	<1%	–
14q15q	–	½%	–	<½%
14q21q	10%–15%	<½%	<1%	<½%
14q22q	–	<½%	–	<½%
15q21q	10%–15%	<½%	<1%	<½%
15q22q	–	<½%	–	<½%
21q22q	10%–15%	–	<1%	–

Note: Estimates for the uncommon rob translocations are extrapolated from data for the common robs.
Unbal., unbalanced, with a full aneuploidy for chromosome 13 or 21; UPD, uniparental disomy; UPD*, abnormal child with syndrome of UPD 14 or UPD 15.

Gardner, Sutherland and Shaffer. 2012

Modes of X-inactivation



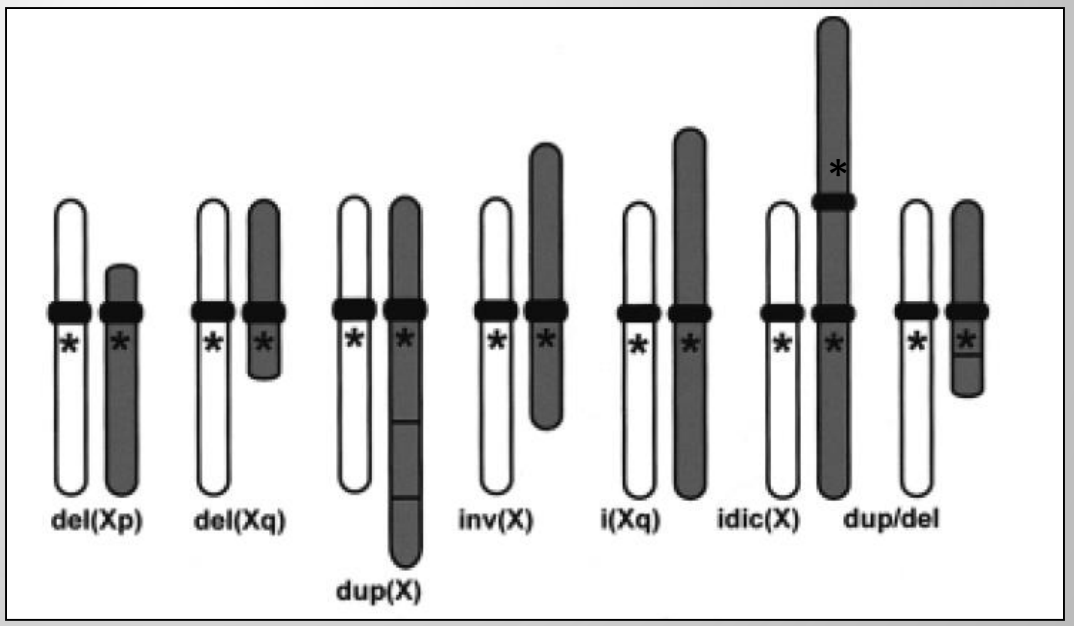
Morey and Avner, 2001

- Most X-inactivation occurs randomly
  - Random X-inactivation often protects against (masks) pathogenic (recessive) mutations in females
- Non-random (skewed) X-inactivation may occur by chance (primary) or through cell selection (secondary)
  - Can lead to expression of X-linked recessive mutations in females
  - Can protect against an otherwise dominant-acting mutation

Non-random X-inactivation can rescue effects of X-chromosome abnormalities in females

- Most structural abnormalities and some mutations lead to non-random inactivation

Key
- Active X = White
- Inactive X = Gray
- * = XIST

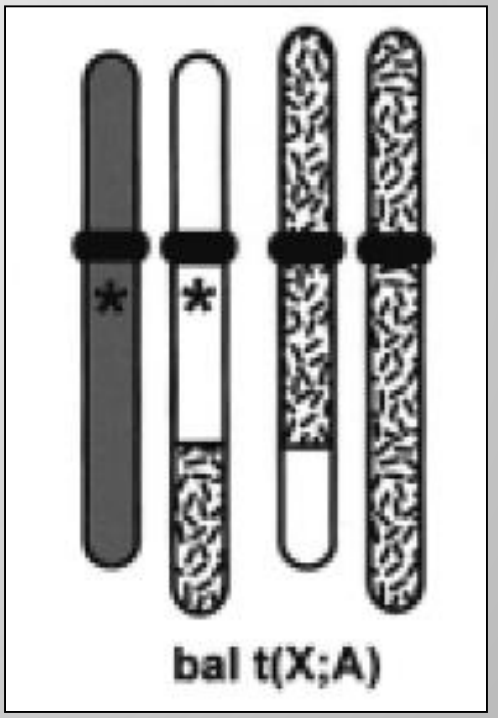


Leppig and Disteche, Semin Reprod Med, 2001

Translocation X;A in females-balanced carriers may also be affected, dependent on X-inactivation

- There is an inherent risk to the balanced female carrier if X inactivation is not skewed to preferentially inactivate the normal X
  - Risk for functional disomy (double expression of X-linked genes relative to their normal level) of the translocated X segment on the der(A)
  - Risk for functional monosomy of the translocated autosomal segment on the der(X)

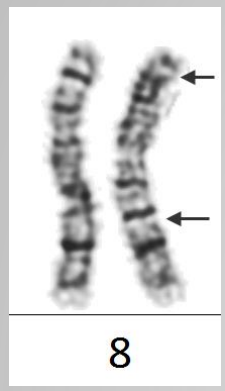
Key
- Active X = White
- Inactive X = Gray
- Autosomal material = hashed
- * = XIST



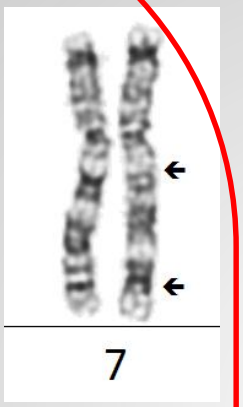
Leppig and Disteche, Semin Reprod Med, 2001

Structural abnormalities

Inversions

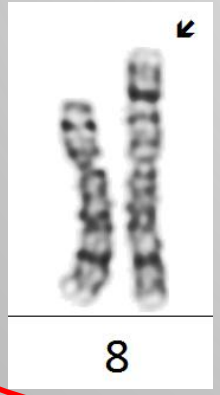


Pericentric inversion



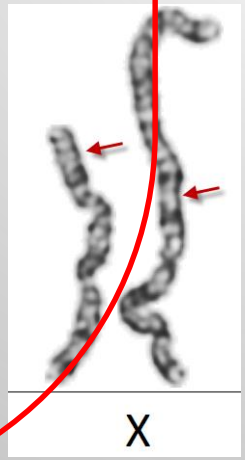
Paracentric inversion

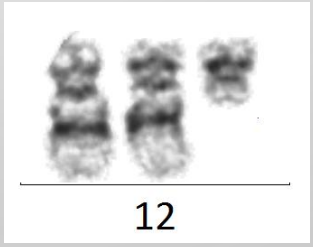
Recombinant chromosomes

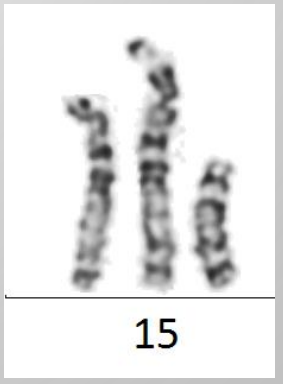


Ring chromosomes

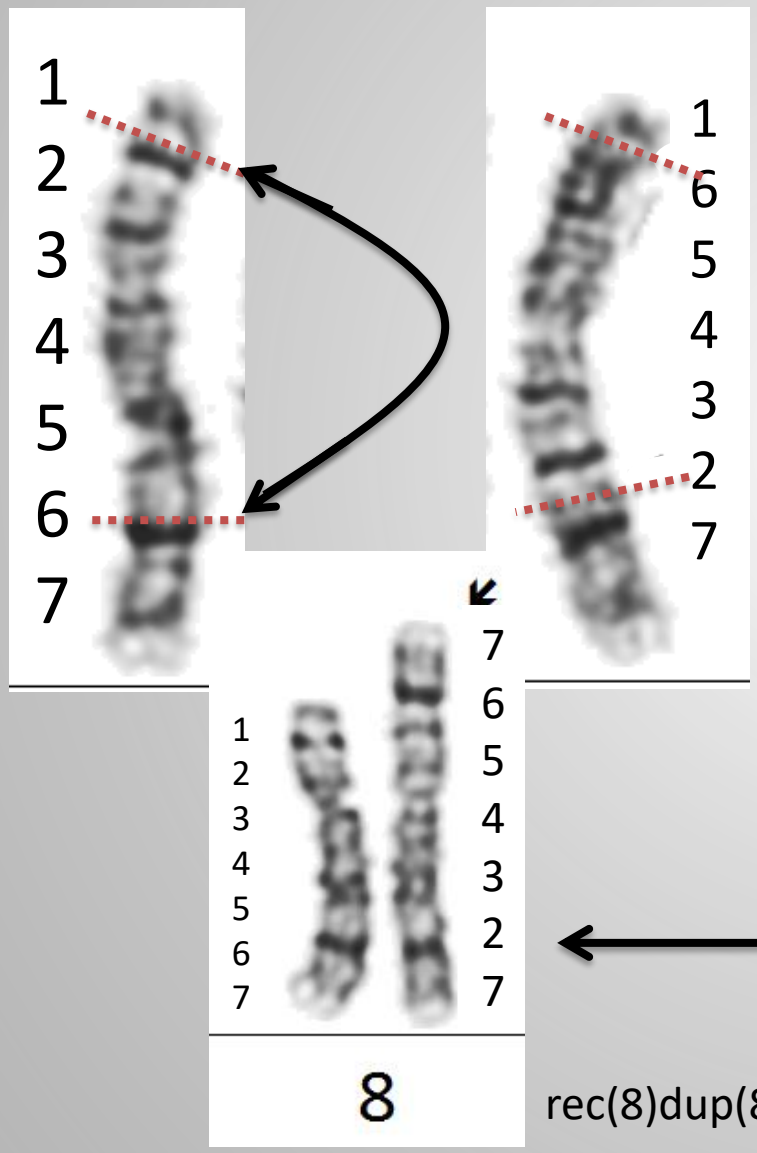
Isochromosomes







Recombinant chromosome arises from a parental pericentric inversion



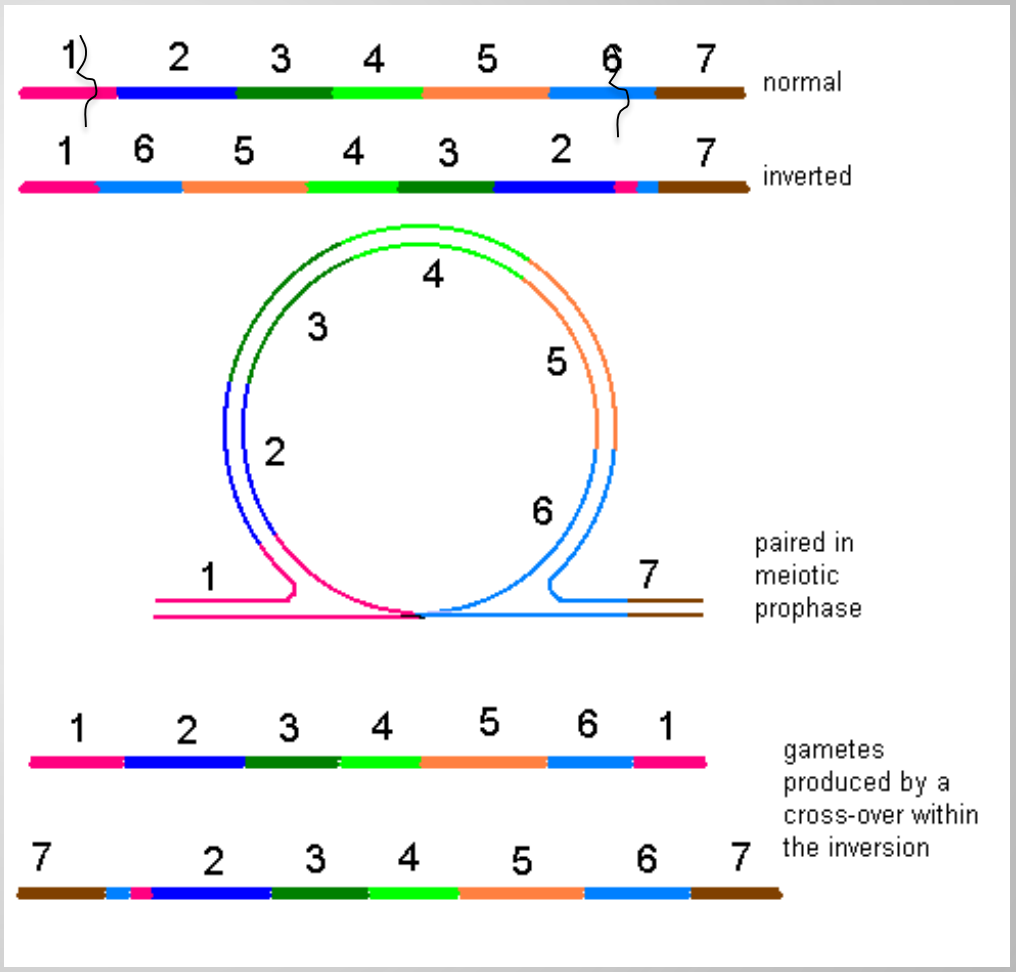


Image source: http://www.ucl.ac.uk/~ucbhjow/bmsi/bmsi_7.html

rec(8)dup(8q)inv(8)(p23.1q23.1)

Cytogenetics in Cancer

- Information from cytogenetic testing is used to:
  - Establish diagnosis
  - Guide therapy
  - Predict outcome
  - Monitor response to therapy or engraftment post-bone marrow transplant (BMT)

Basic terminology for classifying hematologic malignancies

- **Leukemia**: cancer of the blood and/or bone marrow
- **Lymphoma**: cancer in the lymphatic tissue (nodal or extranodal)
- **Myeloid**: cells that arise and differentiate in the bone marrow (RBC's, platelets, WBCs: granulocytes)
- **Lymphoid**: cells that arise in the bone marrow and differentiate and/or function in the lymphatic system (WBC types: B-cells, T-cells, NK cells)

Blood Cell Lineages

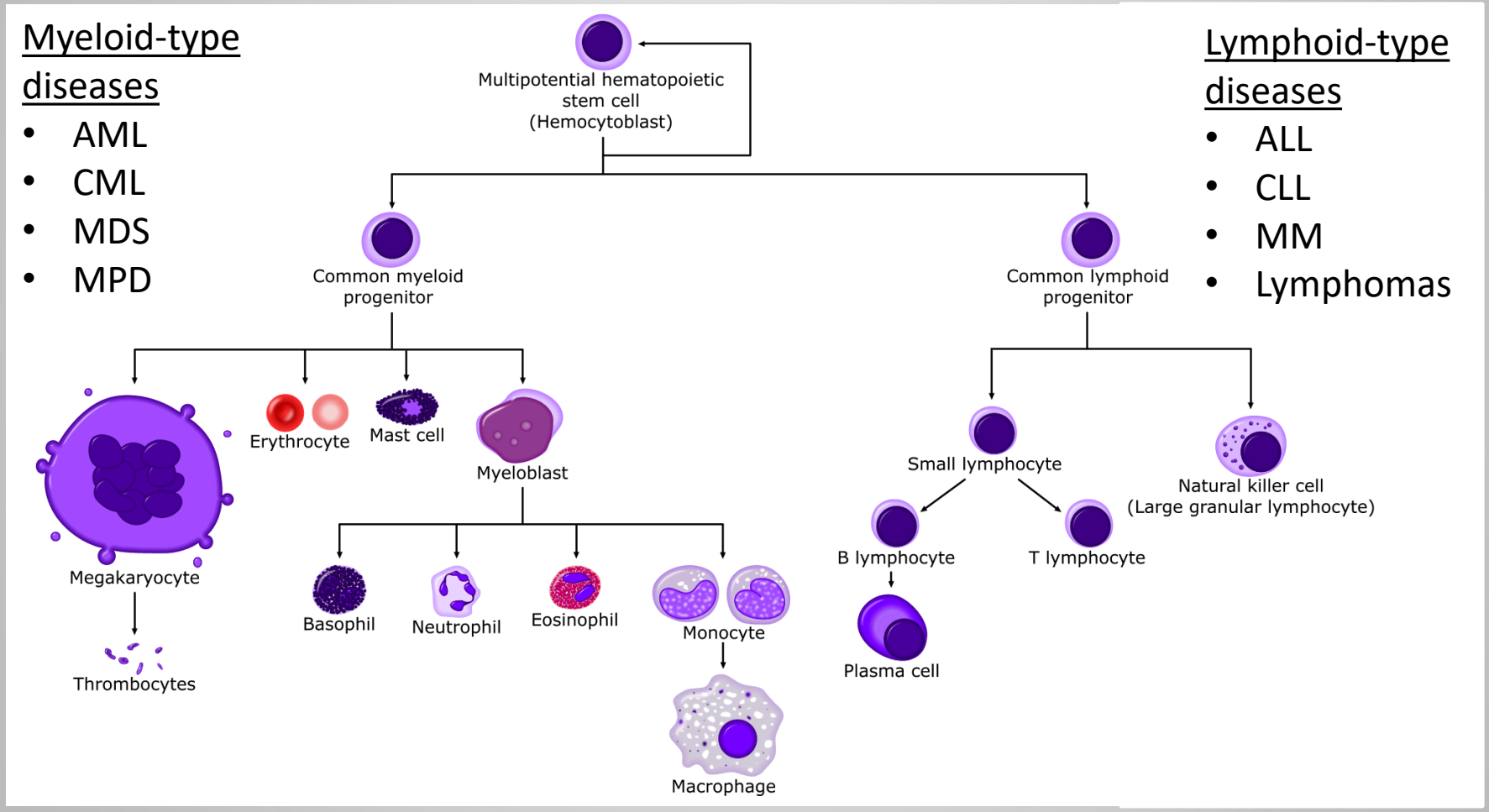


Image source: http://www.allthingsstemcell.com/wp-content/uploads/2009/02/hematopoiesis_simple1.png

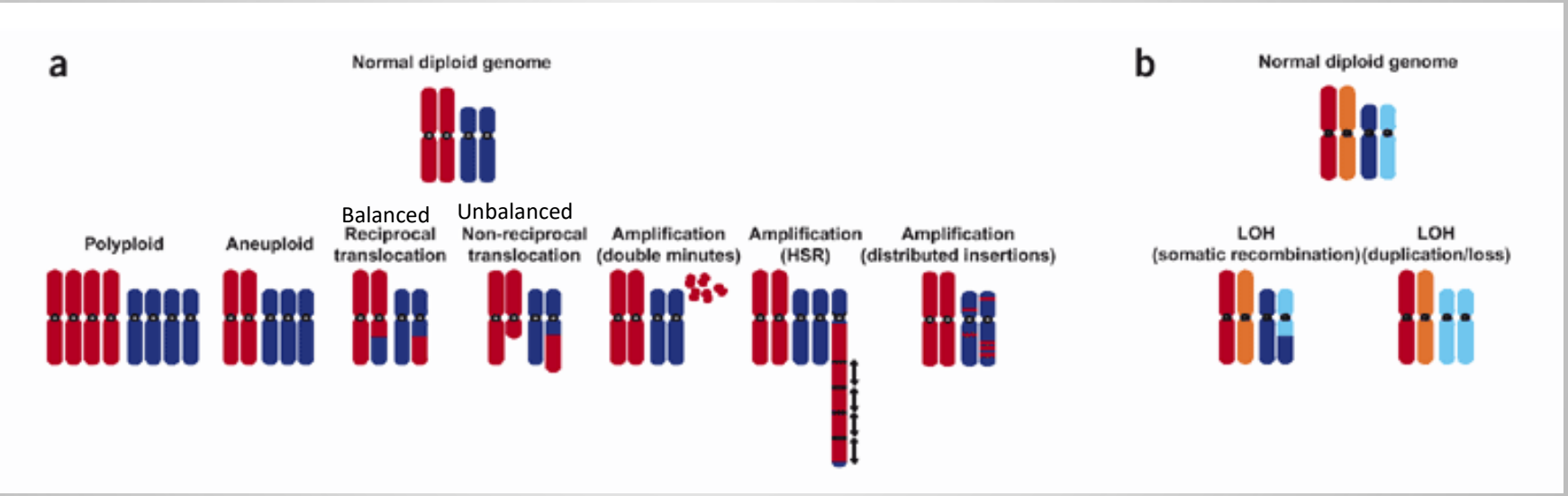
Types of Chromosome Abnormalities in Cancer

- Numerical
  - Aneuploid: 2n - or + chromosomes
    - Monosomy or trisomy
  - Polyploid: 1n, 2n, 3n, 4n, etc. where n=23 chr.
- Structural
  - Deletions
  - Duplications/amplifications
  - Translocations: balanced or unbalanced
  - Inversions
- Copy-neutral loss of heterozygosity (LOH)
  - Mitotic recombination
  - Mitotic malsegregation: uniparental disomy

Comparing technologies…

Aberrations of copy number, structure

Aberrations of genotype



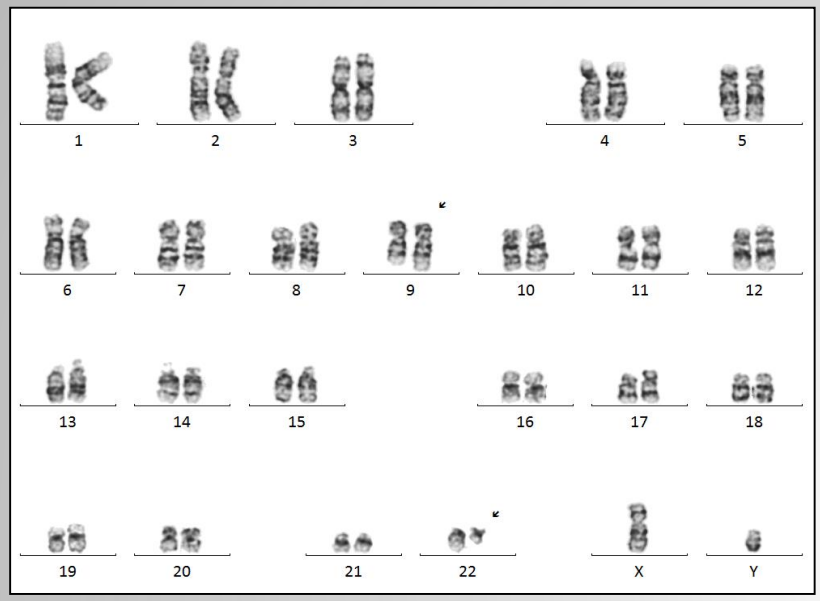
Karyotyping	+	+	+	+	+/-	+	-	-	-
FISH	+	+	+	+	+	+	+	-	-
CMA (SNP)	+	+	-	+	+	+	+	+	+

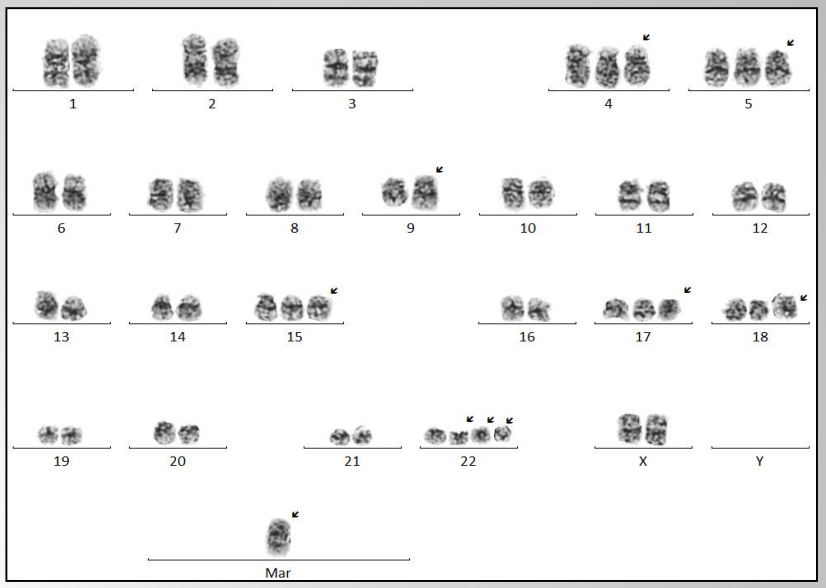
Image modified from Albertson *et al.,* 2003, Nature Genetics

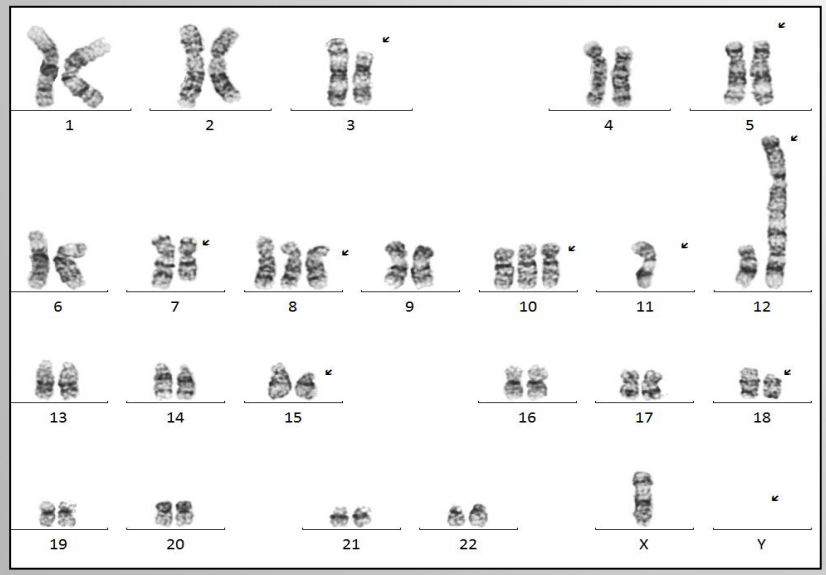
Defining clonality/acquired changes in oncology studies

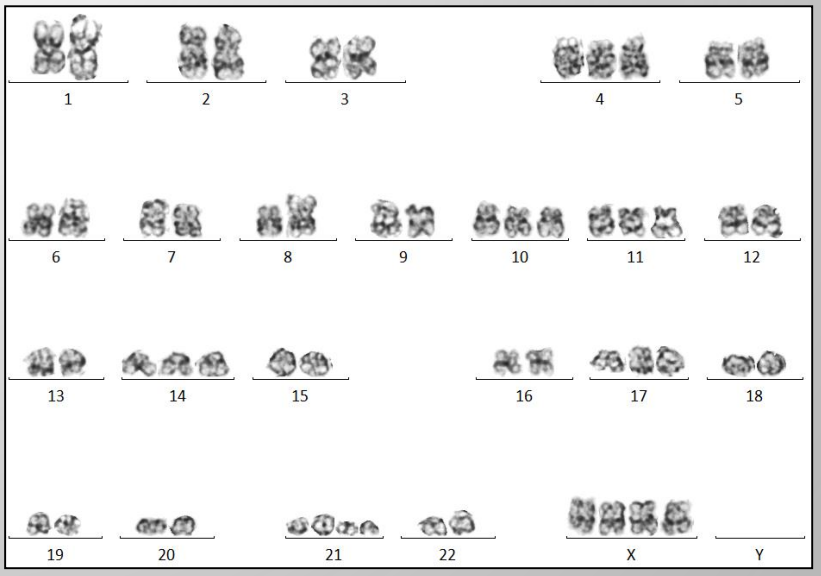
- Karyotyping:
  - At least two metaphase cells with the same extra chromosome, structural abnormality
  - At least three metaphase cells with the same chromosome loss
- FISH:
  - Abnormality observed in a percentage of cells (usually >1-5%), 200 interphase FISH cells are examined
- Genomic microarray:
  - Evidence of mosaicism in the sample as shown by the copy number and/or SNP-containing probes
  - Cannot determine whether multiple mosaic abnormalities represent different clones/evolution (clonal diversity)

Karyotyping in Cancer



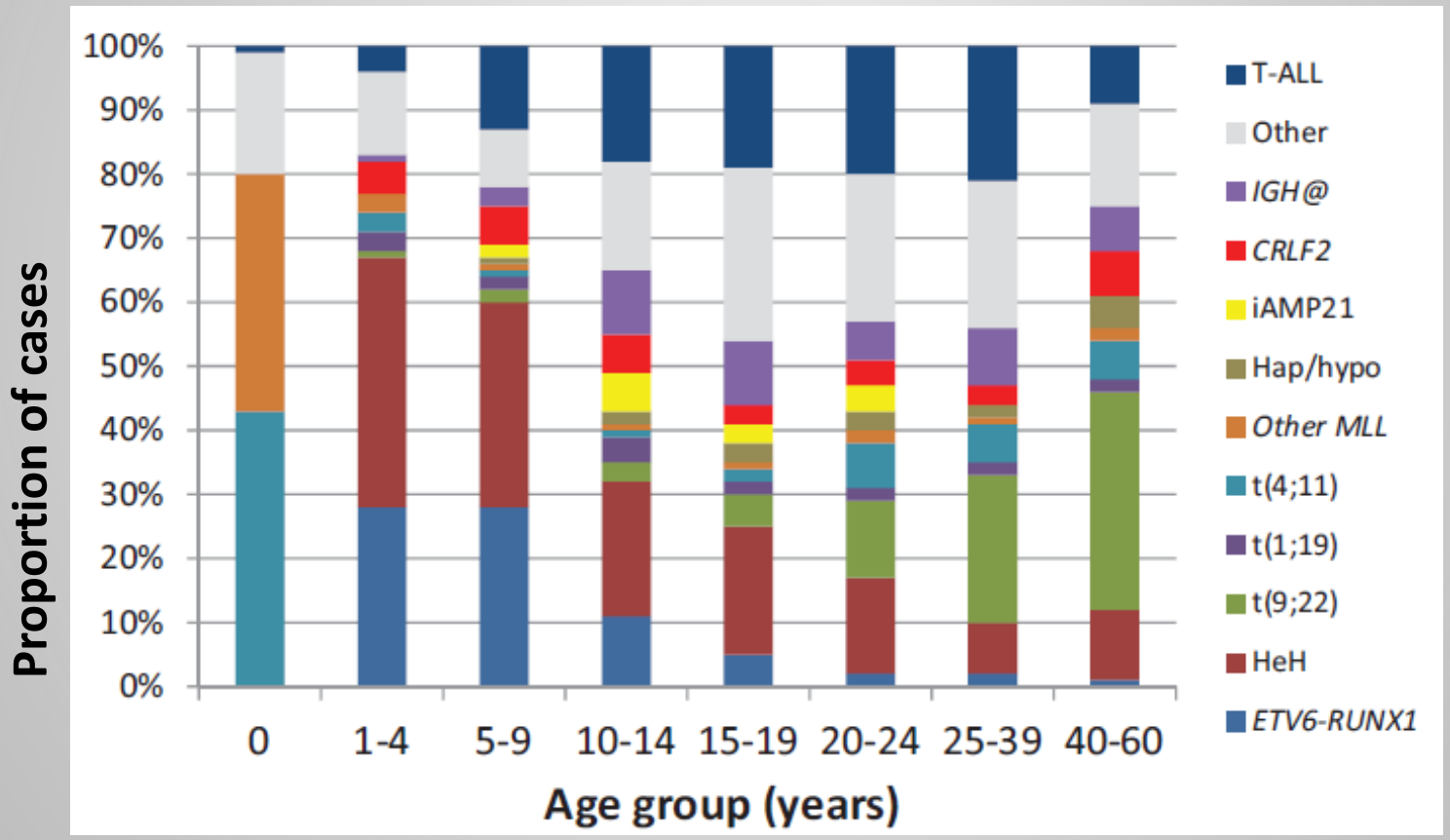






e.g. Clinical Utility of Karyotype in ALL

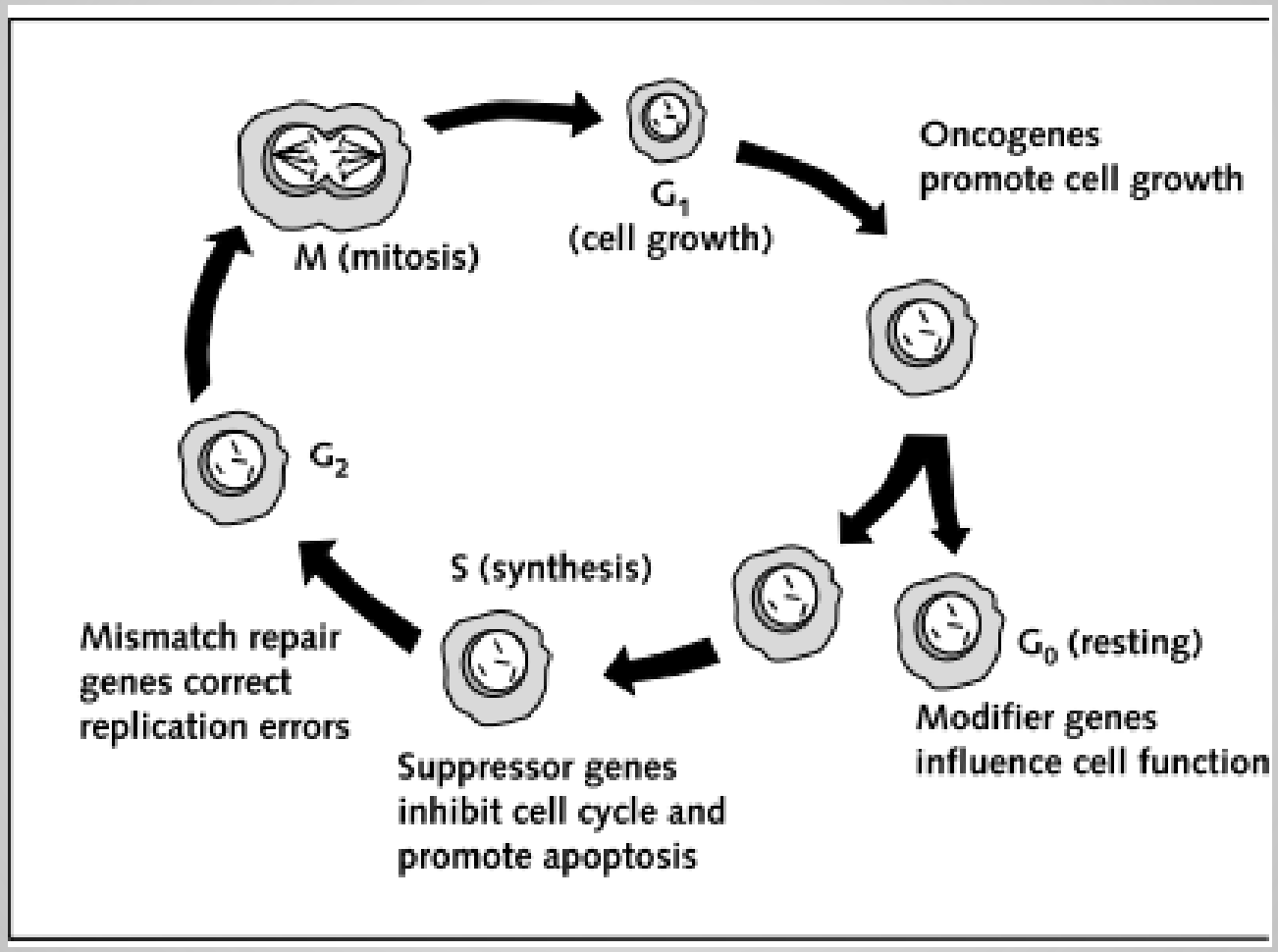
Cytogenetic subtype distribution by age



Harrison. *ASH Education Program* (2013) 118-125

The Genetic Basis of Cancer

Types of genes involved in cancer



Calvert and Frucht, 2002, Ann Int Med

Types of genes in cancer

- **Oncogenes**: mutant forms of genes (proto-oncogenes) that positively regulate cell proliferation and survival
  - Dominant, gain-of-function type mutations

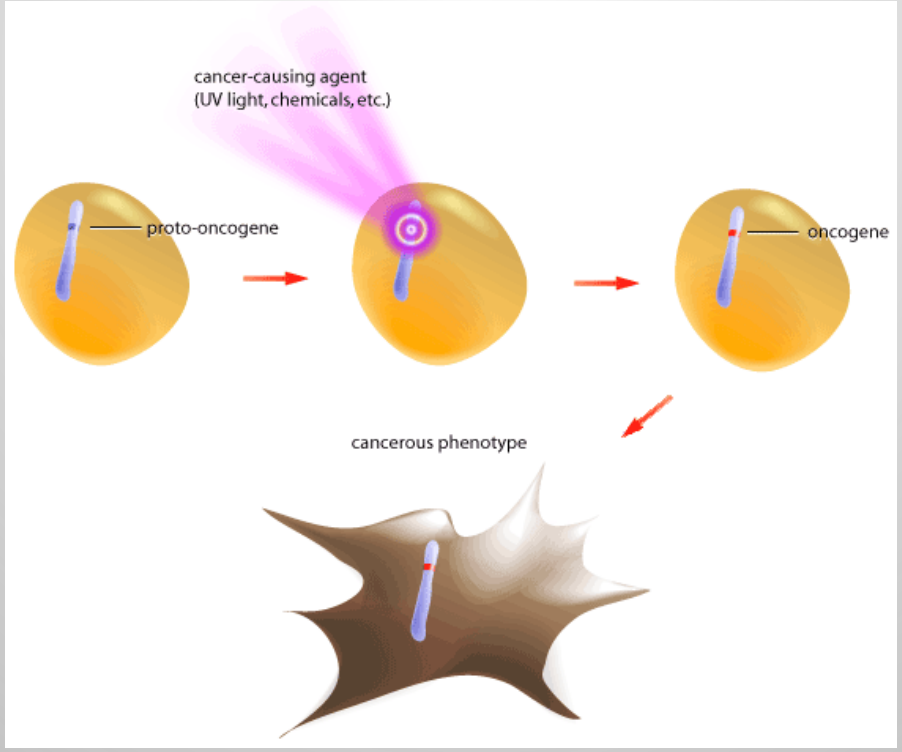
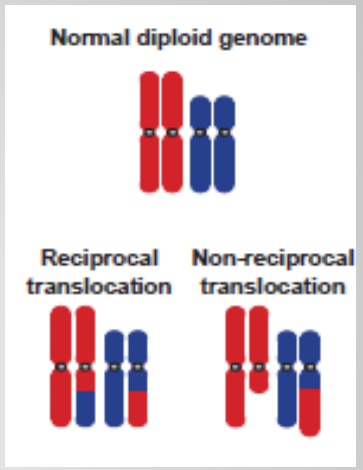
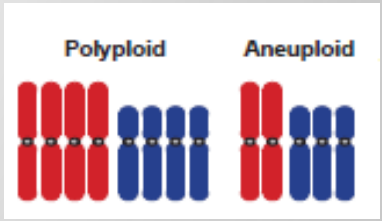


Image source: http://www.scq.ubc.ca/images/oncogeneformation.gif

Mechanisms of oncogene activation

- **Chromosomal rearrangements (translocations, inversions)**
  - A gene fusion creating a chimeric protein
  - Upregulation of gene expression by position effect
- **Copy number gains**
  - Trisomy, tetrasomy, etc.
  - Gene amplification





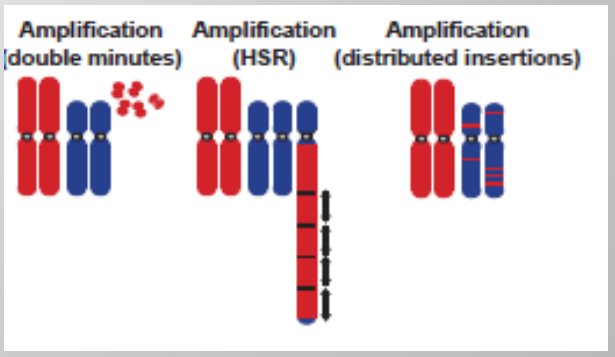


Image modified from Albertson *et al.,* 2003, Nature Genetics

Oncogene Activation by Gene Fusion

t(9;22) in chronic myelogenous leukemia (CML)

- First chromosomal abnormality associated with cancer, discovered in 1960
- Abnormal Chr. 22 named the Philadelphia (Ph) chromosome

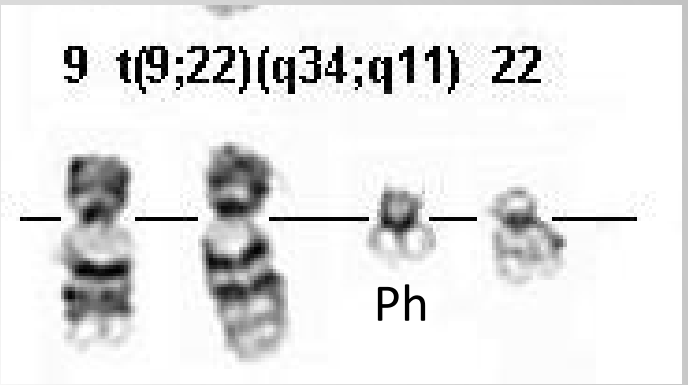
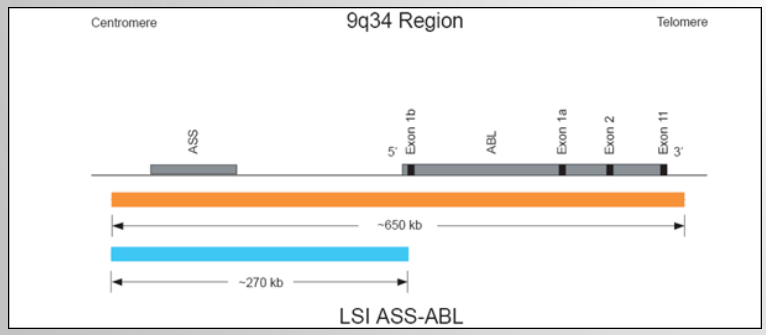
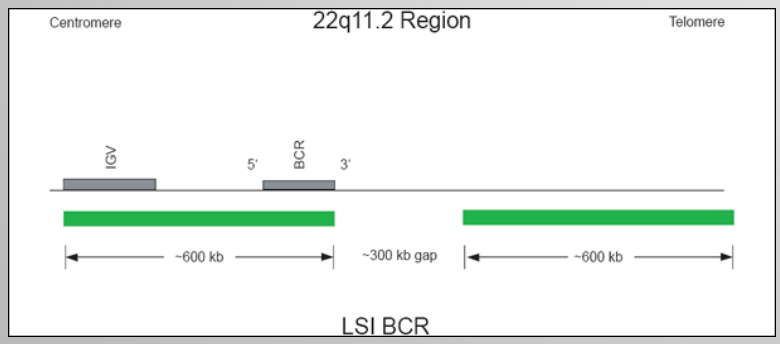
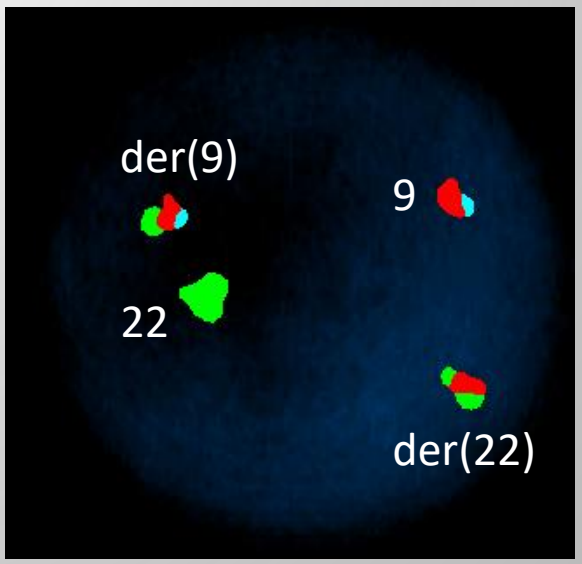


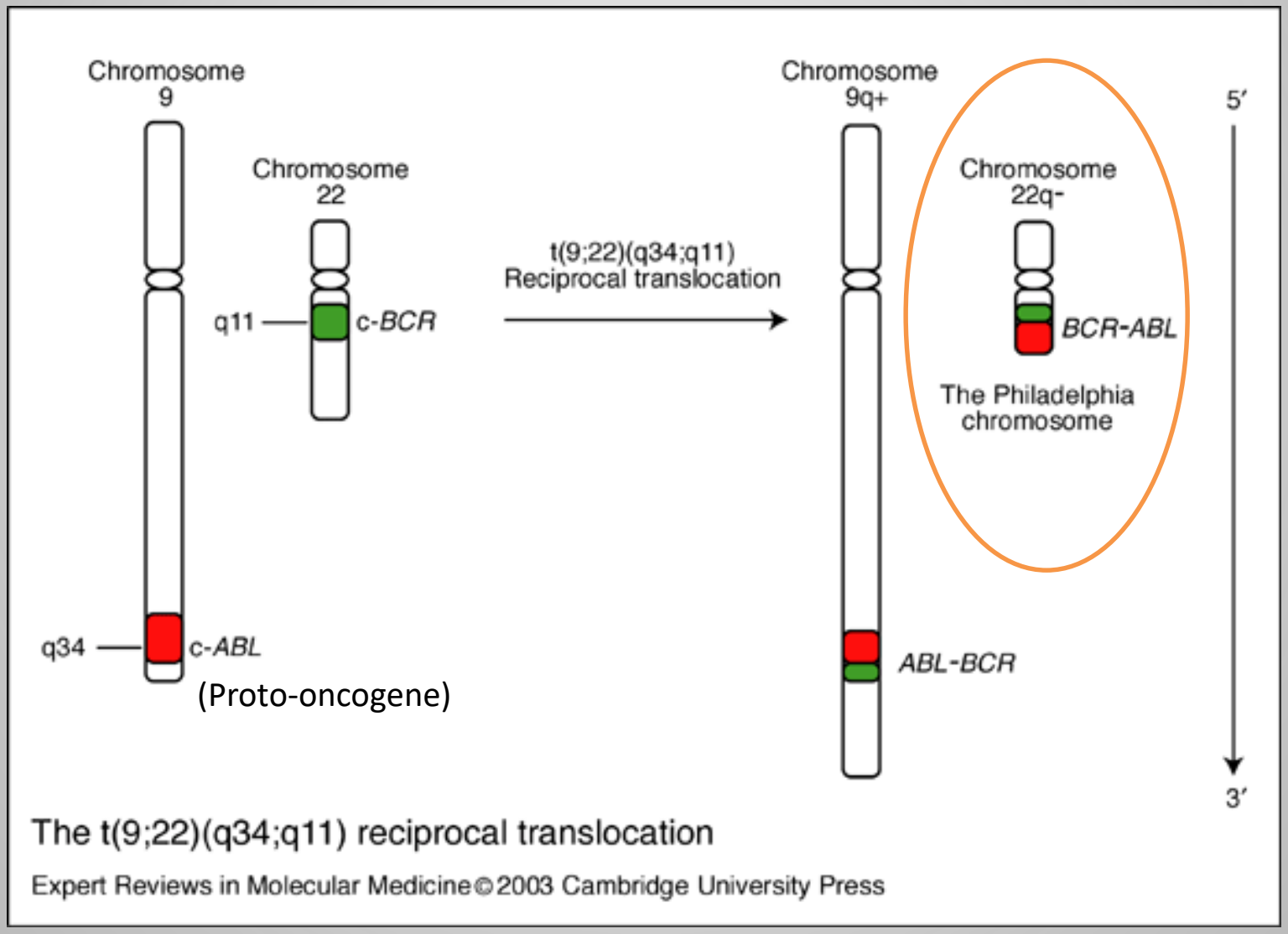
Image source:
http://atlasgeneticsoncology.org/Anomalies/t0922CML.html





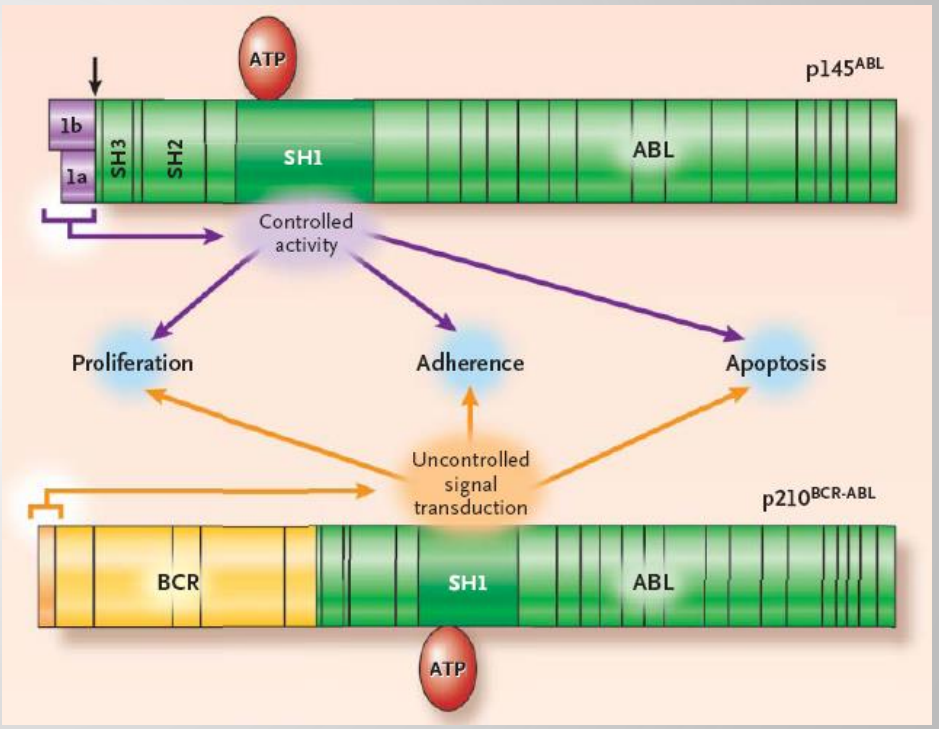


The t(9;22)(q34;q11) reciprocal translocation



BCR/ABL1 protein is a constitutively active tyrosine kinase

- The N-terminal cap regulates controlled ABL kinase activity
- Fusion to 5’ BCR
  - Increases cell proliferation
  - Inhibits programmed cell death
  - Increases invasiveness
  - Inhibits DNA repair



Goldman and Melo, NEJM, 2003

Targeted Therapy: Inhibitors of tyrosine kinase (TKIs)

- Imatinib mesylate (Gleevec) was the first TKI approved by the FDA in 2001
- Mechanism: Competes with ATP for binding sites
- Inhibits progression of CML in the majority of patients
- Drug resistance can develop over time

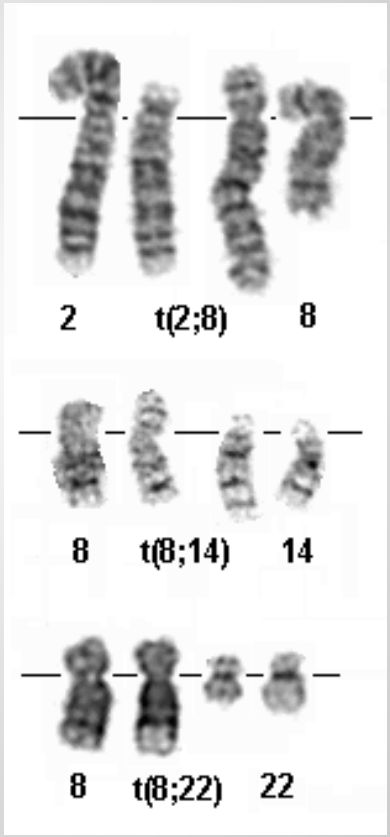
BCR-ABL1 kinase inhibited by Imatinib

Image source: http://upload.wikimedia.org/wikipedia/commons/c/ca/Bcr_abl_STI_1IEP.png

Oncogene Activation by Position Effect

c-MYC rearrangements in Burkitt lymphoma

- Cell of origin is a peripheral memory B-cell
- c-MYC at 8q24 is a proto-oncogene is a transcription factor that induces cell proliferation
- Immunoglobulin genes are strongly expressed in B-cells
- Translocation juxtaposes c-MYC with IG enhancers
- t(8;14)(q24;q32) in 75-85% cases
- t(8;22)(q24;q11) in ~10% cases
- t(2;8)(p12;q24) in ~5% cases



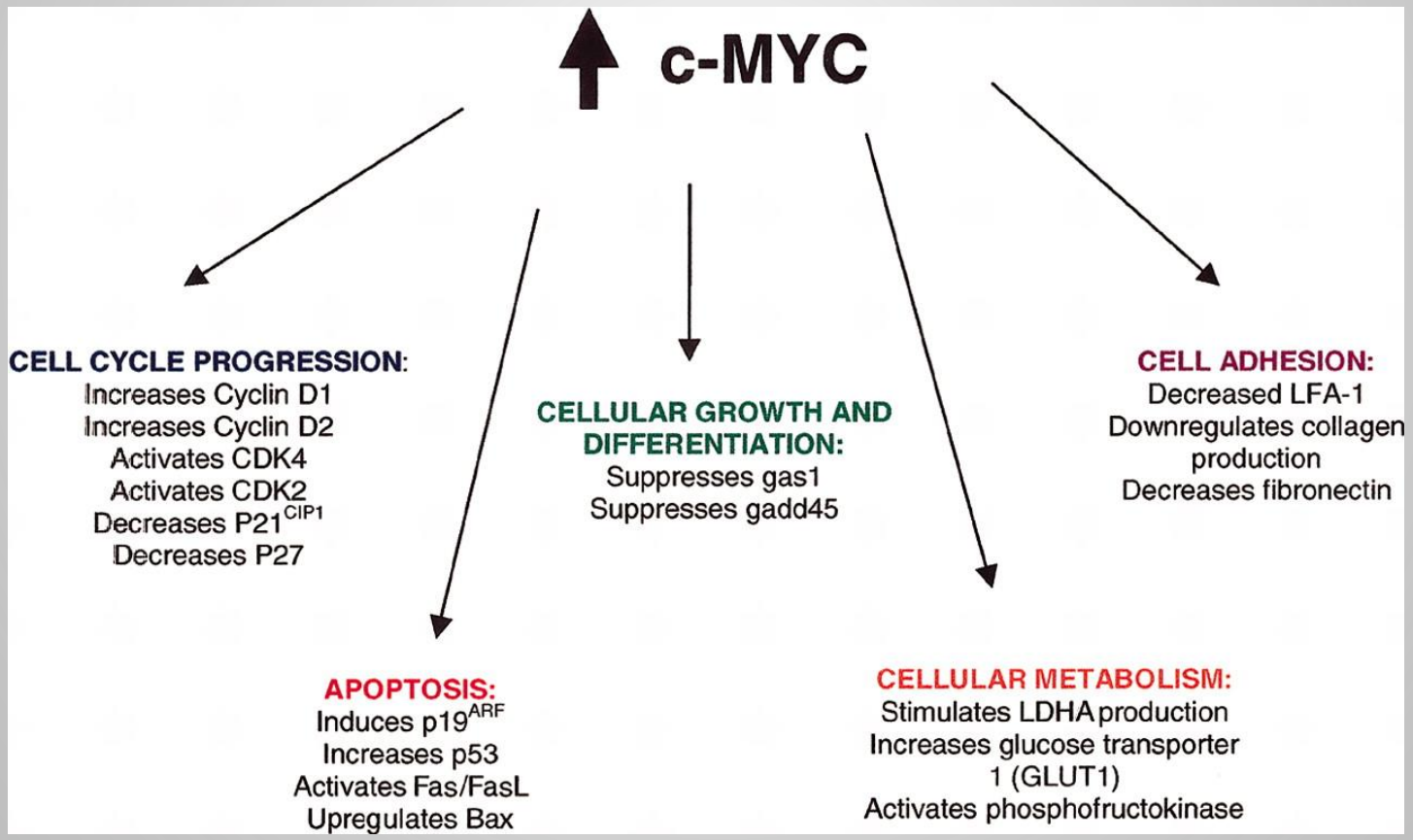
IGK locus on 2p

IGH locus on 14q

IGL locus on 22q

Image source: http://atlasgeneticsoncology.org/Anomalies/t0814ID1050.html

C-Myc influences the transcription of a variety of proteins involved in the cell cycle



Blum et al., Blood. 2004

Selected Rearrangements in Cancer

Neoplasm	Translocation	Percentage of Cases	Oncogene
Chronic myelogenous leukemia	t(9;22)(q34;q11)	100% (includes variant fusions)	BCR-ABL1
Acute lymphocytic leukemia	t(9;22)(q34;q11)	10-15%	BCR-ABL1
Acute lymphocytic leukemia	t(4;11)(q21;q23)	5-10%; 40% <1y	KMT2A-AFF1
Acute promyelocytic leukemia	t(15;17)(q22;q21)	100%	PML-RARA
Acute myeloid leukemia	t(8;21)(q22;q22)	5-10%	RUNX1T1-RUNX1
Acute myeloid leukemia	inv(16)(p13.3q22) or t(16;16)(p13;q22)	5-10%	CBFB-MYH11
Burkitt lymphoma	t(8;14)(q24;q32)	75-85%	MYC
	t(8;22)(q24;q11)	10-15%	
	t(2;8)(q11;q24)	2-5%	

Types of genes in cancer

- **Tumor suppressors**: genes that block tumor development by negatively regulating cell growth and proliferation
  - Recessive, loss-of-function type mutations

Knudson's Two-Hit Hypothesis

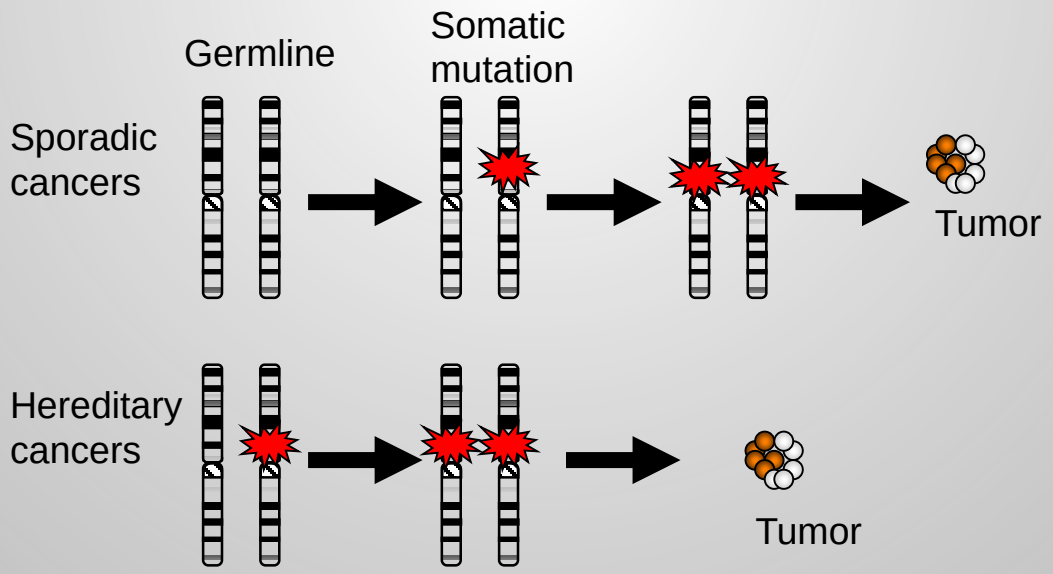


Image modified from UW Cytogenetics Lab

Mechanisms of tumor suppressor inactivation

- **Copy number losses**
  - Monosomy
  - Deletions
  - Note: copy number loss may in itself be pathogenic or may unmask a recessive mutant allele
- **Loss of heterozygosity (LOH)**
  - Somatic recombination
  - Uniparental disomy

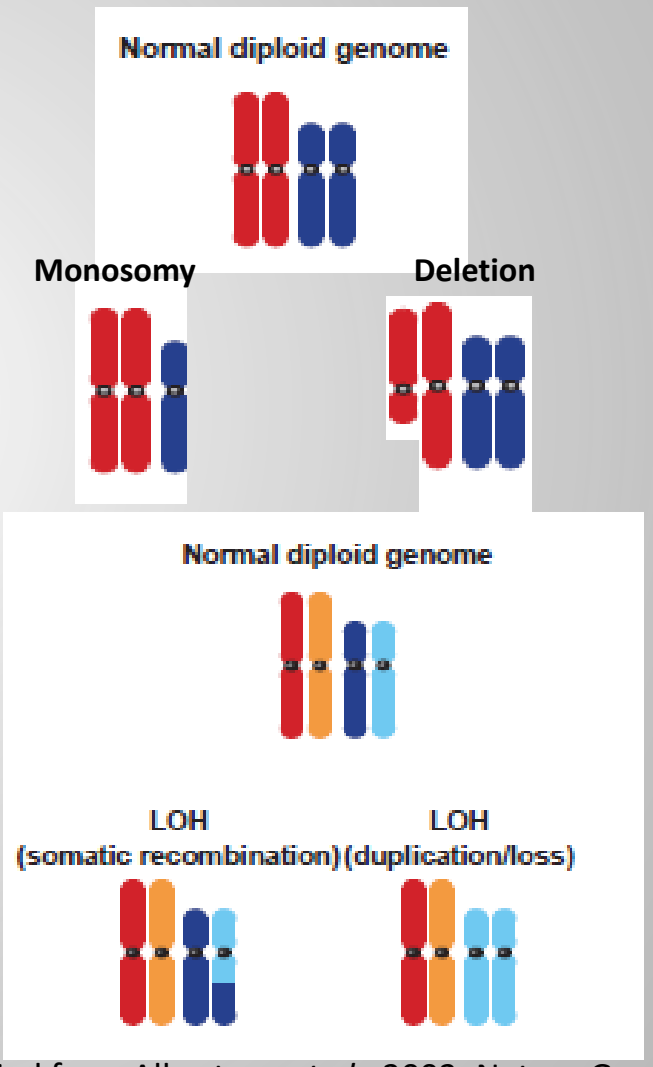


Image modified from Albertson *et al.,* 2003, Nature Genetics

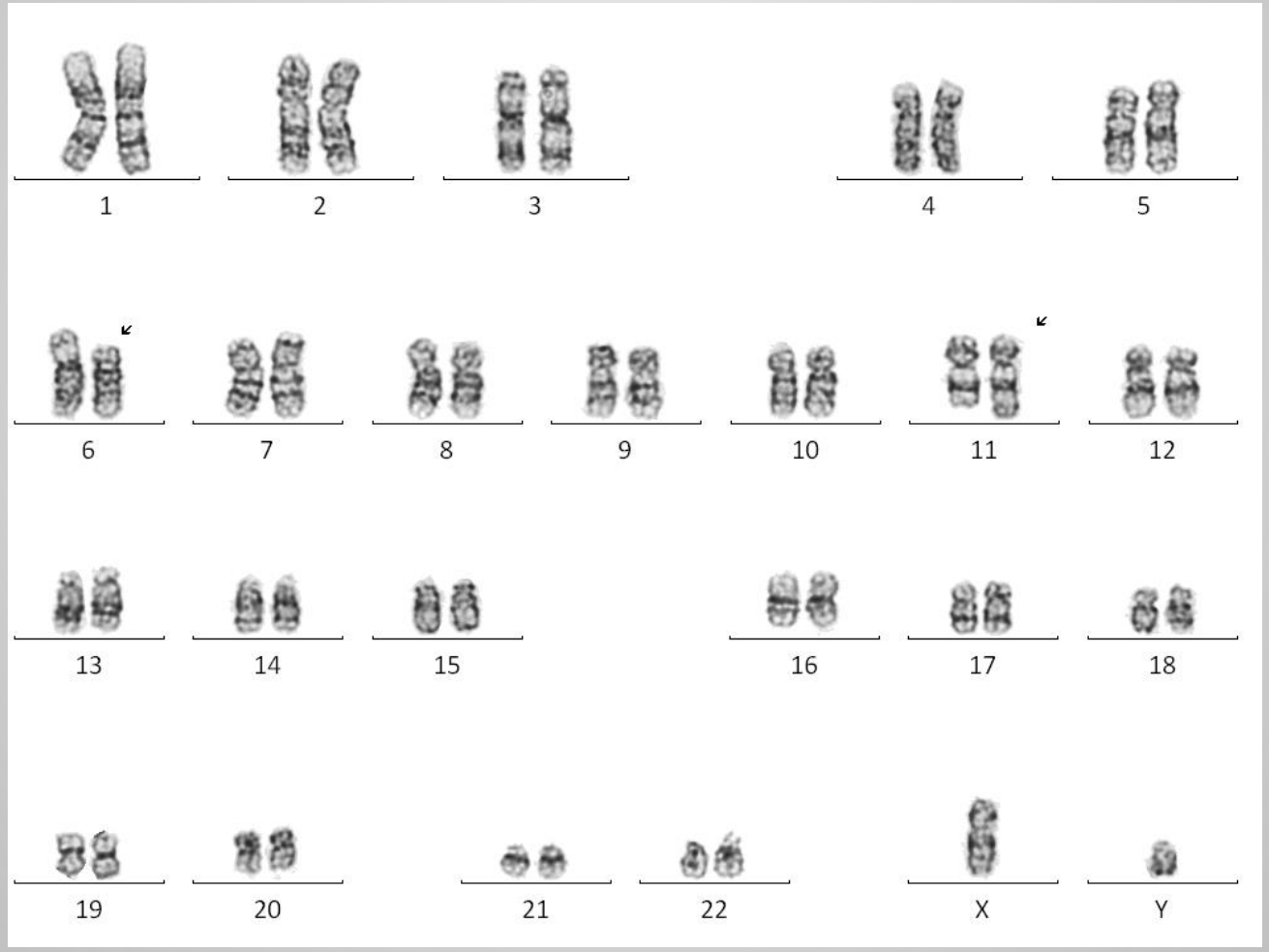
Nomenclature in Cancer

Common symbols and abbreviated terms

+	additional normal or abnormal chromosome (trisomy)
-	loss of a chromosome (monosomy)
add	added material of unknown origin, typically resulting in a loss of material distal to breakpoint
c	constitutional
cp	composite (clonal, but variable across cells)
del	deletion
der	derivative chromosome, due to structural rearrangement(s)
dic	dicentric chromosome
dmin	double minute chromosome
dup	duplication
i	isochromosome (composed of two identical chromosome arms)
idic	isodicentric chromosome (isochromosome w/ two centromeres)
ins	insertion
inv	inversion
mar	marker chromosome, unknown origin
r	ring chromosome
sl	stemline (used with clonal evolution)
sdl	sideline (used with clonal evolution)
t	translocation
?	designates uncertainty (used in place of, or in front of a finding)
/	separates clones (for mosaic karyotypes)
//	separates clones (for chimeric karyotypes)
[ ]	indicate number of cells (for mosaic or chimeric karyotypes)

Case 1: CHR BM for a patient after treatment for AML shows disease persistence

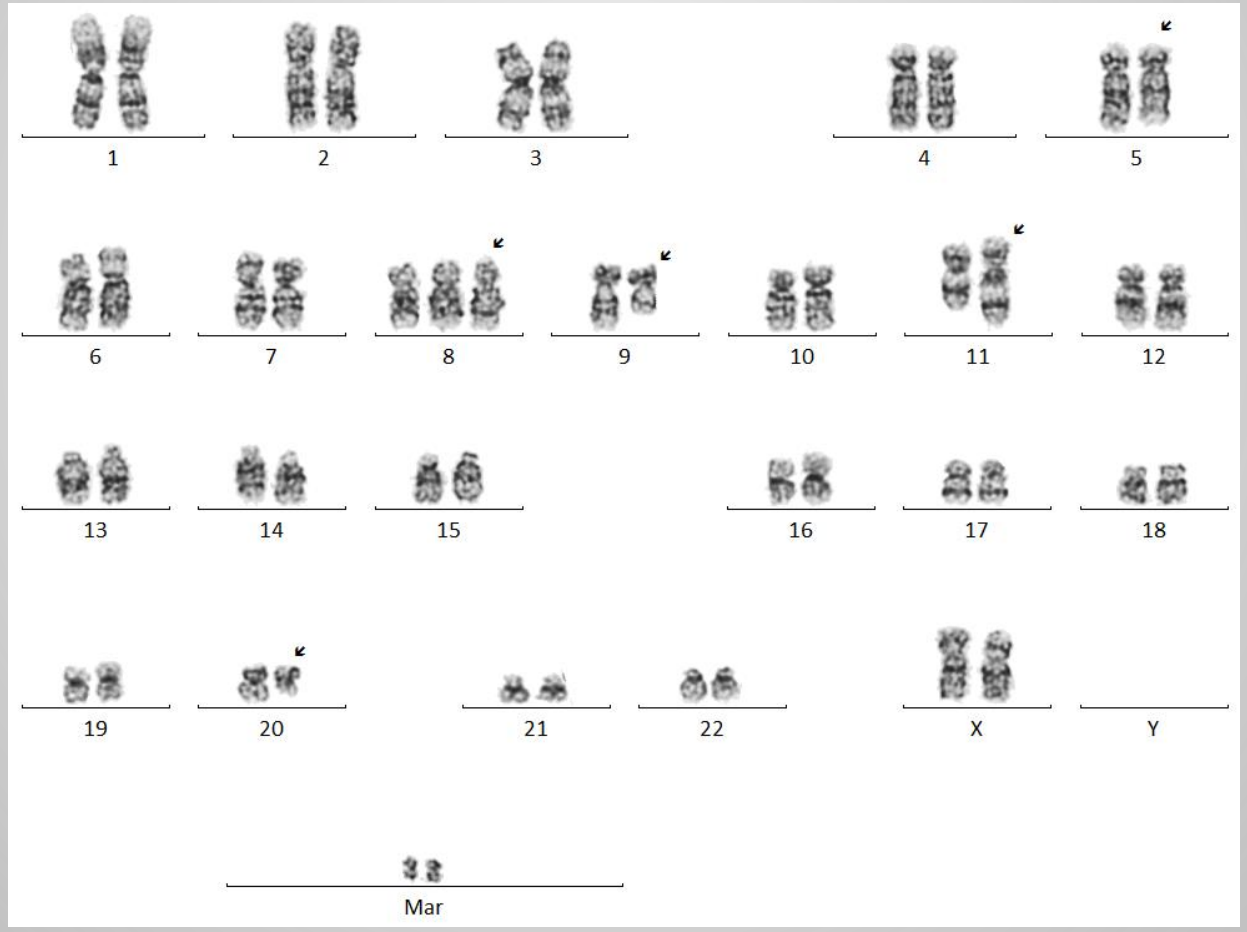
46,XY,t(6;11)(p21.1;q23)[2]/46,XY[18]



Rearrangement involving 11q23 (MLL/KMT2A) associated w/ a poor prognosis in AML

Case 2: AML, CHR BM reveals complex karyotype with multiple related abnormal clones, shows clonal evolution

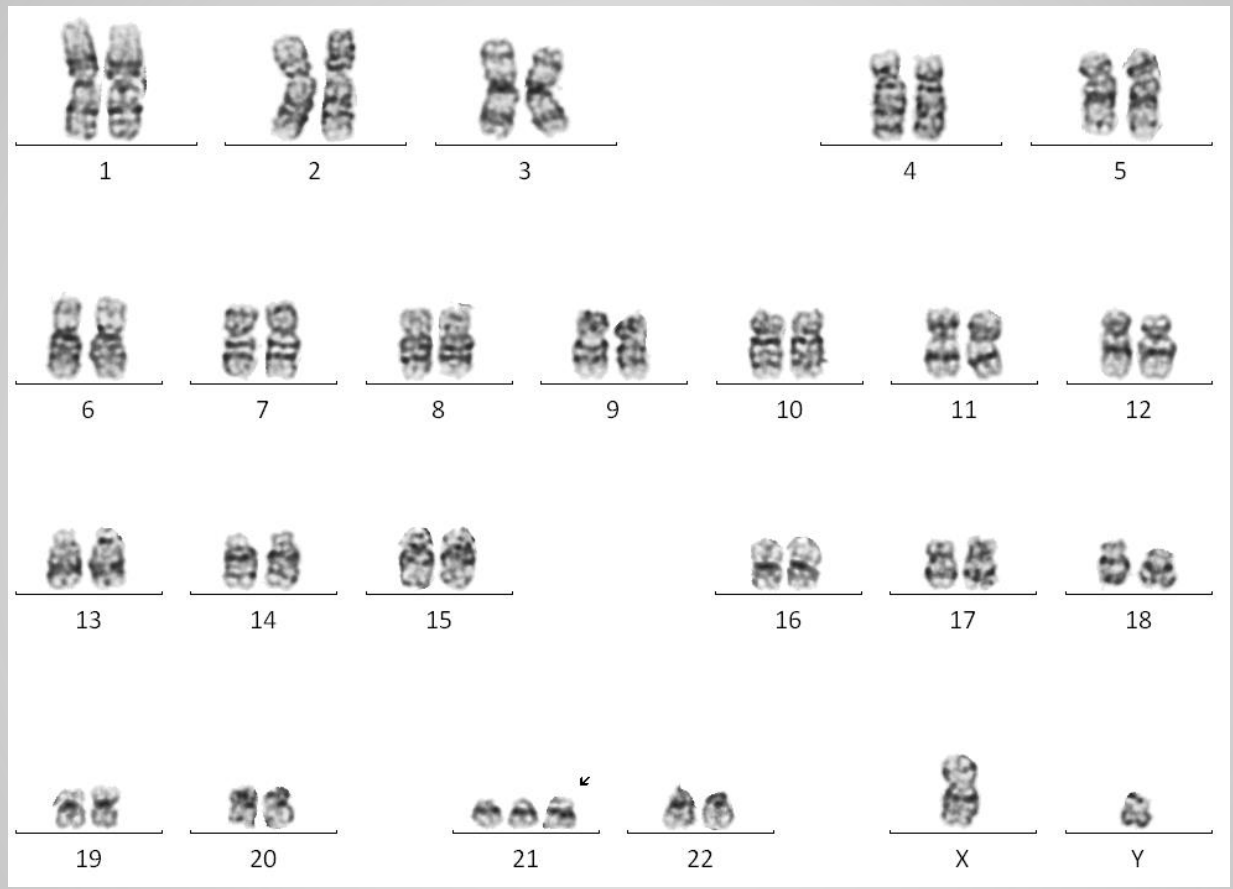
46,XX,add(5)(q15),del(9)(q31),del(20)(q11.2q13.1)[4]/46-47,sl,+8,ins(11;?)(q13;?),2-12dmin[cp13]/46,XX[3]



Complex karyotypes are associated w/ a poor prognosis in AML

Case3: CHR BM reveals trisomy 21 in a newborn male with pancytopenia (uncertain if patient has Down syndrome)

47,XY,+21[20]?c

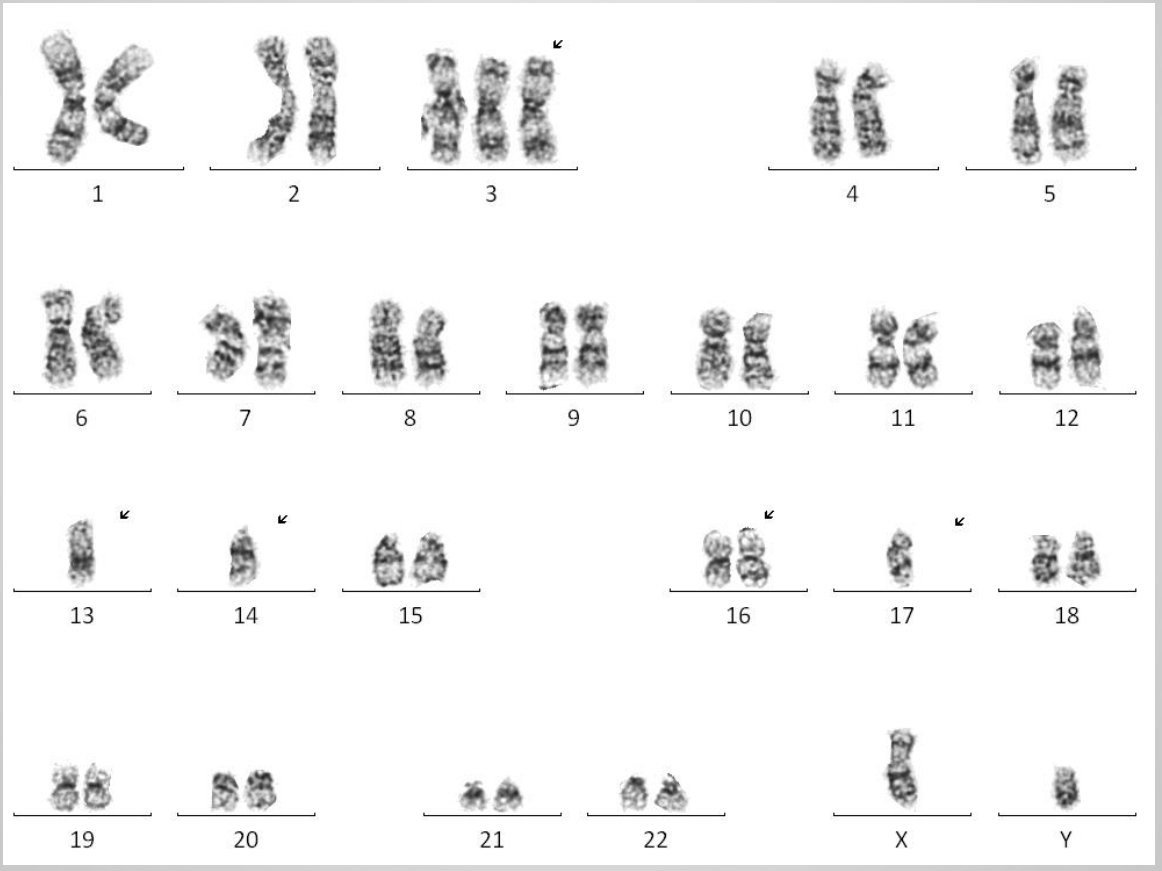


- Careful with abnormalities present in every cell ?constitutional
- DS patients have an increased risk of transient myeloid disease and ALL
  - Trisomy 21 is a recurrent acquired change in hematologic disease

➢ Test PB lymphocytes to see whether abnormality is constitutional/clonal

Case 4: CHR BM on a patient with multiple myeloma (MM) reveals a complex karyotype

44-45,XY,+3,-13,-14,der(16)t(16;17)(q11.2;q21),-17[5]/46,XY[19]



- Loss of Chromosome 17 (*TP53* gene) is associated with unfavorable prognosis in MM (and virtually all other cancers)

Principles of Cytogenetics
Categorical Course
Introduction to Cytogenetics 2

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