BASIC MEDICAL GENETICS CONCEPTS

- mutation effect on protein function
- phenotypic expression
- classes of genetic disease

Mutations result in different alleles

- alleles are classified as “dominant” or “recessive”
- dominant phenotypes – observable in heterozygotes
- recessive phenotypes – observable only in homozygotes

Mutations are classified by effect on protein function

- **loss-of-function (most common)**
  e.g. Decreased amount normal protein:
  Inborn errors of metabolism as in **Tay-Sachs** [recessive]
  Haploinsufficiency as in **FH** [dominant]

- **gain-of-function**
  e.g. Gene dosage effects as in **trisomy 21** [dominant];
  Dominant-negative effect as in **OI** [dominant]
  Abnormal protein properties as in **HD** [dominant]

- **novel property**
  e.g. **HbS** [recessive]

- **inappropriate expression**
  e.g. Oncogenes in **cancer**

Variations in phenotypic manifestation of mutant alleles are due to:

- complementation as in **XP, profound hearing loss**
- penetrance (100% - achondroplasia - unusual)
- variable expression

Causes of variable expression:

- allelic heterogeneity: **hemophilia** variants
- locus heterogeneity: **hyperphenylalanemias**
- modifier loci: **Waardenburg syndrome** (methylation); **Alzheimer's** (multiple genes); **SNPs**
- environment (**XP, α-1 antitrypsin deficiency**)

Common classes of genetic disease:

1. enzyme defects (**PKU; Lesch-Nyhan; Tay-Sachs; I-cell disease; XP**)
   - Almost always recessive.
   - Pathophysiology due to substrate accumulation, product deficiency, or both.
   - When substrate is diffusible, the pathophysiology is unpredictable; when substrate can't diffuse, the cell in which it accumulates is damaged.
   - Several enzyme functions can be affected.

Common classes of genetic disease (cont.):

2. Defects in receptor proteins (**Familial hypercholesterolemia**)
3. Transport defects (**Cystic fibrosis**)
4. Disorders of structural proteins (**Duchenne muscular dystrophy; Osteogenesis imperfecta**)
5. Neurodegenerative disorders (**Alzheimer's disease**; triplet repeat disorders)
6. Mitochondrial diseases (**MELAS, MERRF**)
7. Pharmacogenetic diseases (**malignant hyperthermia; G6DP**)

Triplet Repeat Disorders

- Dynamic expansion of DNA triplet repeats
- Normal alleles polymorphic
- Inheritance dominant or recessive
- Presymptomatic, symptomatic expansion size varies
- Base sequence, location of repeat varies
- Parent-of-origin effects on repeat expansion varies (anticipation)
- Stability during meiosis and mitosis varies (variable expression)

Polyglutamine disorders

- **Huntington Disease** (**autosomal dominant**)
- **Spinobulbar muscular atrophy** (**X-linked recessive; androgen receptor**)
- CAG repeat
- Anticipation: expansion occurs preferentially during **male** gametogenesis
- Variable expression: mitotic instability low (limited mosaicism)
- Protein aggregation, not loss-of-function

Fragile X Syndrome

- **X-linked recessive**
- CGG repeat in 5' untranslated region of FRA gene (posttranscriptional regulator; methylation effects)
- Most common form of hereditary mental retardation
- Anticipation: expansion occurs preferentially in **female** gametogenesis
- Variable expression: Mitotic instability high
- Disease caused by loss of function; very large expansions needed

Myotonic Dystrophy

- **Autosomal dominant**
- CTG repeat in 3' untranslated region of protein kinase gene; mechanism of pathophysiology unknown.
- Anticipation: either parent can transmit amplified copy; massive expansion occurs only in **maternal** gametogenesis
- Variable expression: mitotic instability high
- Abnormal transcript processing, not deletions, point mutations, etc.

Freidreich ataxia

- **Autosomal recessive**
- GAA repeat in intron of mitochondrial gene frataxin (involved in iron metabolism).
- Anticipation: no parent of origin effects
- Variable expression: mitotic instability low
- Loss of function
- 4% are compound heterozygotes (expansion/point mutation)

Mitochondrial Disorders

3 types of mutations

- missense mutations in coding regions of genes that alter activity of OXPHOS proteins (**Leigh disease**-ATPase)
- point mutations in tRNA or rRNA genes that impair mitochondrial protein synthesis (**MELAS; MERRF**)
- rearrangements that generate deletions/duplications in mtDNA (not usually transmitted from affected mother to offspring; disorders occur as sporadic new cases-**Kearns-Sayre syndrome**)

Maternal inheritance

Usually heteroplasmic (phenotypic expression: reduced penetrance, variable expression, pleiotropy)

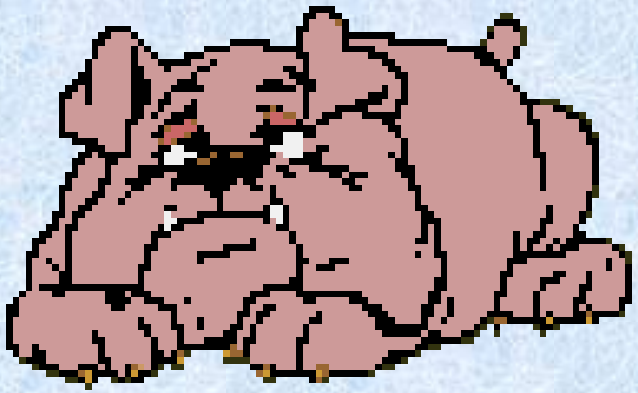
Pharmacogenetic Diseases

- Unanticipated reactions to medications largely/entirely genetic (6.7% incidence in American hospitals; 0.3% fatal).
- Single gene defects or multifactorial

Examples:

- **Malignant hyperthermia** (autosomal dominant-Ca^{+} release channel; other loci)
- **Acute Intermittent Porphyria** (autosomal dominant disease: drug-related alteration in gene expression of heme biosynthetic enzyme)
- **G6PD** (X-linked recessive; more than 400 variants; most common disease-producing single gene enzyme defect of humans)
- **Acetylation polymorphism** (slow or rapid drug inactivation)

PRINCIPLES OF CLINICAL CYTOGENETICS



- Common chromosome structural disorders
- Chromosome banding
- Aneuploidies: nondisjunction
- Chromosome breakage syndromes; translocation
- Faulty DNA metabolism chromosome syndromes
- Genomic imprinting; UDP
- Sex reversal

AUTOSOMAL DISORDERS

Common Aneuploidies

- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edward syndrome)
- Trisomy 13 (Patau syndrome)

Structural Abnormalities: Deletion Syndromes

- Cri du Chat syndrome (5p-)

Structural Abnormalities: Microdeletion Syndromes

- Di George syndrome (22q11)
- Prader-Willi syndrome (pat 15q11-q13)
- Angelman syndrome (mat 15q11-q13)

Structural Abnormalities: Trinucleotide Expansion Disorders

- Huntington Disease (4p16.3)
- Myotonic Dystrophy (19q13.2)
- Freidreich Ataxia (9q13)

SEX CHROMOSOMAL DISORDERS

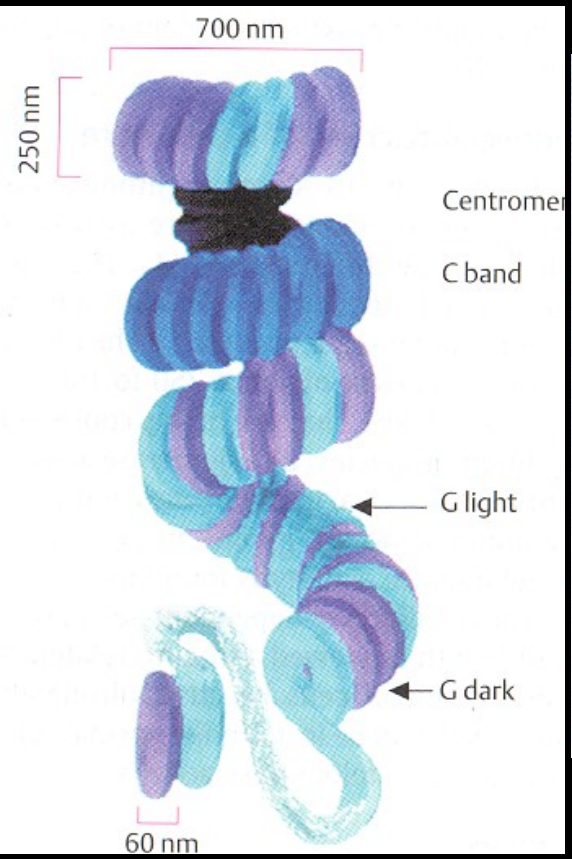
Common Aneuploidies

- Klinefelter syndrome (47,XXY)
- 47,XYY syndrome
- Turner syndrome (45,X and variants)

Structural Abnormalities

- Fragile X syndrome (trinucleotide expansion; Xq27.3)
- Sex Reversal (deletion, translocation; Yp11.32)

Banding



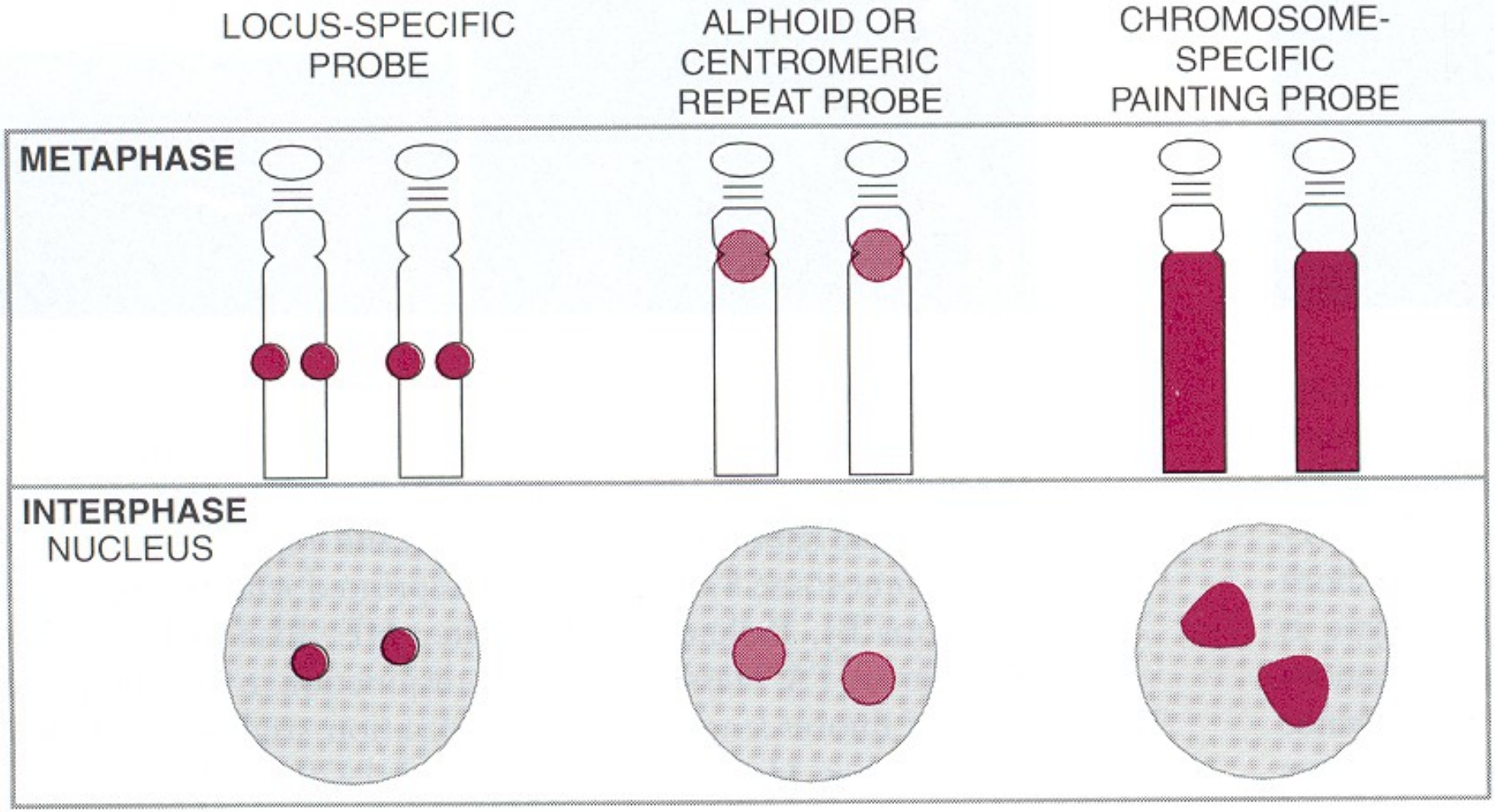
CORRELATION OF STRUCTURE AND FUNCTIONAL PROPERTIES IN EUCHROMATIN	
Light G Bands	**Dark G Bands**
GC-rich	AT-rich
Fluorescence with G-specific fluorochromes	Fluorescence with AT-specific fluorochromes
Early replicating	Late replicating
Gene-rich	Gene-poor
Alu repeats	LINE repeats
SINE repeats	HMG-1 nonhistone proteins bound to AT-rich areas
Z-DNA conformation possible	Minisatellites

Banding

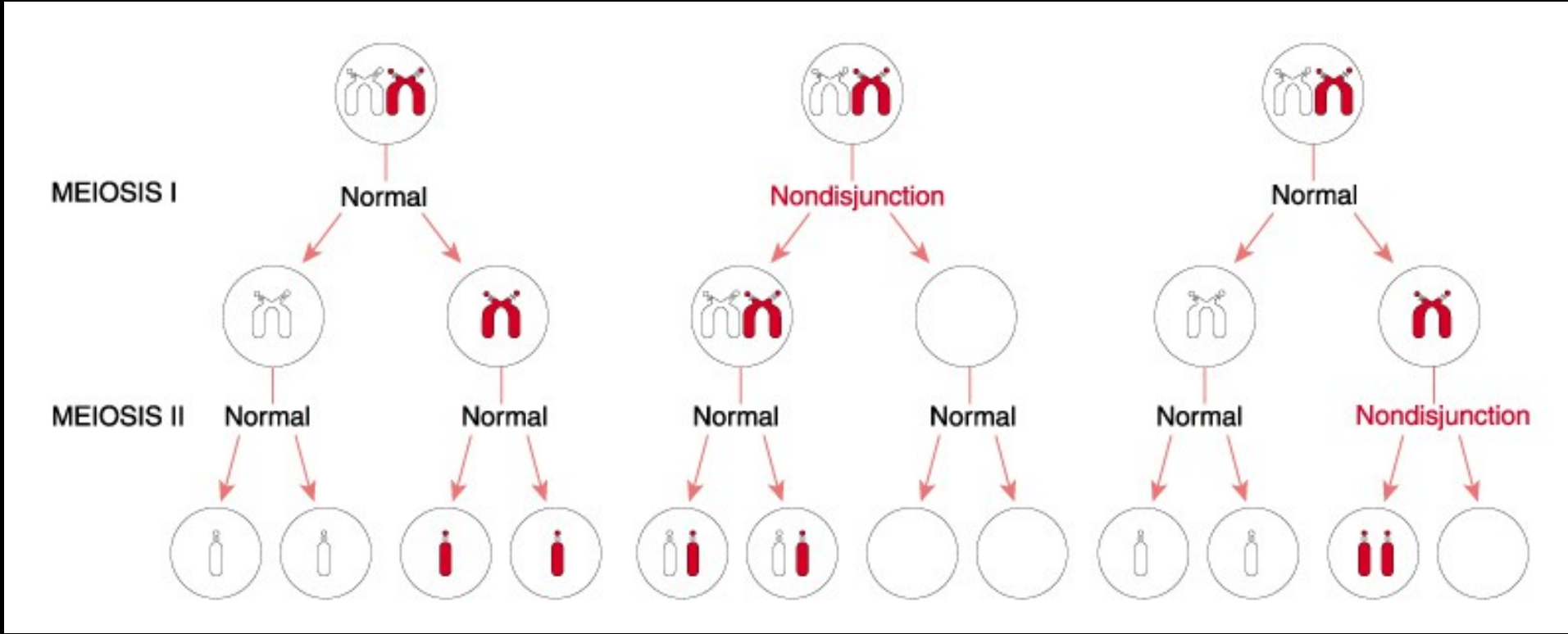
MAIN TYPES OF CHROMOSOME BANDS		
Banding Methods	**Type**	**Principle Use**
Trypsin-induced Giemsa stain	G	Differentiates light and dark bands
AT-specific fluorochrome (quinicrine, Hoechst 3325B)	Q	Light fluorescence in the region of dark G-bands, some centromere regions, distal long arm of Y-chromosome
Reverse bands	R	Opposite of G
Centromere stain	C	Centromere region darkly stained
Bromodeoxyuridine (BrdU) for 2 cell cycles	SCE	Differential staining of sister chromatids (SCEs)
Distamycin A-DAPI	DA/DAPI	Light fluorescence in the short arm of chromosome 15, centromere regions of 1, 9, and 16; distal long arm of Y
Silver nitrate stain	NOR	Short arms of all acrocentric chromosomes
Giemsa II	GII	Centromere of chromosome 11

Sister chromatid exchanges in Bloom syndrome

Banding (FISH)



Aneuploidy: Nondisjunction



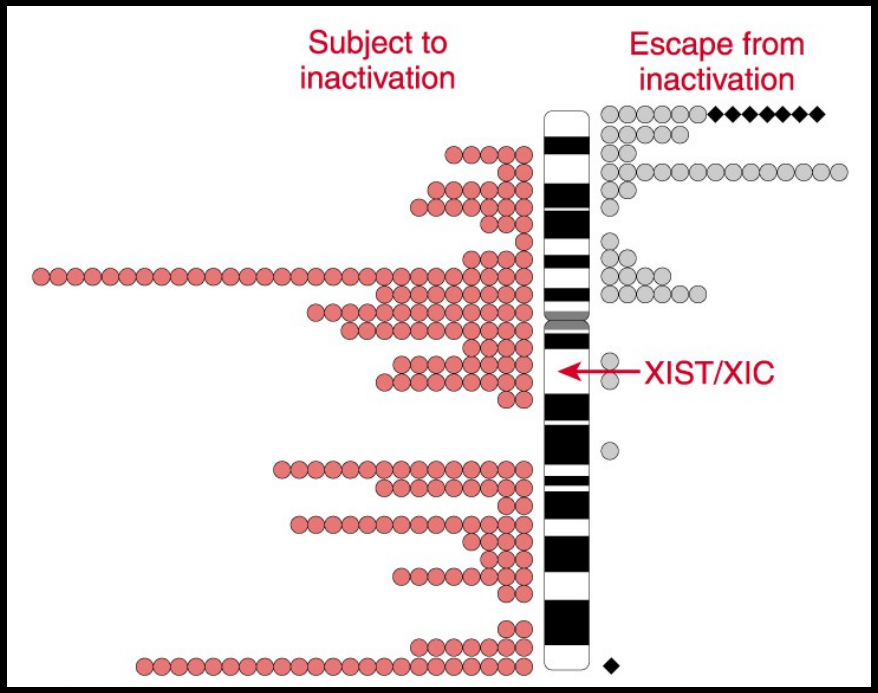
The phenotypes associated with sex chromosome trisomies are less severe than those associated with autosomal trisomies.

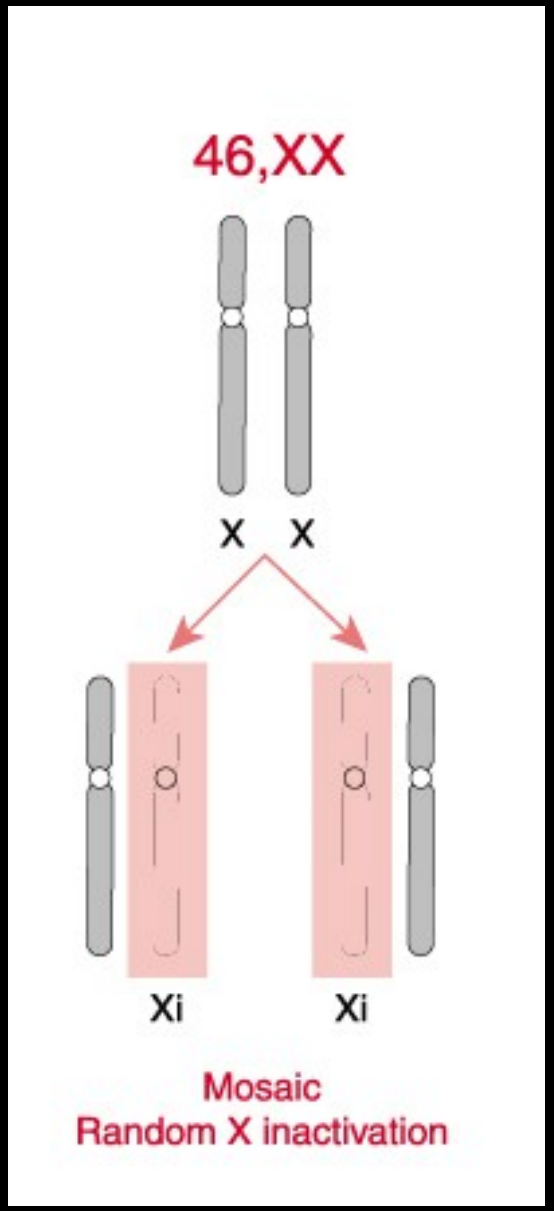
TABLE 10–4

Follow-Up Observations on Patients with Sex Chromosome Aneuploidy

Disorder	Karyotype	Phenotype	Sexual Development	Intelligence	Behavioral Problem
Klinefelter syndrome	47,XXY	Tall male (see text)	Infertile; hypogonadism	Learning difficulties (some patients)	May have poor psychosocial adjustment
XYY syndrome	47,XYY	Tall male	Normal	Normal	Frequent
Trisomy X	47,XXX	Female, usually tall	Usually normal	Learning difficulties (some patients)	Occasional
Turner syndrome	45,X	Short female, distinctive features (see text)	Infertile; streak gonads	Normal (but see text)	Rare

Clinical phenotype of Turner syndrome is due to haploinsufficiency.

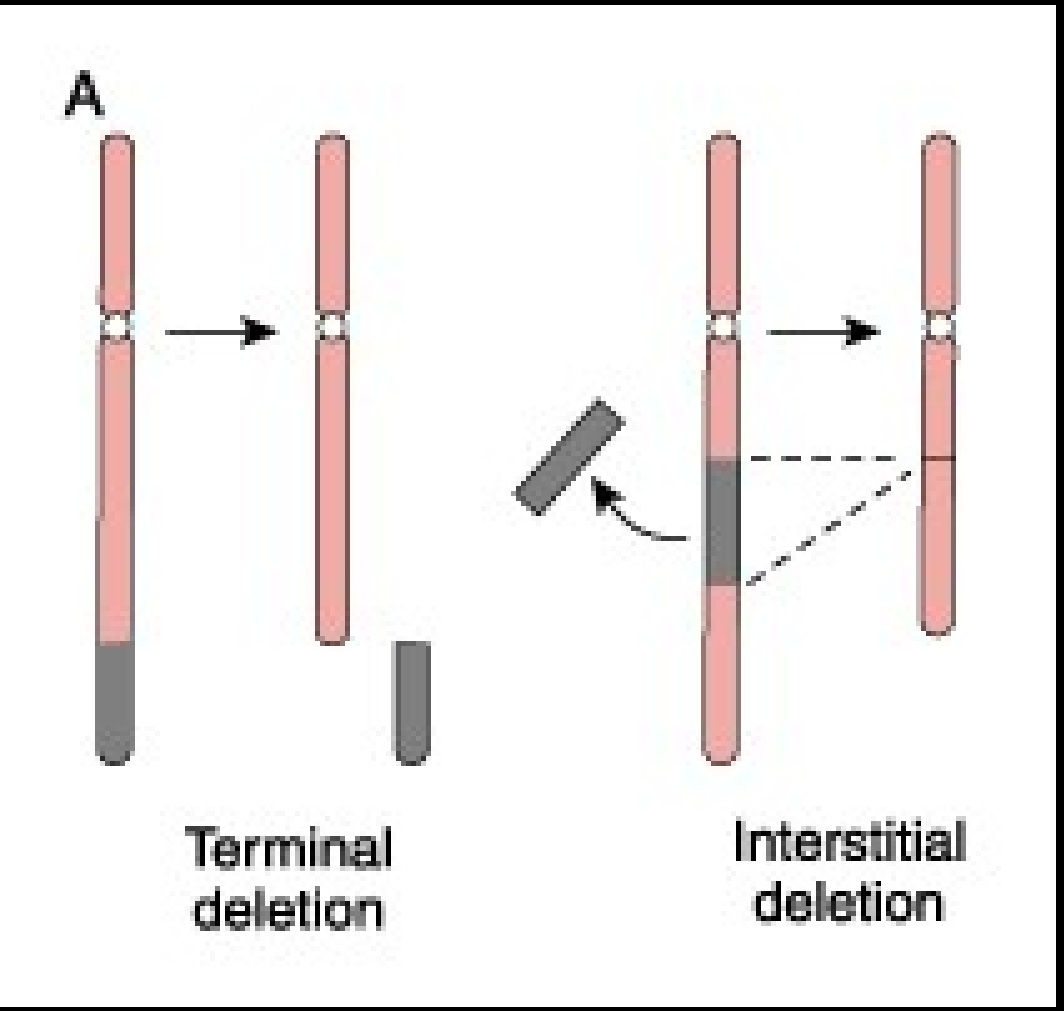


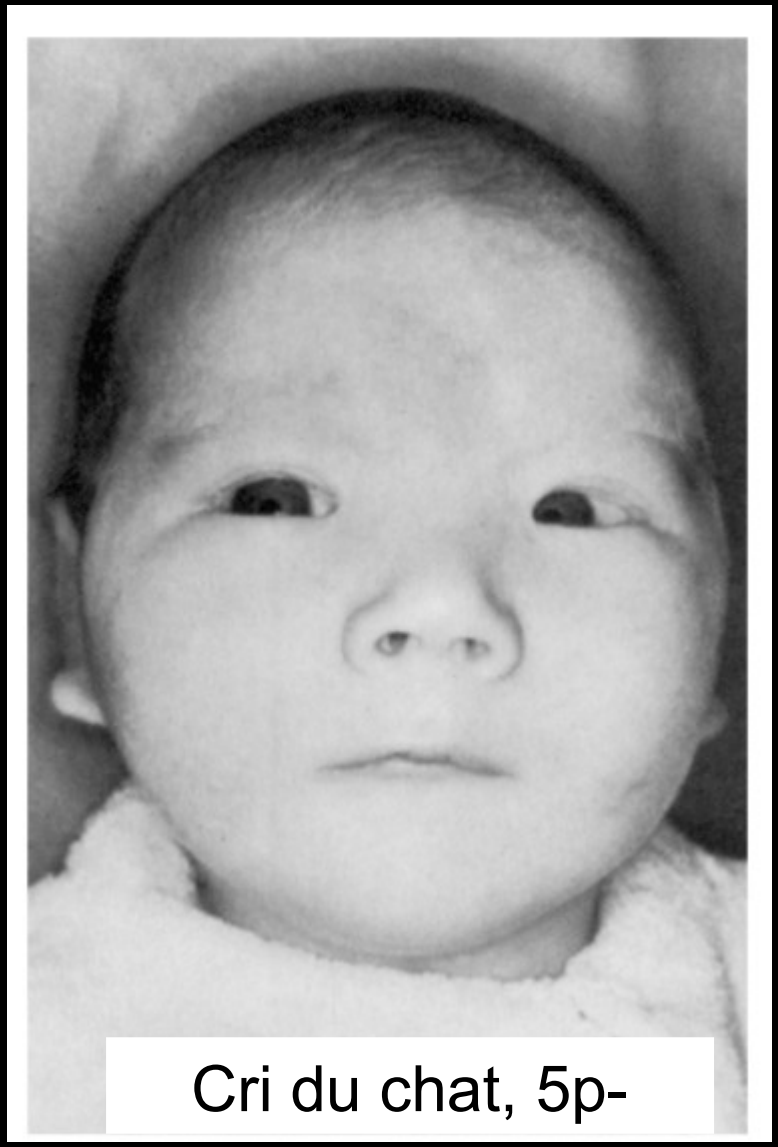


Structural chromosome abnormalities arising from chromosome breakage:

- Deletions
- Ring chromosomes
- Isochromosomes
- Translocation

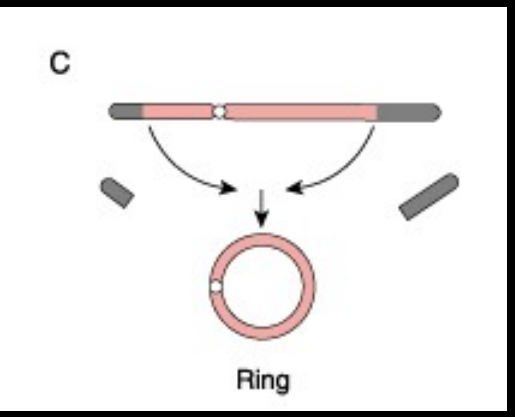
Deletions

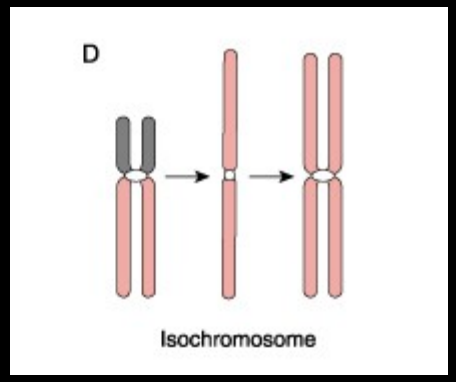




Cri du chat, 5p-

Ring Chromosomes; Isochromosomes





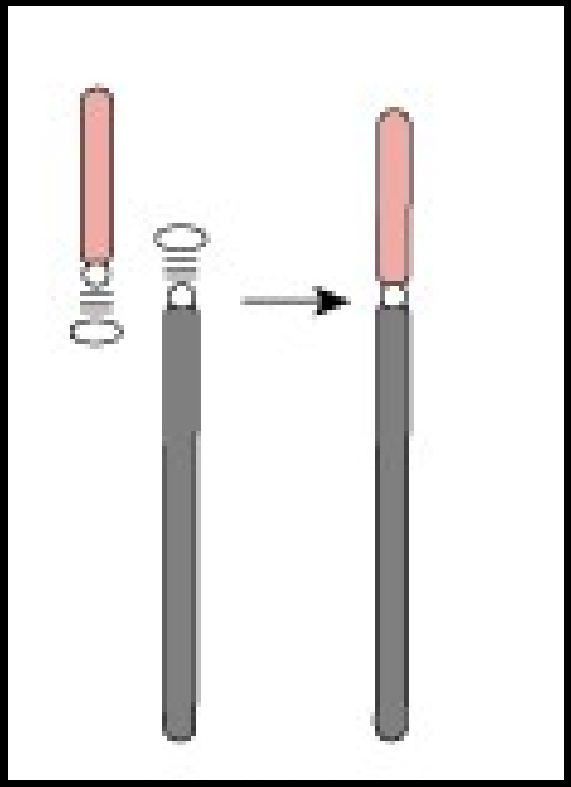
FREQUENCY OF TURNER SYNDROME KARYOTYPES	
Karyotype	**Frequency**
45,X	50%
46,X,i(Xq)	15%
45,X/46,XX mosaics	15%
45,X/46,X,i(Xq) mosaics	About 5%
45,X,other X abnormality	About 5%
Other 45,X/? mosaics	About 5%

Translocation

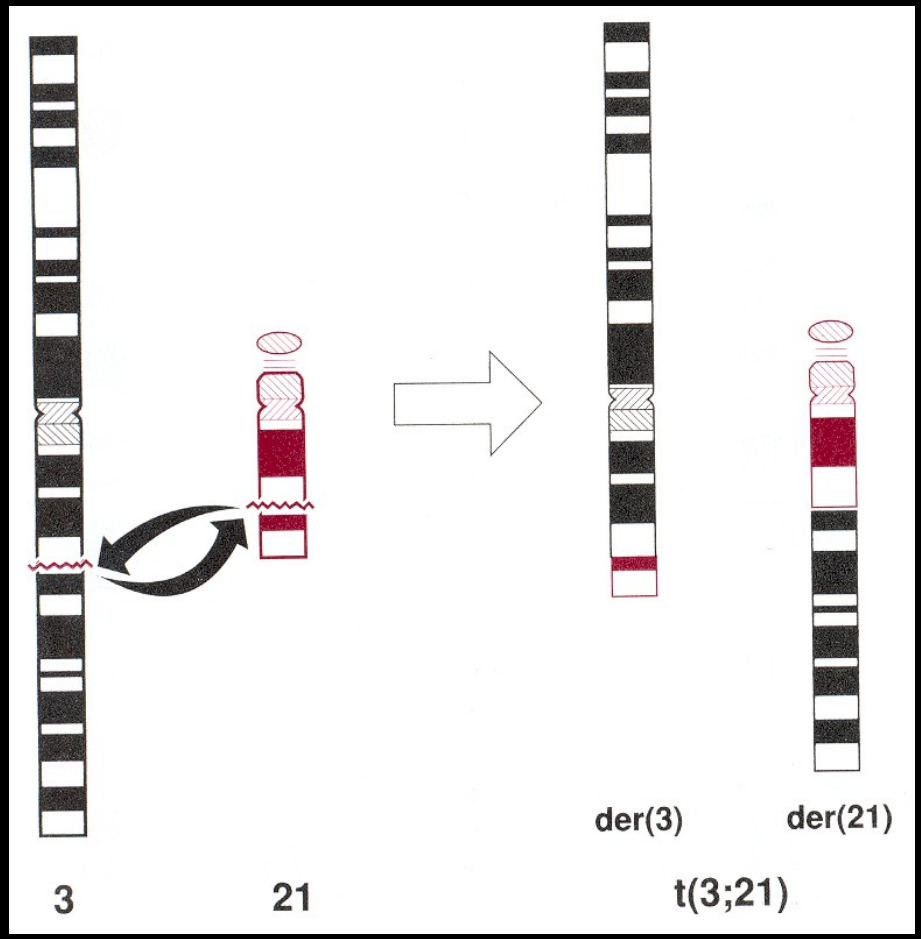
–

examples and consequences

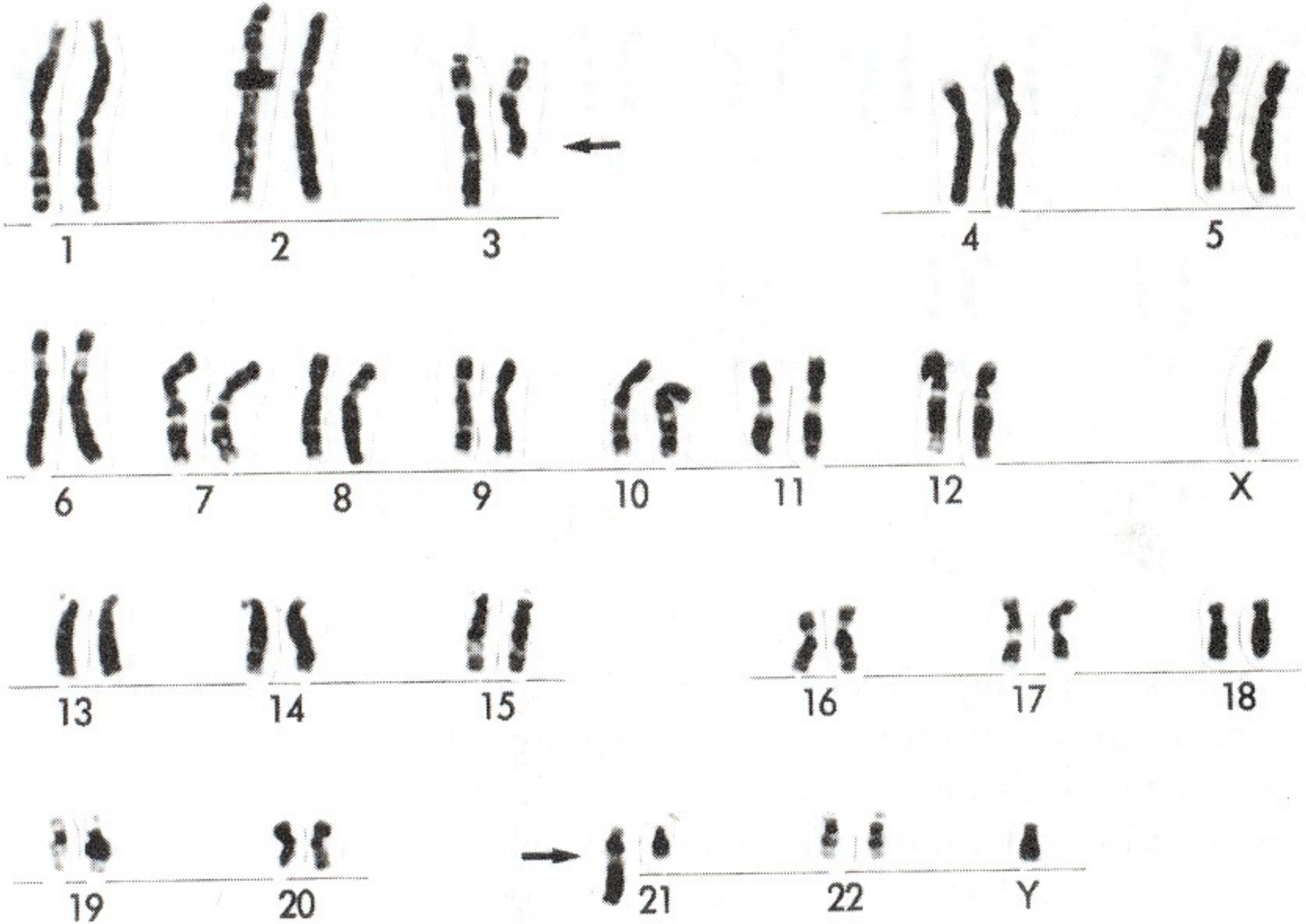
Translocation



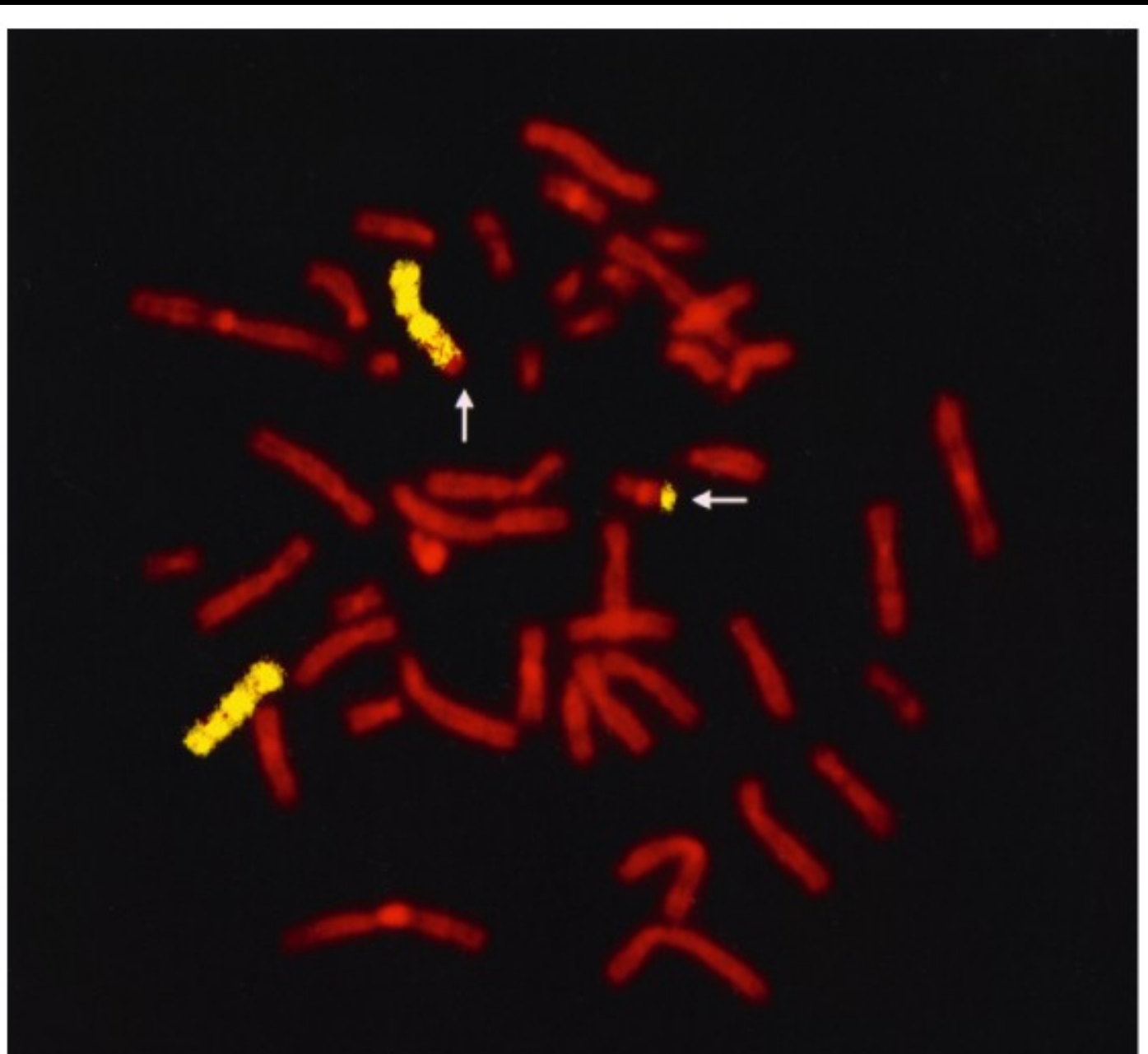
Robertsonian translocation



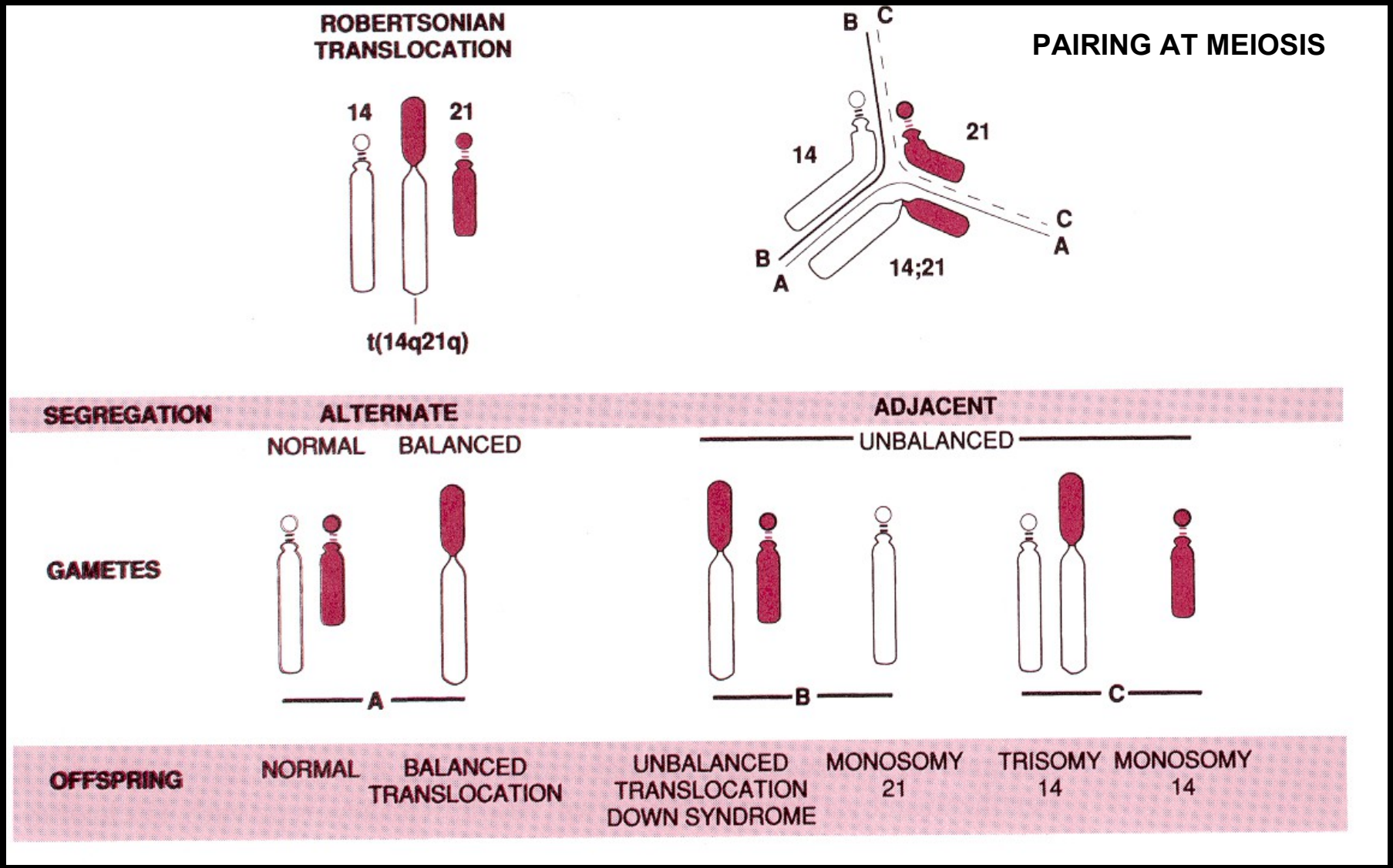
Reciprocal translocation

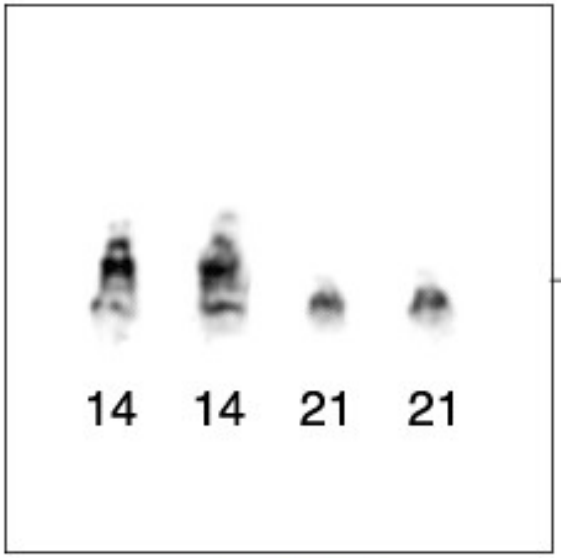

1
2
3
4
5
6
7
8
9
10
11
12
X
13
14
15
16
17
18
19
20
21
22
Y

46,XY,t(11;16)(q24;q23)

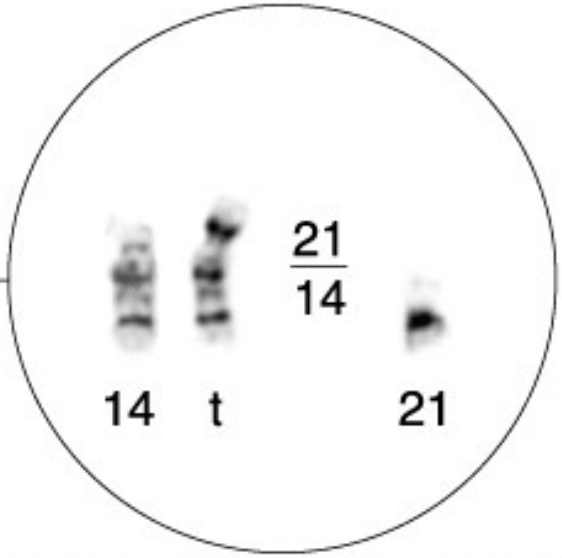


Translocation

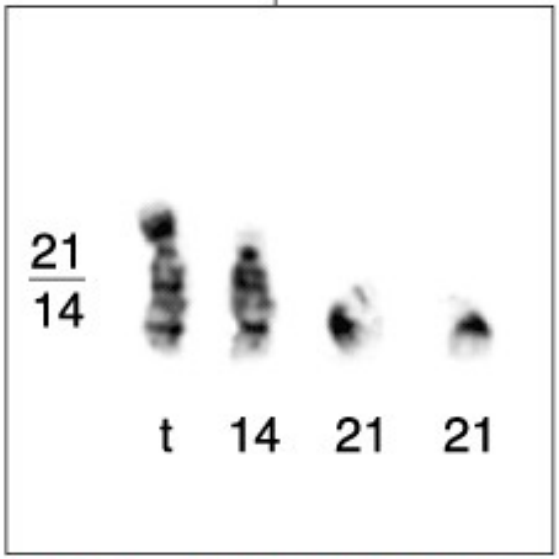




46,XY

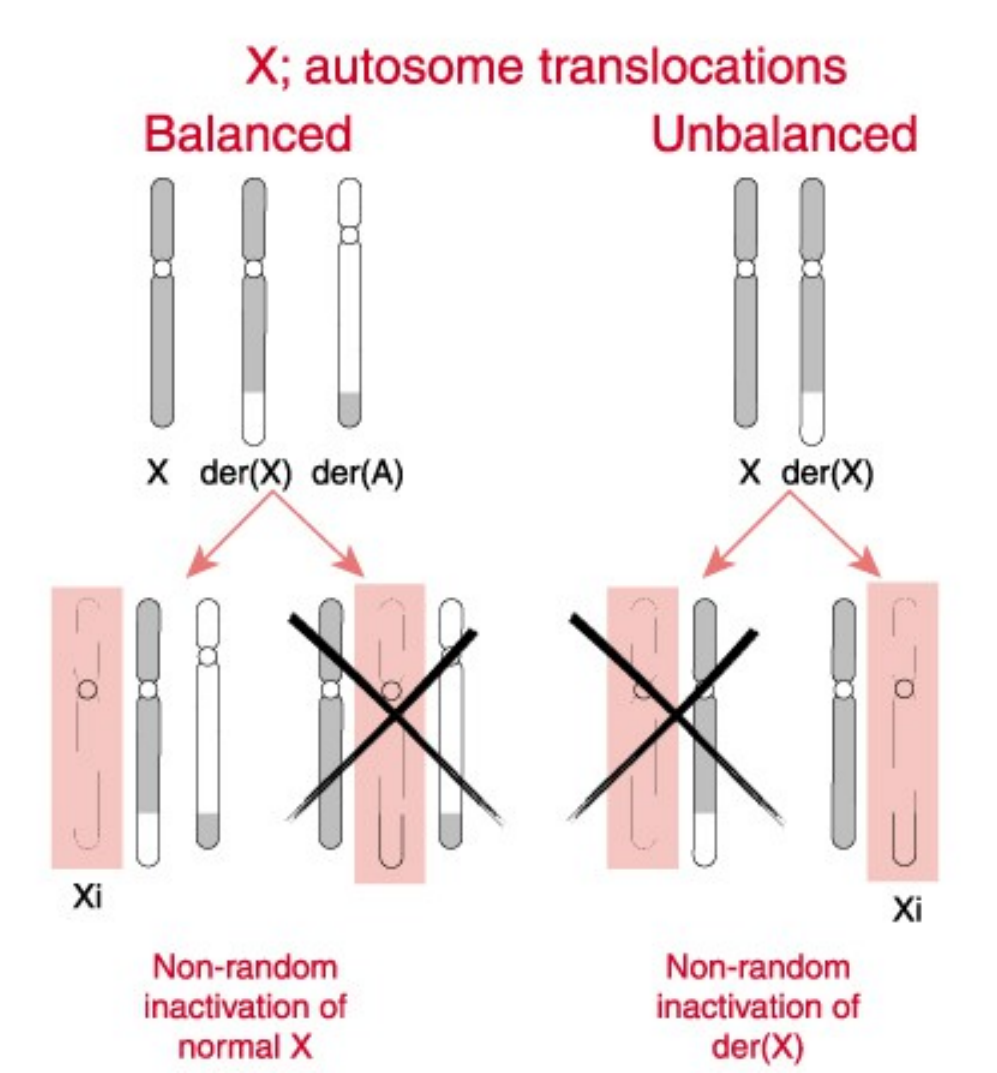


45,XX,rob(14;21)



46,XY,rob(14;21),+21

Translocation: non-random X-inactivation



Structural chromosomal abnormalities arising from faulty DNA metabolism:

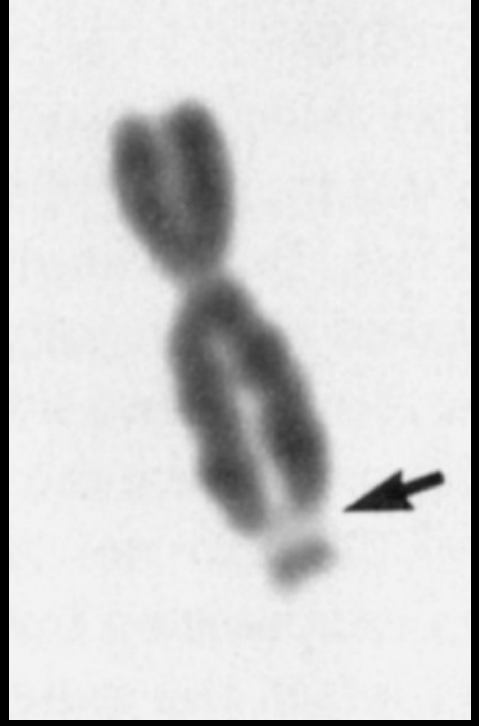
- **Slipped mispairing during DNA replication**
- **Nonreciprocal recombination**

Slipped mispairing during DNA replication

TABLE 12–12

Four Representative Examples of Triplet Repeat Diseases

Disease	Inheritance Pattern	Triplet Repeat	Gene Affected	Location in Gene	Mechanism of Disease	Repeat Number		
						Normals	*Unstable Intermediate*	*Affected*
Huntington disease	Autosomal dominant	CAG	huntingtin	coding region	?toxic effect of glutamines	<36	29–35 usually unaffected	>35
Fragile X	X-linked	CGG	*FMR1*	5′ untranslated	causes excessive methylation leading to reduced *FMR1* expression	<60	60–200 usually unaffected	>200
Myotonic dystrophy	Autosomal dominant	CTG	*DMPK*	3′ untranslated	?unclear	<30	50–80 usually mildly affected	80–2000
Friedreich ataxia	Autosomal recessive	AAG	frataxin	intron	interferes with RNA processing, leading to reduced frataxin expression	<34	36–100 (uninterrupted)	>100



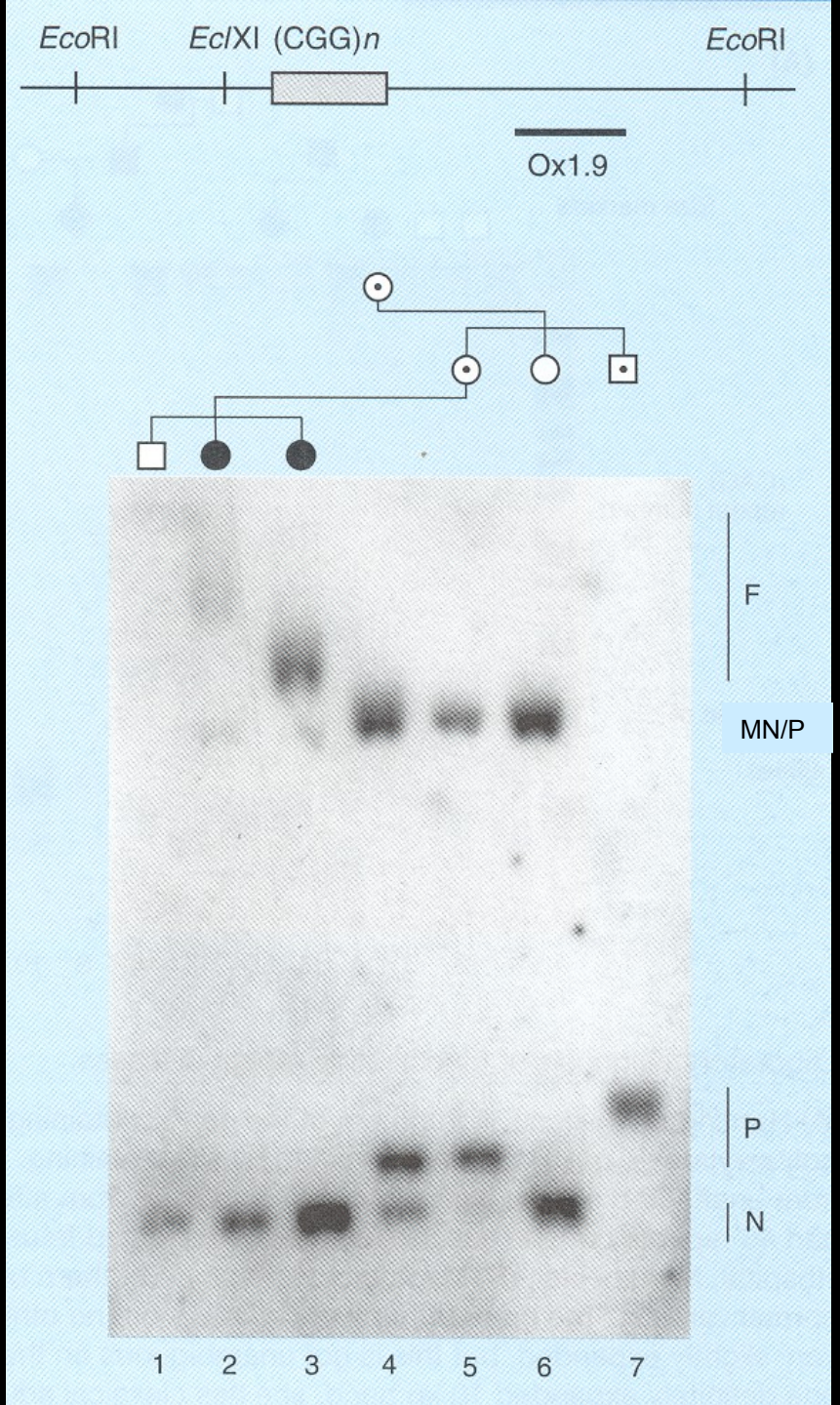
N = normal

P = unmethylated premutation

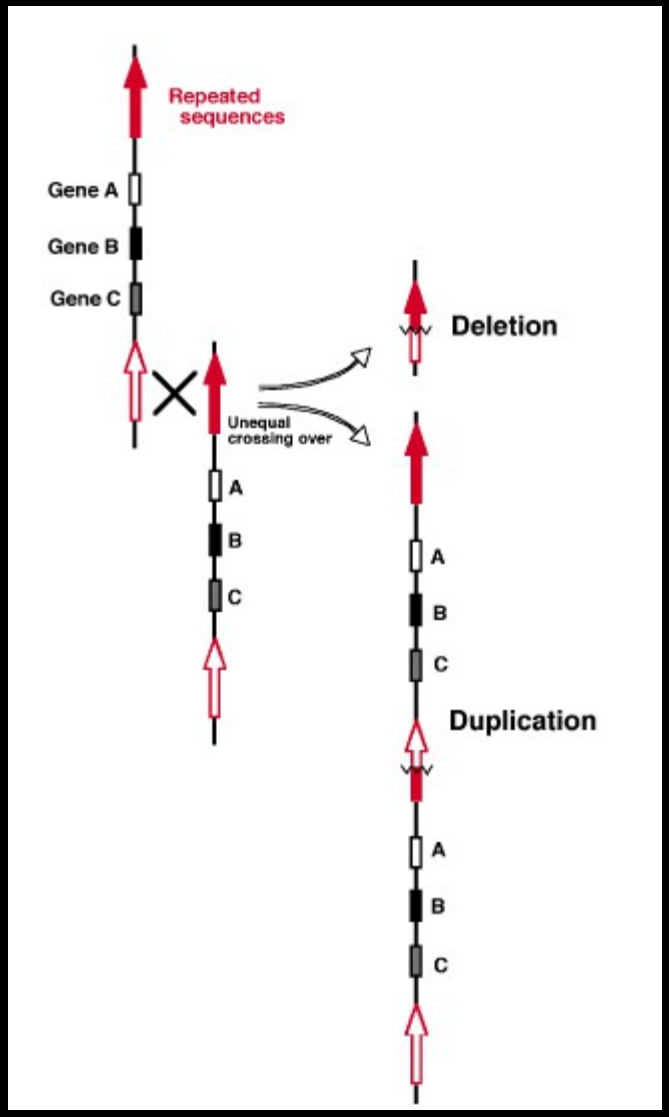
MN/P = methylated normal or premutation

F = methylated full mutation

*Ecl*XI: methylation sensitive



Non-reciprocal recombination



Non-reciprocal recombination

TABLE 10–2

Microdeletion or Contiguous Gene Syndromes Involving Recombination Between Repeated Sequences

Disorder	Location	Rearrangement		Repeat Length (kb)
		Type	*Size (kb)*	
Smith-Magenis syndrome	17p11.2	Deletion	5000	200
dup(17)(p11.2)		Duplication		
Prader-Willi/Angelman syndromes	15q11-q13	Deletion	4000	~50–400
Williams syndrome	7q11.23	Deletion	2000	>30
Ichthyosis	Xp22.3	Deletion	1900	20
Neurofibromatosis	17q11.2	Deletion	1500	~15–100
Charcot-Marie-Tooth (*CMT1A*)/HNLPP	17p12	Duplication	1500	24
		Deletion		
DiGeorge syndrome/ velocardiofacial syndrome	22q11	Deletion	3000	200
Cat-eye syndrome		Duplication		

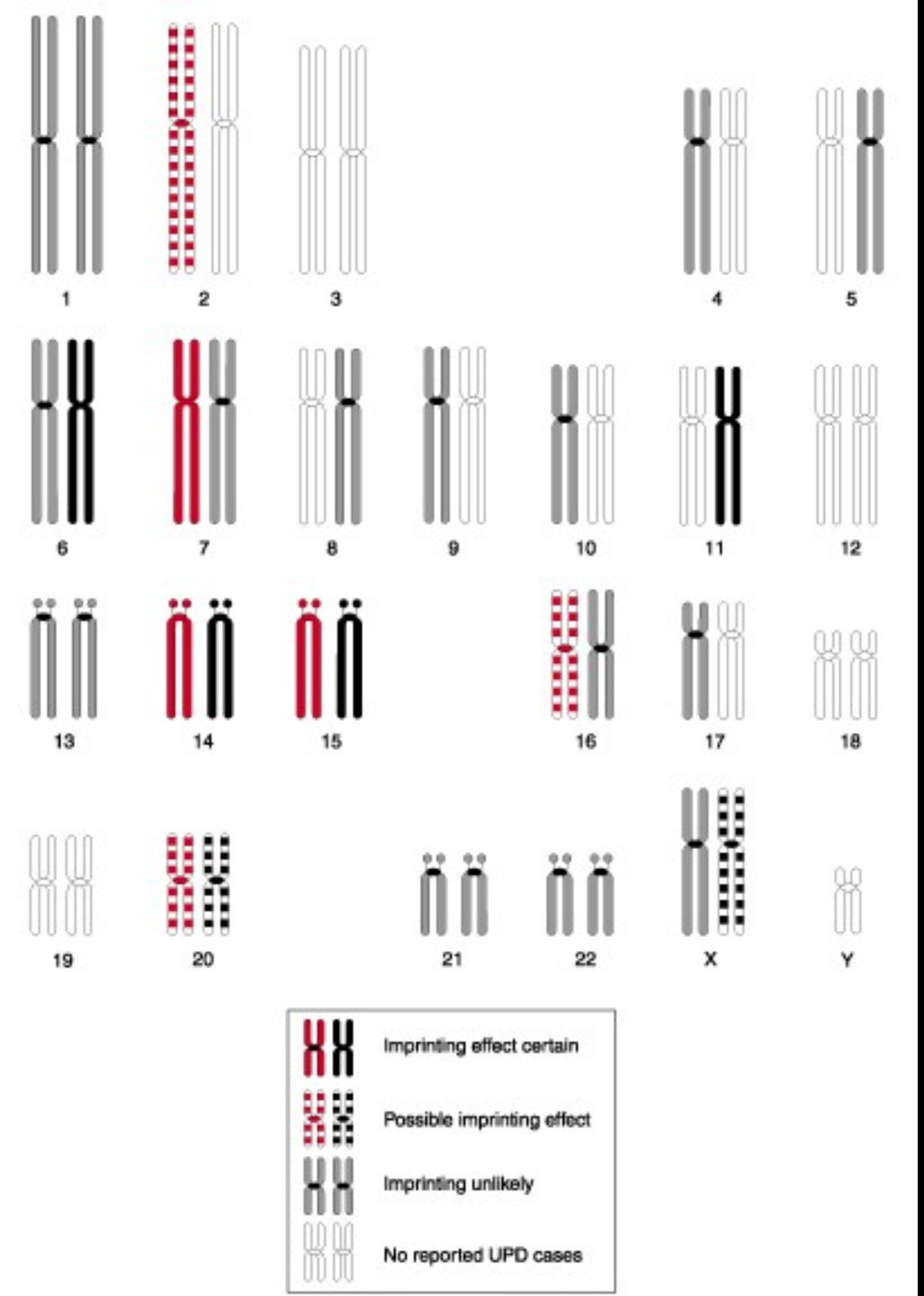
Genomic Imprinting:

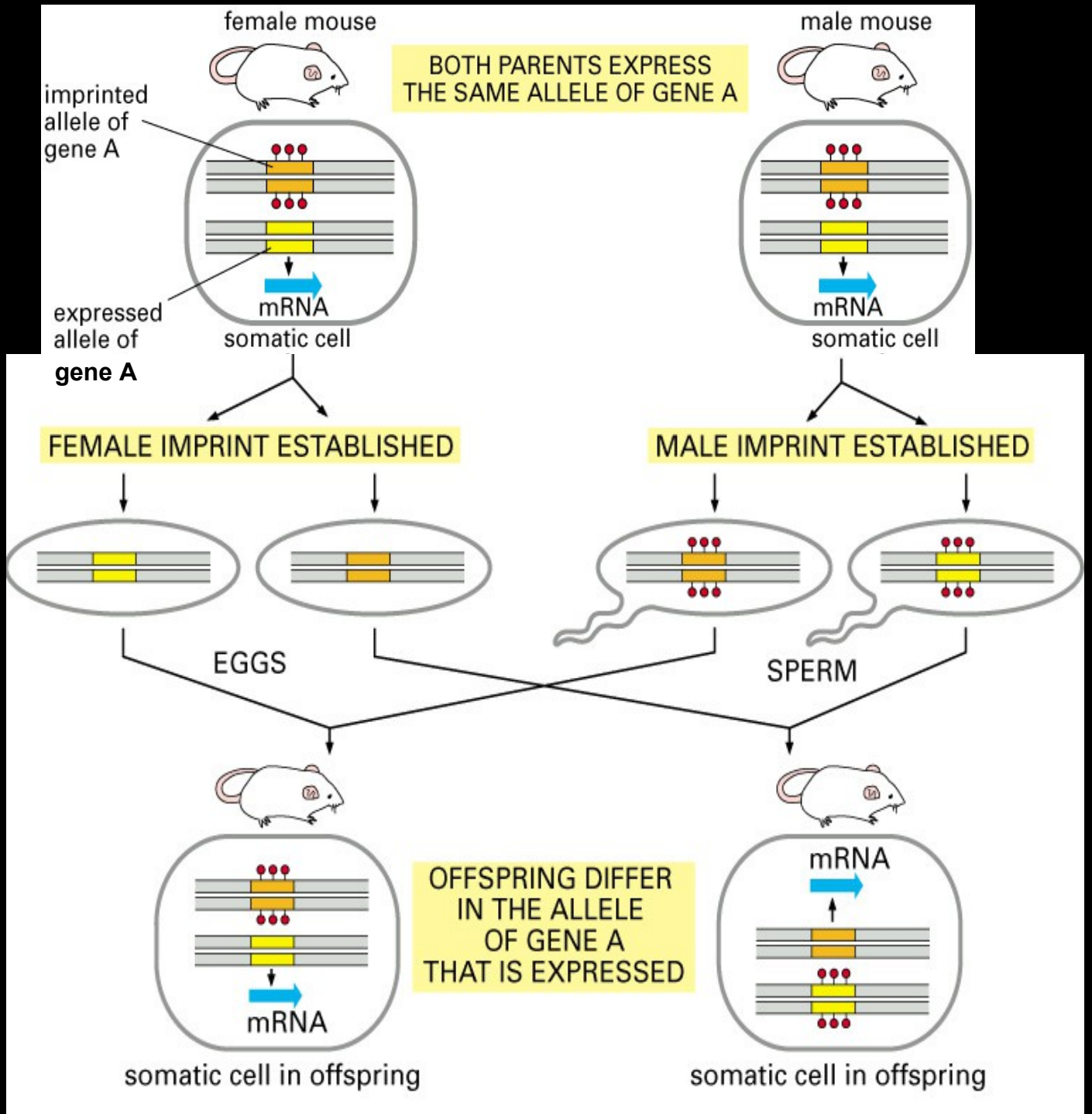
- mechanism
- distribution
- consequences

Map of Imprinted Regions in Human Genome

Maternally inherited homolog (left)

Paternally inherited homolog (right)



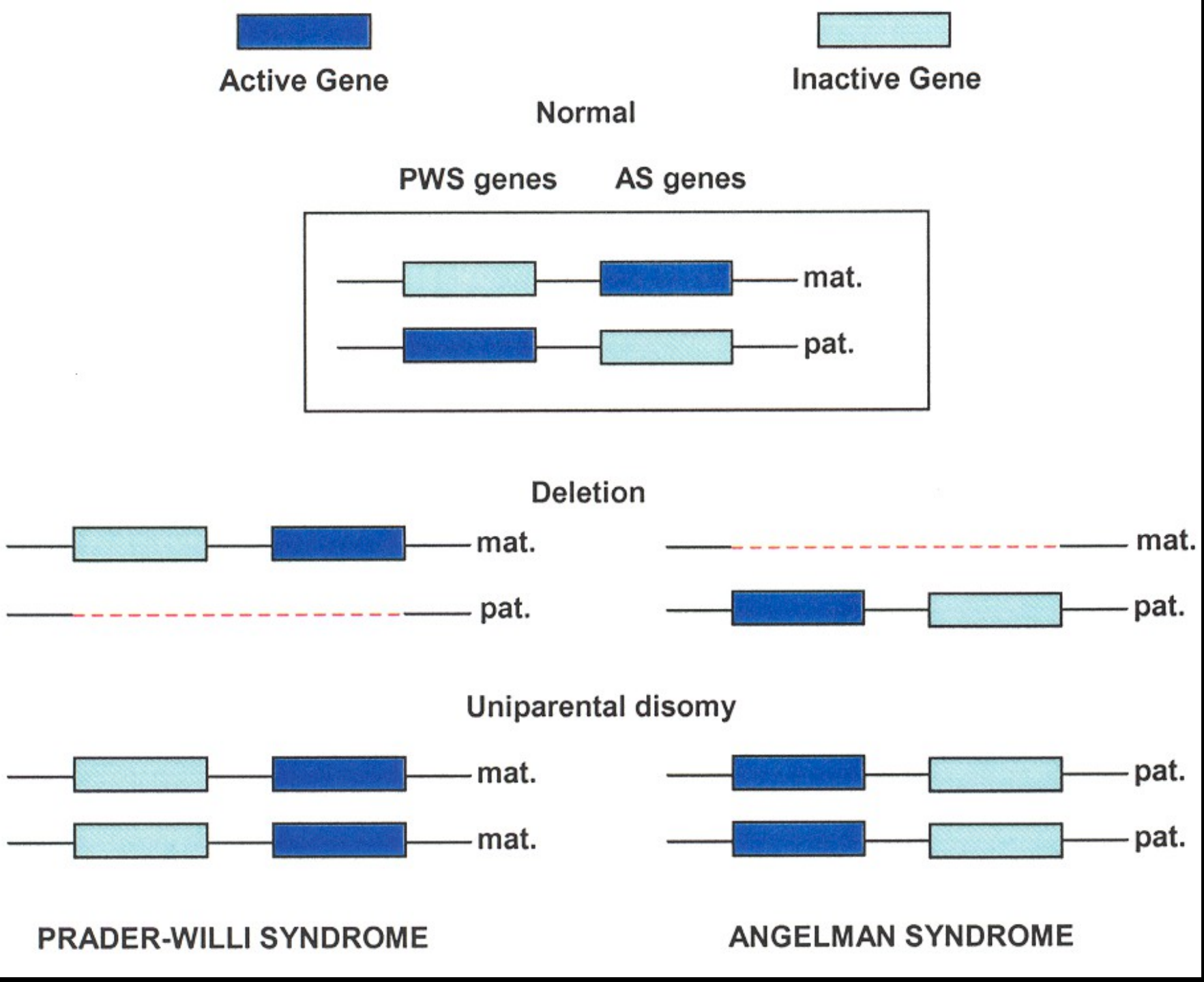

female mouse
male mouse
BOTH PARENTS EXPRESS THE SAME ALLELE OF GENE A
imprinted allele of gene A
expressed allele of gene A
mRNA
somatic cell
mRNA
somatic cell
FEMALE IMPRINT ESTABLISHED
MALE IMPRINT ESTABLISHED
EGGS
SPERM
mRNA
OFFSPRING DIFFER IN THE ALLELE OF GENE A THAT IS EXPRESSED
mRNA
somatic cell in offspring
somatic cell in offspring

Genomic Imprinting

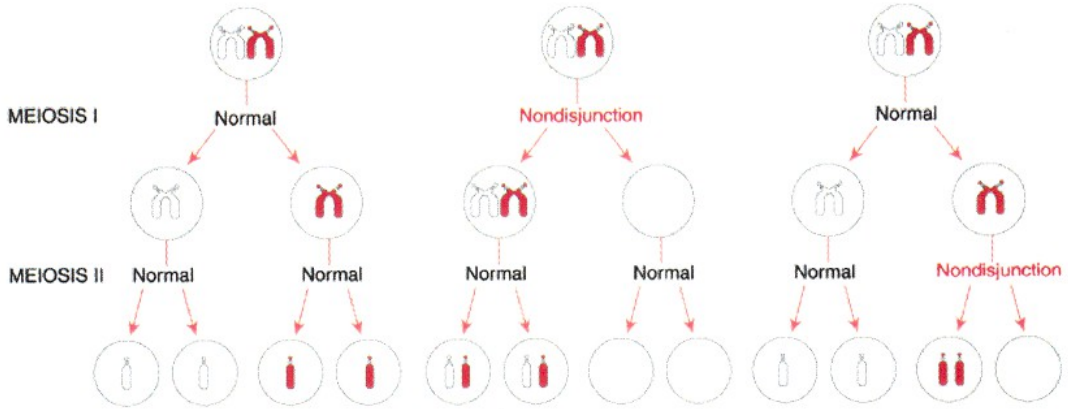
TABLE 5–3

Molecular Mechanisms Causing Prader-Willi and Angelman Syndromes

	Prader-Willi Syndrome	Angelman Syndrome
15q11-q13 deletion	~70 percent (paternal)	~70 percent (maternal)
Uniparental disomy	~30 percent (maternal)	~3–5 percent (paternal)
Single-gene mutation	ND	E6-AP ubiquitin-protein ligase (2–4 percent of total but seen only in familial cases)
Imprinting center mutation	1–2 percent	7–9 percent
Other	ND	10–20 percent


Active Gene
Inactive Gene
Normal
PWS genes
AS genes
mat.
pat.
Deletion
mat.
pat.
mat.
pat.
Uniparental disomy
mat.
mat.
pat.
pat.
PRADER-WILLI SYNDROME
ANGELMAN SYNDROME

Etiology of Uniparental Disomy



Nondisjunction produces egg with 2 maternal chromosome 15 - both chromosomes with maternal imprint

Fertilization produces trisomic zygote (not viable)

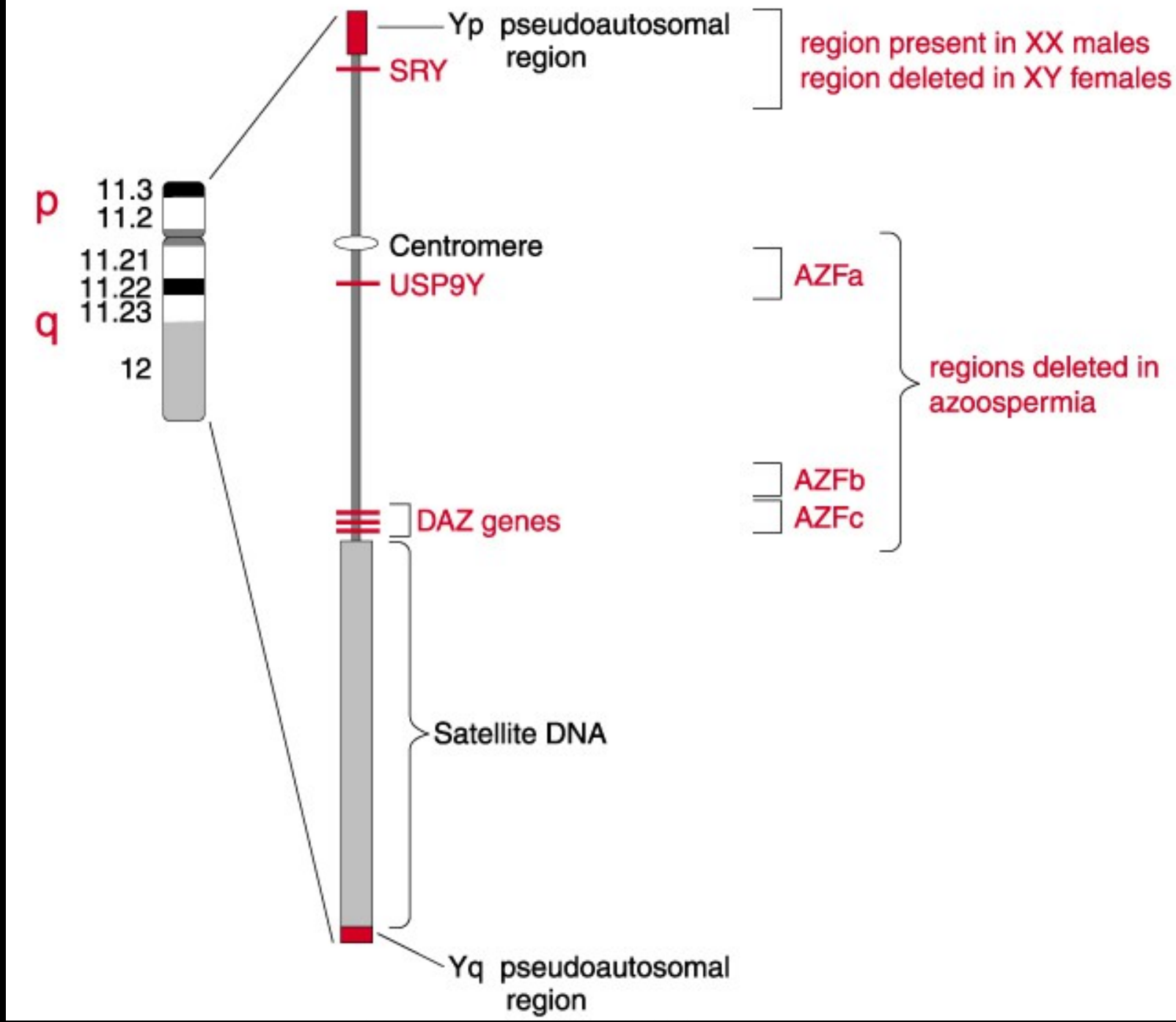
One chromosome in zygote is eliminated: Trisomy Rescue

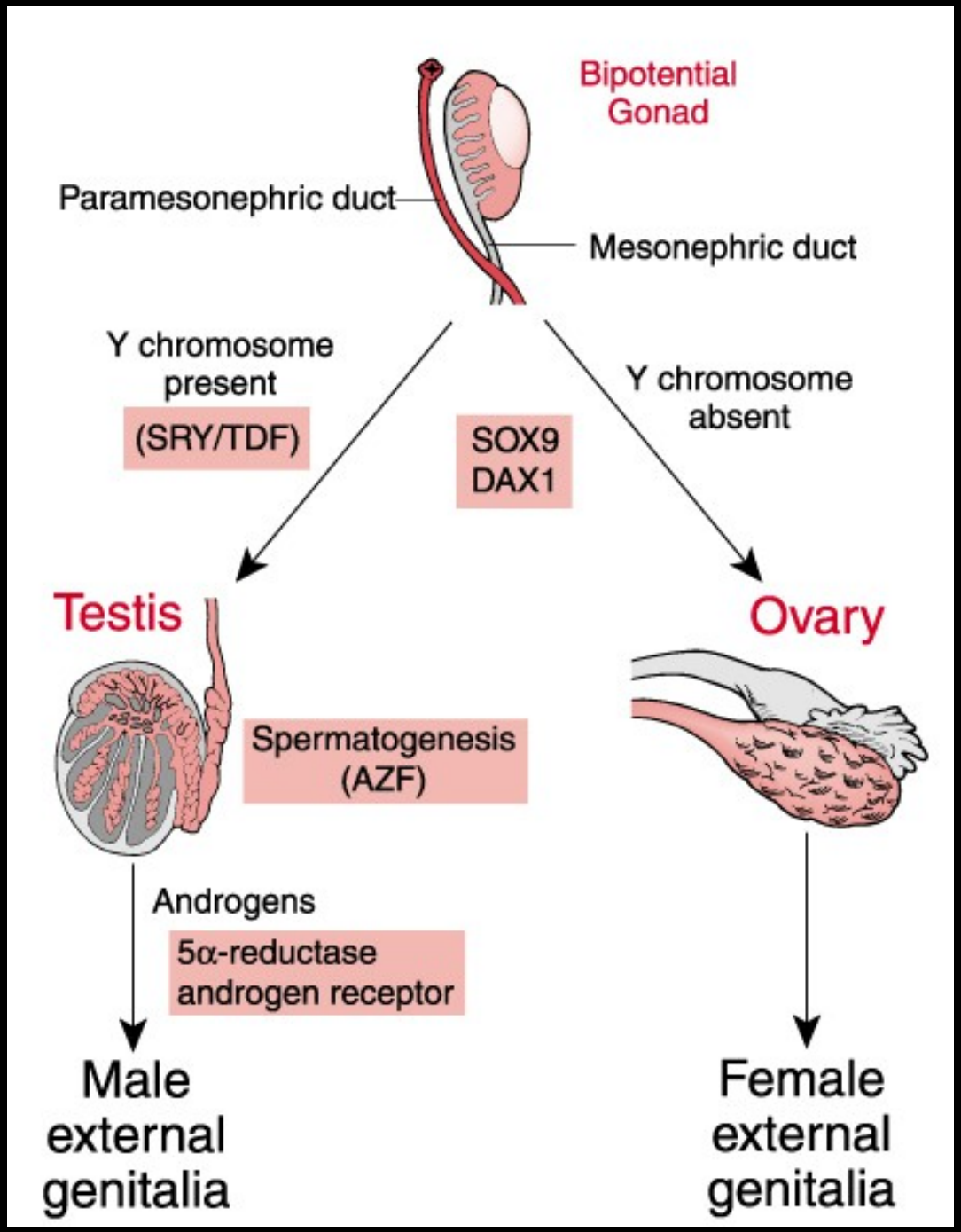
Fertilization by a sperm missing chromosome 15 due to nondisjunction: Gamete Complementation

Nondisjunction produces egg with no maternal chromosome 15; fertilization produces zygote with one chromosome 15 with paternal imprint (monosomy not viable)

A second copy of the single paternal chromosome 15 in the zygote is made: Monosomic Rescue

Sex Reversal:
Role of the *sry* gene


Yp pseudoautosomal region
SRY
region present in XX males
region deleted in XY females
p
q
11.3
11.2
11.21
11.22
11.23
12
Centromere
USP9Y
AZFa
regions deleted in azoospermia
AZFb
AZFc
DAZ genes
Satellite DNA
Yq pseudoautosomal region


Bipotential Gonad
Paramesonephric duct
Mesonephric duct
Y chromosome present
(SRY/TDF)
SOX9
DAX1
Y chromosome absent
Testis
Ovary
Spermatogenesis
(AZF)
Androgens
5α-reductase
androgen receptor
Male external genitalia
Female external genitalia

Sex reversal due to translocation of SRY from Y to X

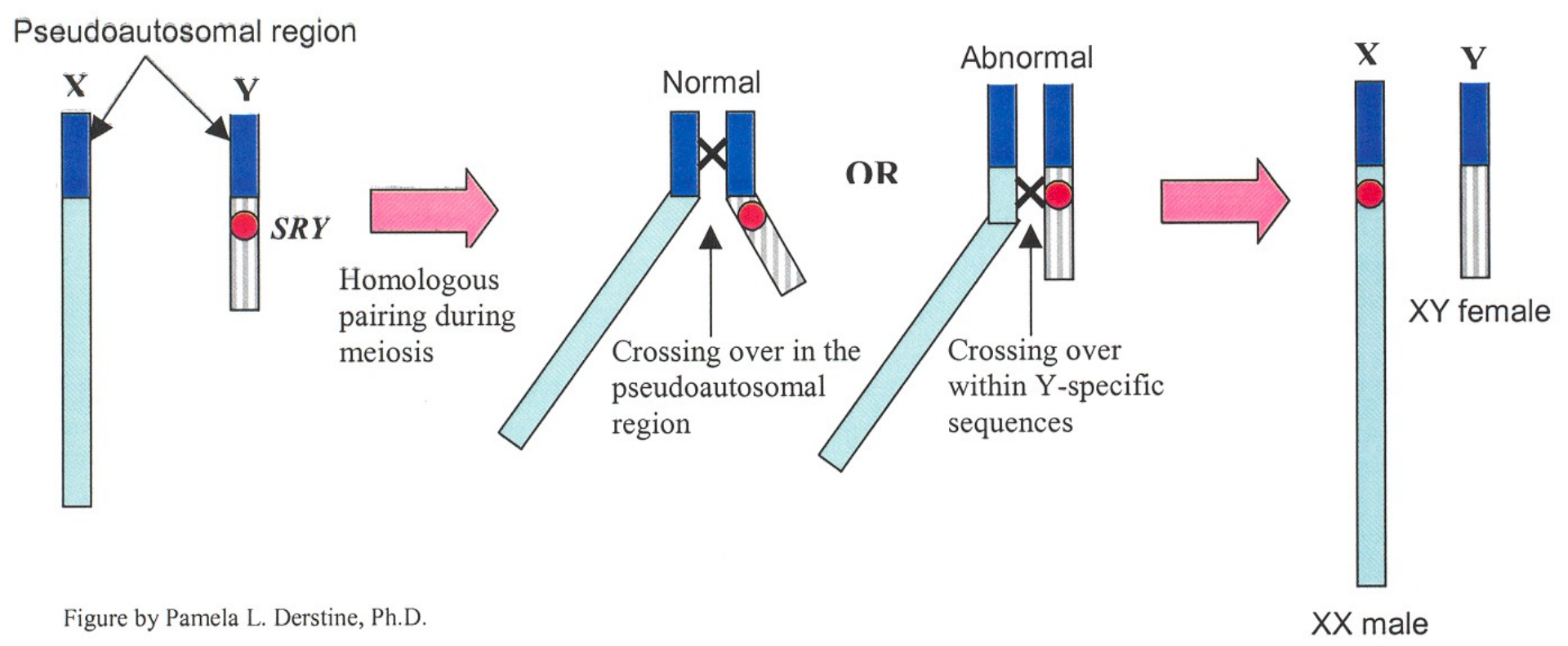


Figure by Pamela L. Derstine, Ph.D.