Chromosomal Disorders

Causes of Chromosomal Disorders

- Ionising radiation, virus infections and chemical toxins in the pathogenesis of certain disorders.

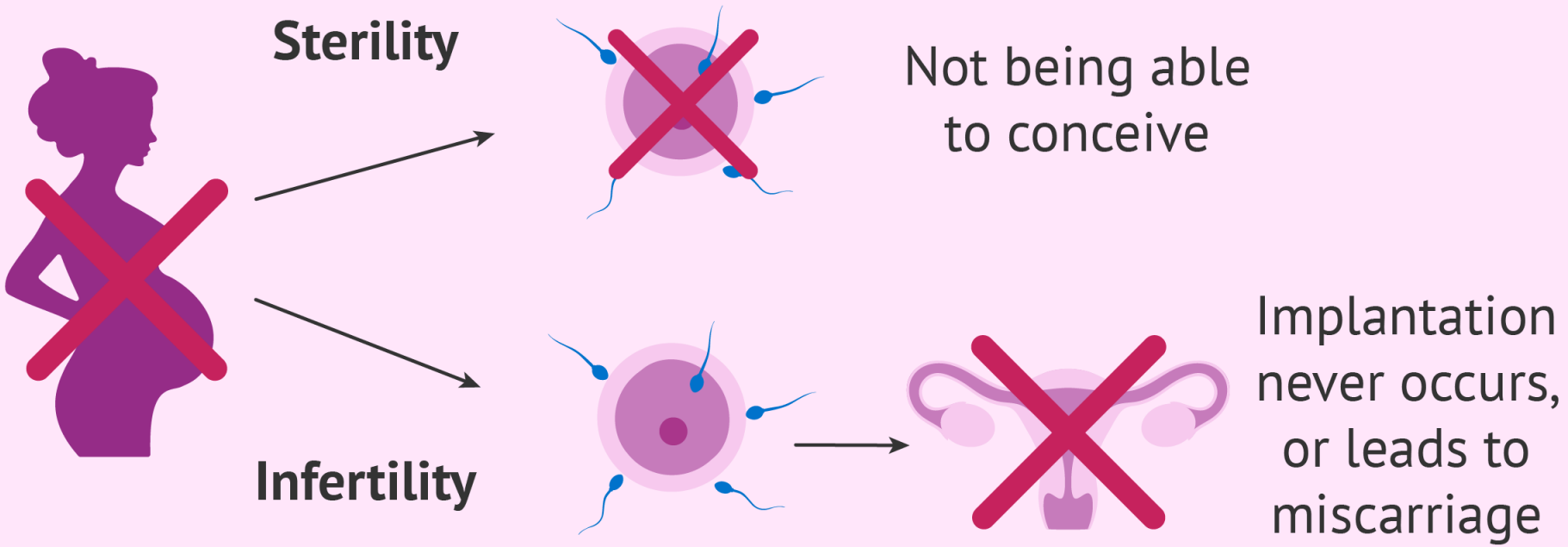
- Most cases of simple aneuploidy - monosomy or trisomy - are likely due to meiotic non-disjunctions

- Mitotic nondisjunction: it could happened!!

Clinical presentation suggestive of chromosomal abnormality

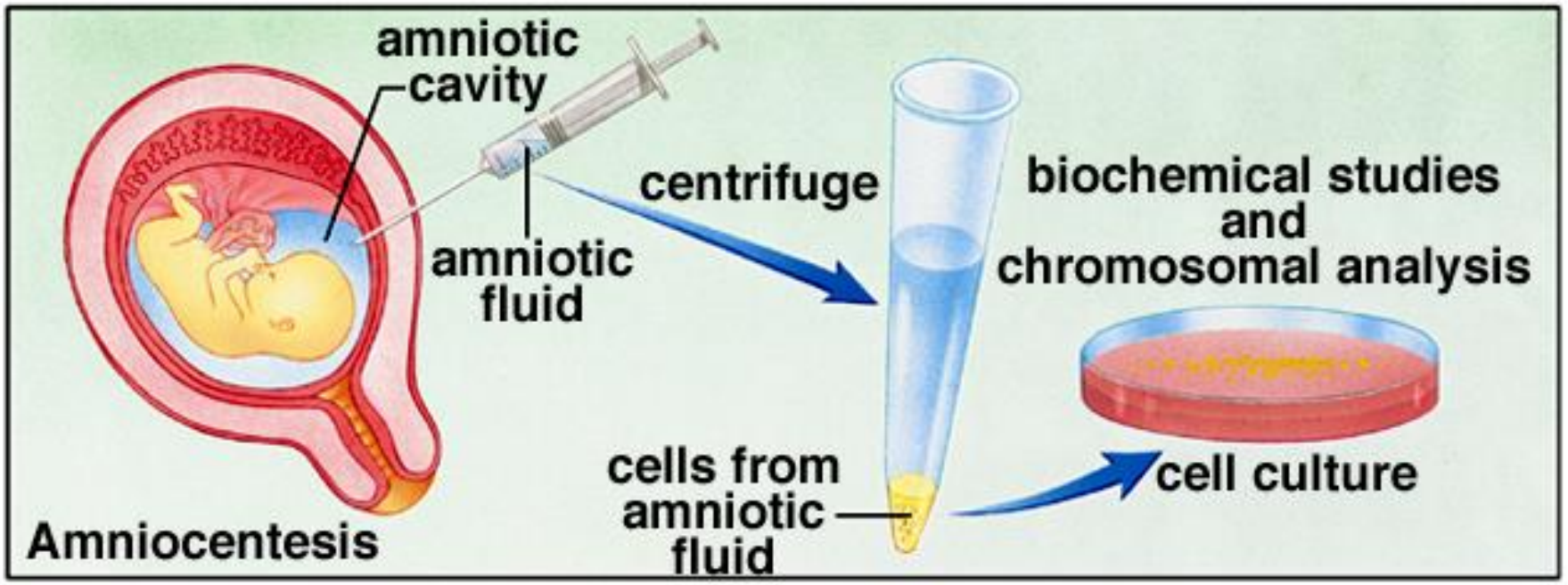
- Infertility and sterility: Cytogenetic analysis of such individuals is often warranted
- Intersexes: genetic and phenotypic sex do not correspond.
- Multiple congenital malformations: seen with many types of chromosomal abnormalities, particularly deletions and aneuploidy.
- Mental retardation: Well-known examples of this are Down and fragile X syndromes.

Sterility vs infertility



Genetic defect testing before birth – amniocentesis

14 and 16 weeks gestation



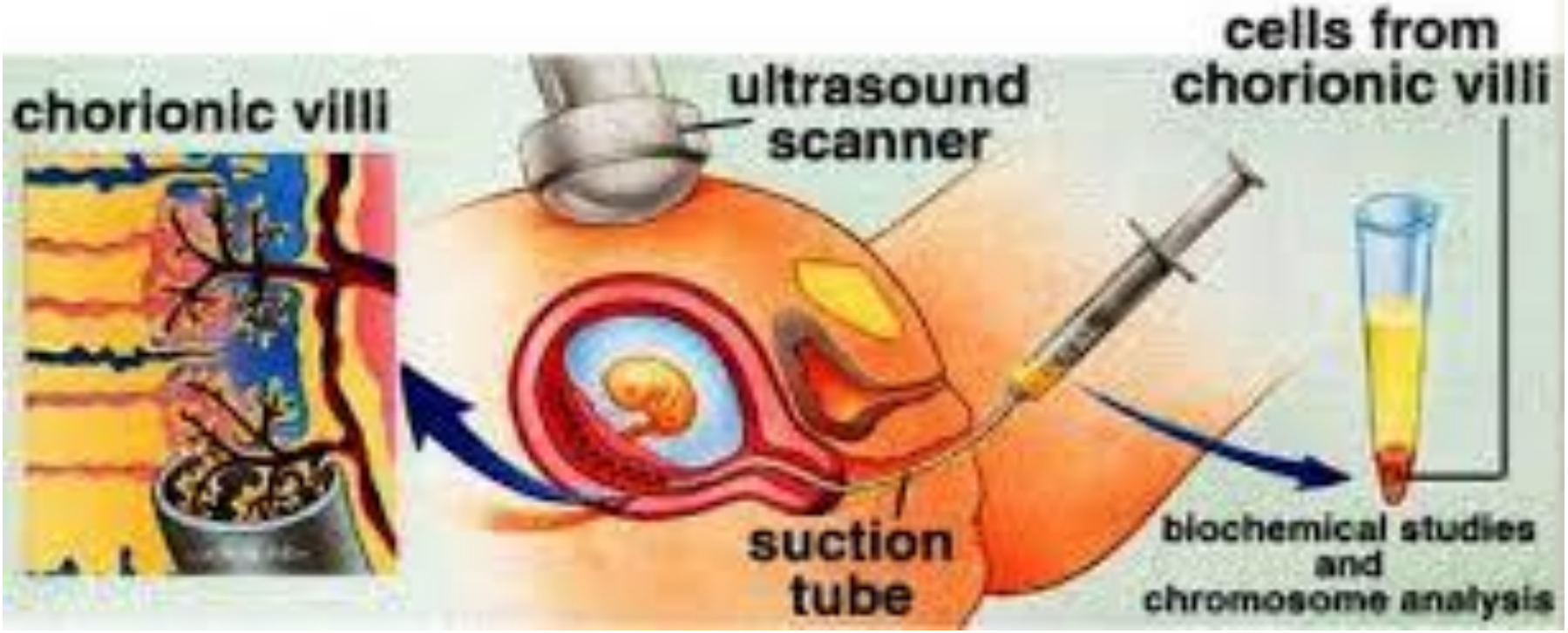
a.

Chorionic villus sampling uses what tissue to analyze the fetal cells and provide a karyotype?

A) fetal blood tissue
B) cells floating in the amniotic fluid
C) a small biopsy from the embryo itself but it readily heals
D) membrane tissues from the embryo side of the placenta
E) membrane tissues from the mother's side of the placenta

Answer: D

Chorionic Villi Sampling



10–12 weeks' gestation
Risk:
miscarriage (1-2%)
Infection
Amniotic fluid leakage

Chromosomal abnormalities

1. Alterations in chromosome number.

Euploid - normal set (2n)

Polyploidy – extra set of the entire genome. (3n, 4n etc) (triploidy,tetraploidy)

Aneuploidy – less or more than the normal diploid number.

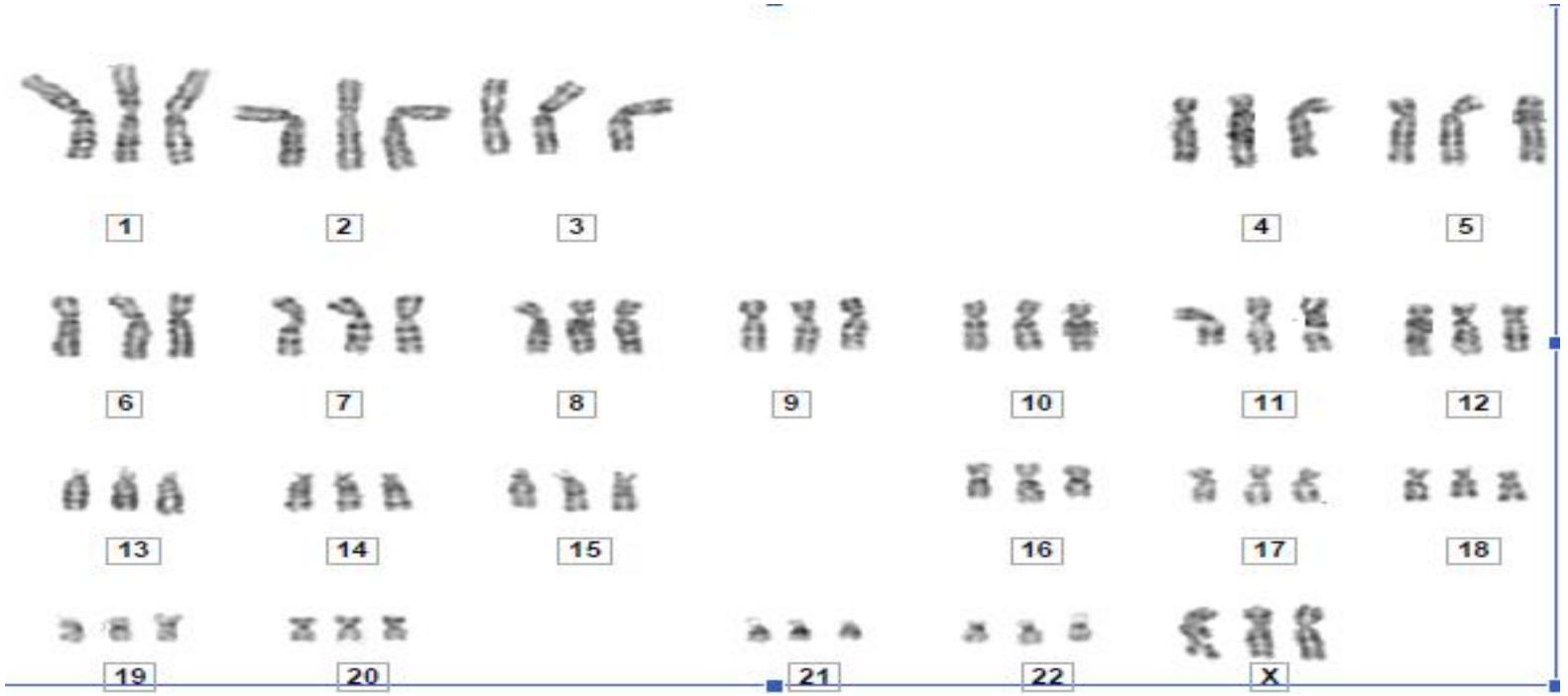
-Monosomy - one member of a chromosome pair is missing (2n-1)

-Trisomy - one chromosome set consists of 3 copies of a chromosome (2n+1)

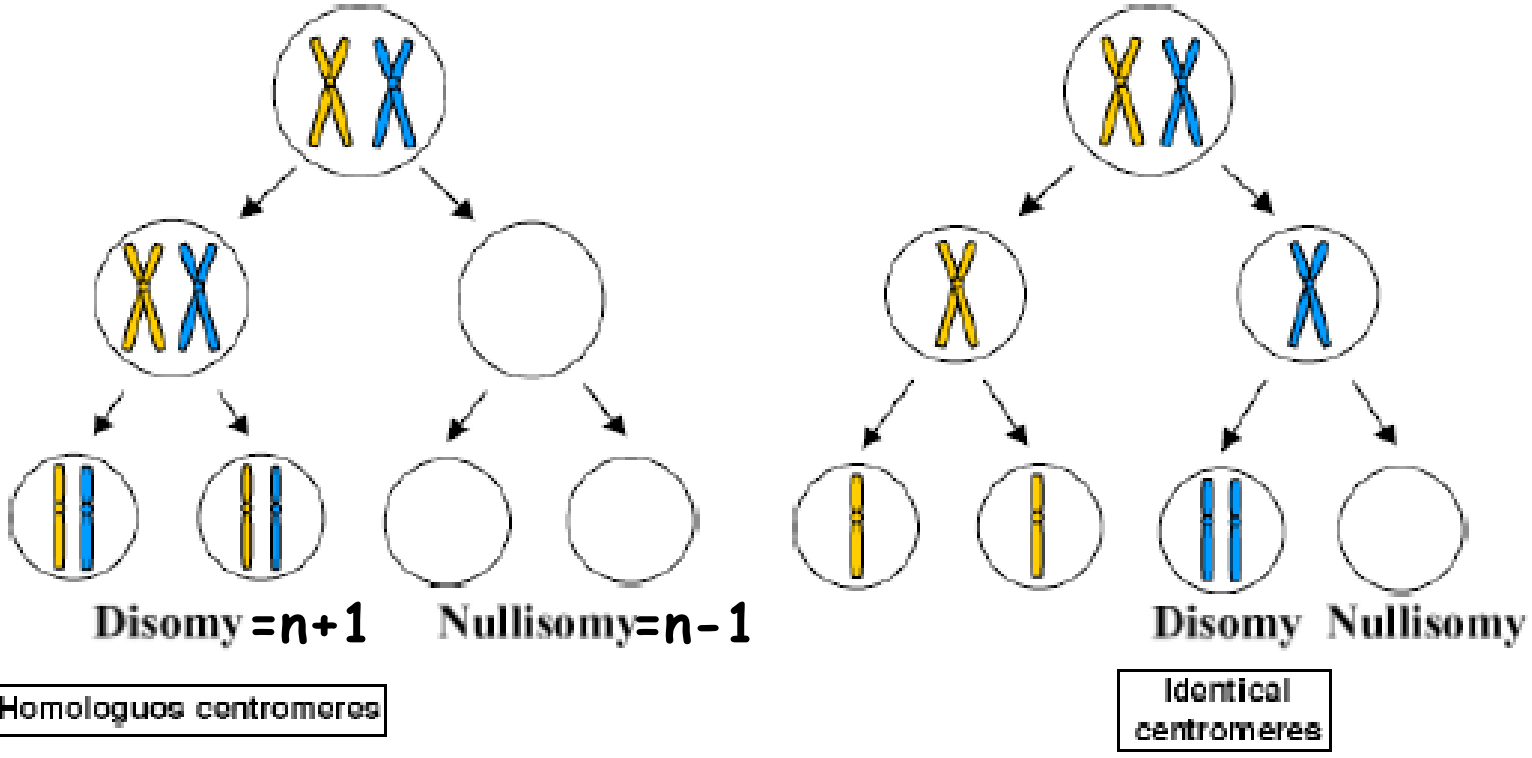
Haploid-No. of chromosome in germ cells:	23
Diploid- No. of chromosome in somatic cells:	46
Tripoloid- 3x 23	69
Tetraploid-4x23	92
Aneupoloid	46±n

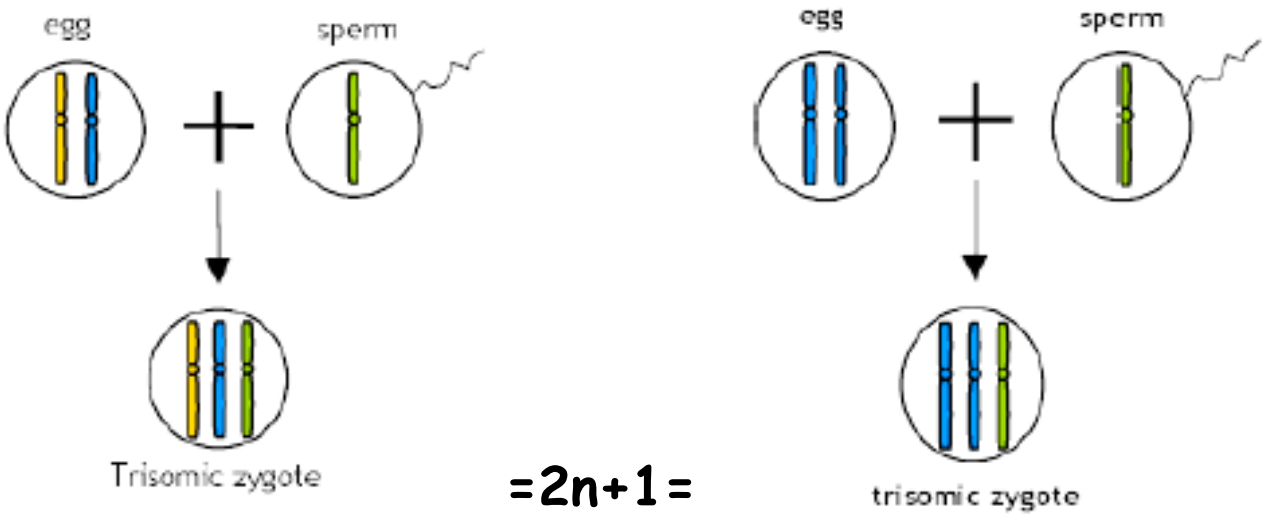
Triploidy: [23 X3] 69XXX

- Fertilization by two sperm cells or
- fertilization of a diploid egg

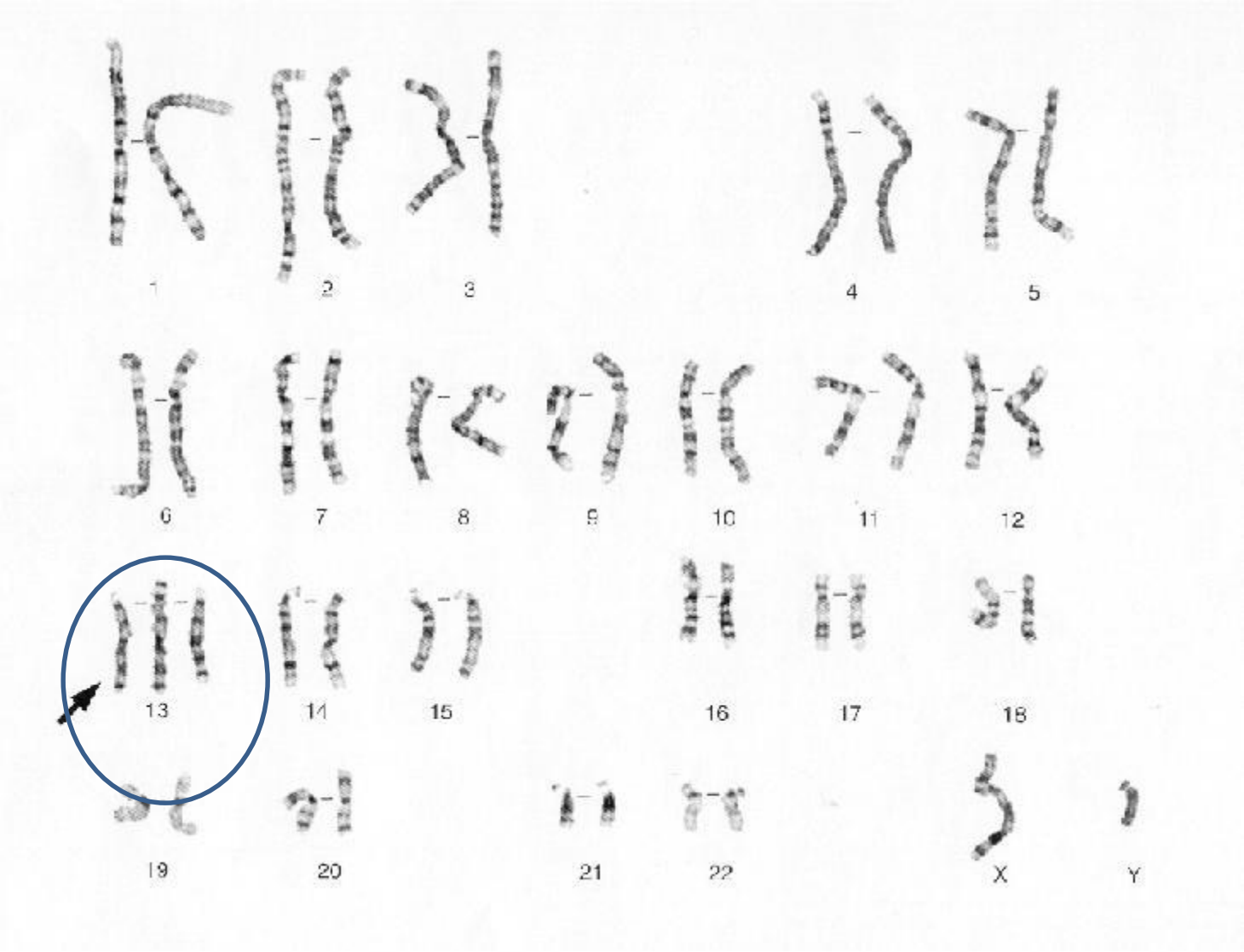


Meiotic Non-Disjunction

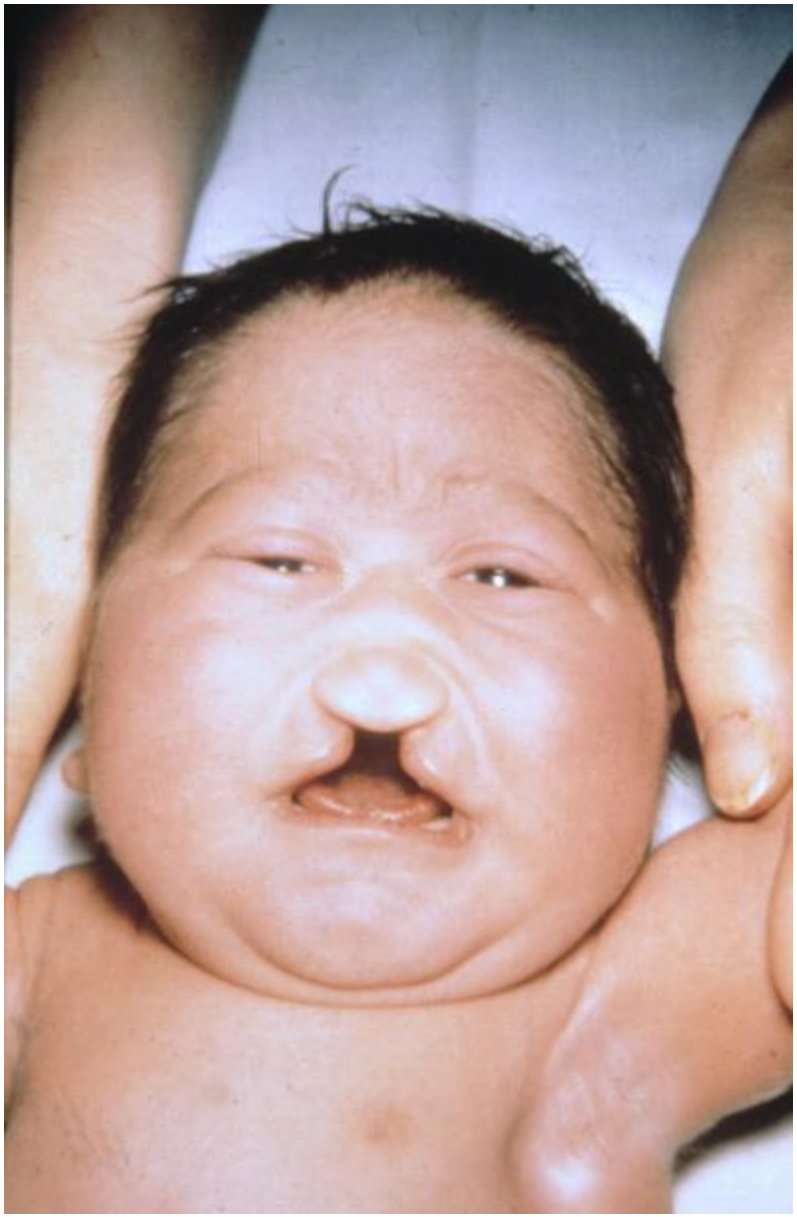


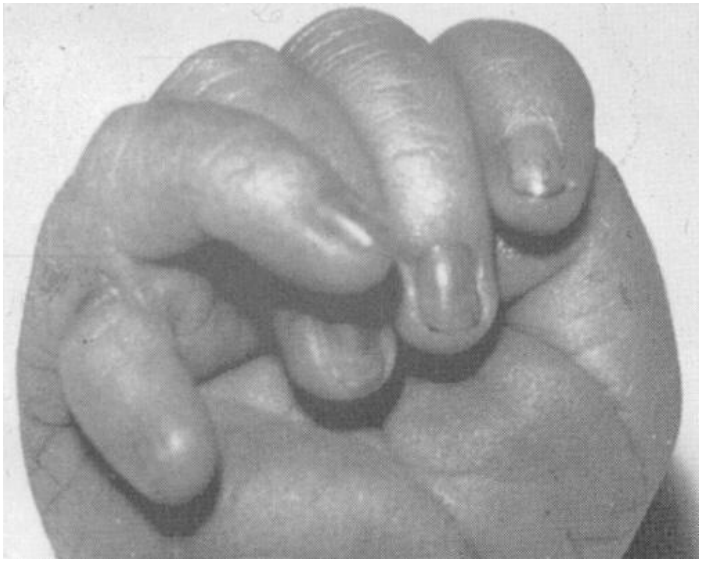

egg
sperm
Trisomic zygote
=2n+1=
egg
sperm
trisomic zygote

Aneuploidy - Trisomy 13



Trisomy 13 (Patau syndrome)



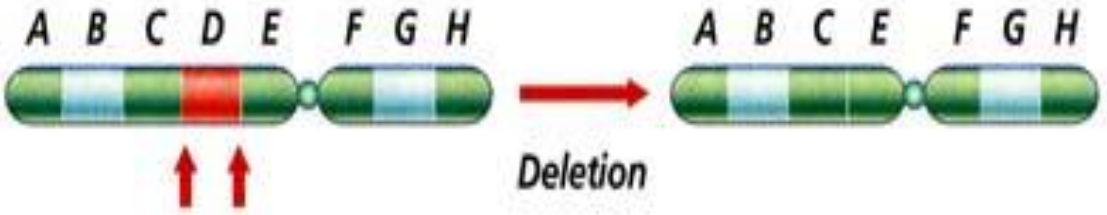


Cleft lip and palate
Small eyes
Extra fingers & toes
    polydactylism
Defects
    Heart
    Brain
    Kidney
Most abort
Live span < 1 month

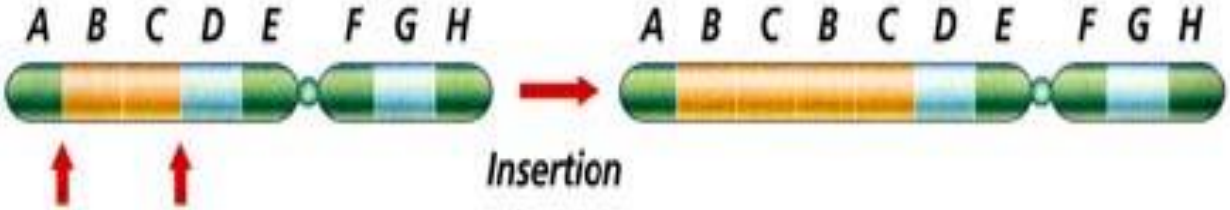
2. Anomalies of chromosome structure

- Translocations
  - **Robertsonian**
  - **Reciprocal (balance and un balanced)**
- Deletions
- Duplications
- Ring chromosomes
- Inversion : paracentric and pericentric.

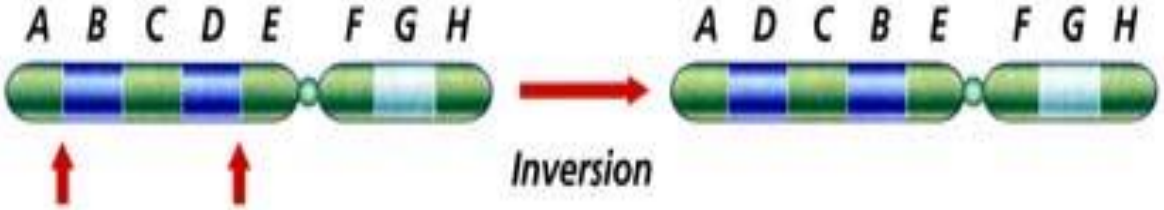
A When a part of a chromosome is left out, a deletion occurs.



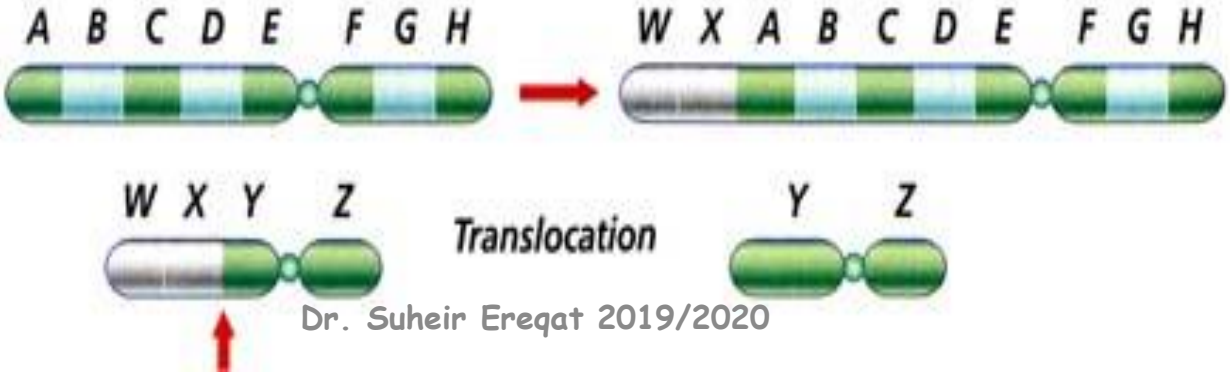
B When part of a chromatid breaks off and attaches to its sister chromatid, an insertion occurs. The result is a duplication of genes on the same chromosome.



C When part of a chromosome breaks off and reattaches backwards, an inversion occurs.



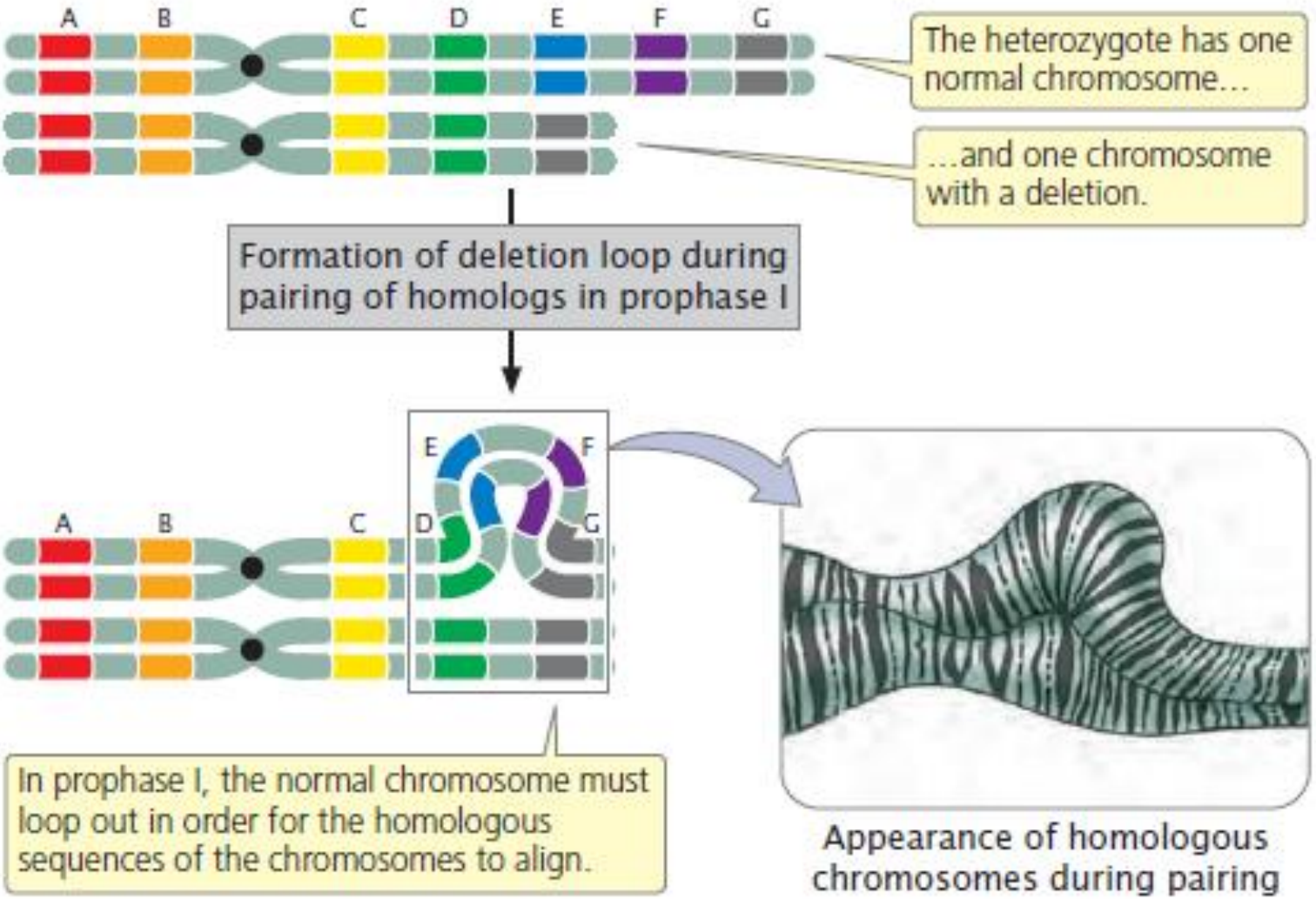
D When part of one chromosome breaks off and is added to a different chromosome, a translocation occurs.



Deletion

1. End of chromosome or ends of chromosome pair break off
2. Cri du chat- portion of chromosome 5 deleted

Deletion


A
B
C
D
E
F
G
The heterozygote has one normal chromosome…
…and one chromosome with a deletion.
Formation of deletion loop during pairing of homologs in prophase I
In prophase I, the normal chromosome must loop out in order for the homologous sequences of the chromosomes to align.
Appearance of homologous chromosomes during pairing

Effect of deletion

- If the deletion includes the centromere, the chromosome will not segregate in meiosis or mitosis and will usually be lost.
- Lethal (homozygous condition)
- imbalances in the amounts of gene products (heterozygous condition)

-haploinsufficient gene=single copy not sufficient to produce wild type phenotype**.**

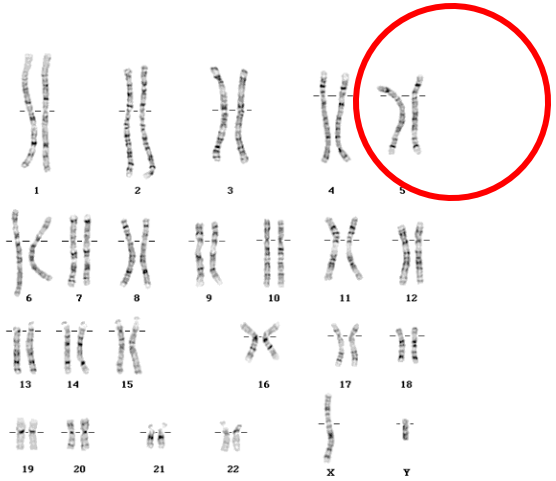
-Pseudodominance=recessive mutations not masked

Cri du Chat

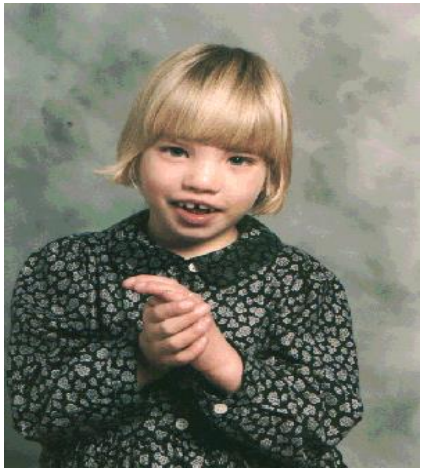
Cry of the Cat individuals sound like cats crying.
Why?
The larynx of the child is improperly developed.

Cri-Du-Chat Syndrome

- 1 in 216,000 births
- 46 chromosomes
- #5 Deletion of band p15.3
- The deletion occurs most often as a random



Symptoms:
Moon-shaped face
Heart disease
Mentally retarded
Malformed larynx
Normal lifespan

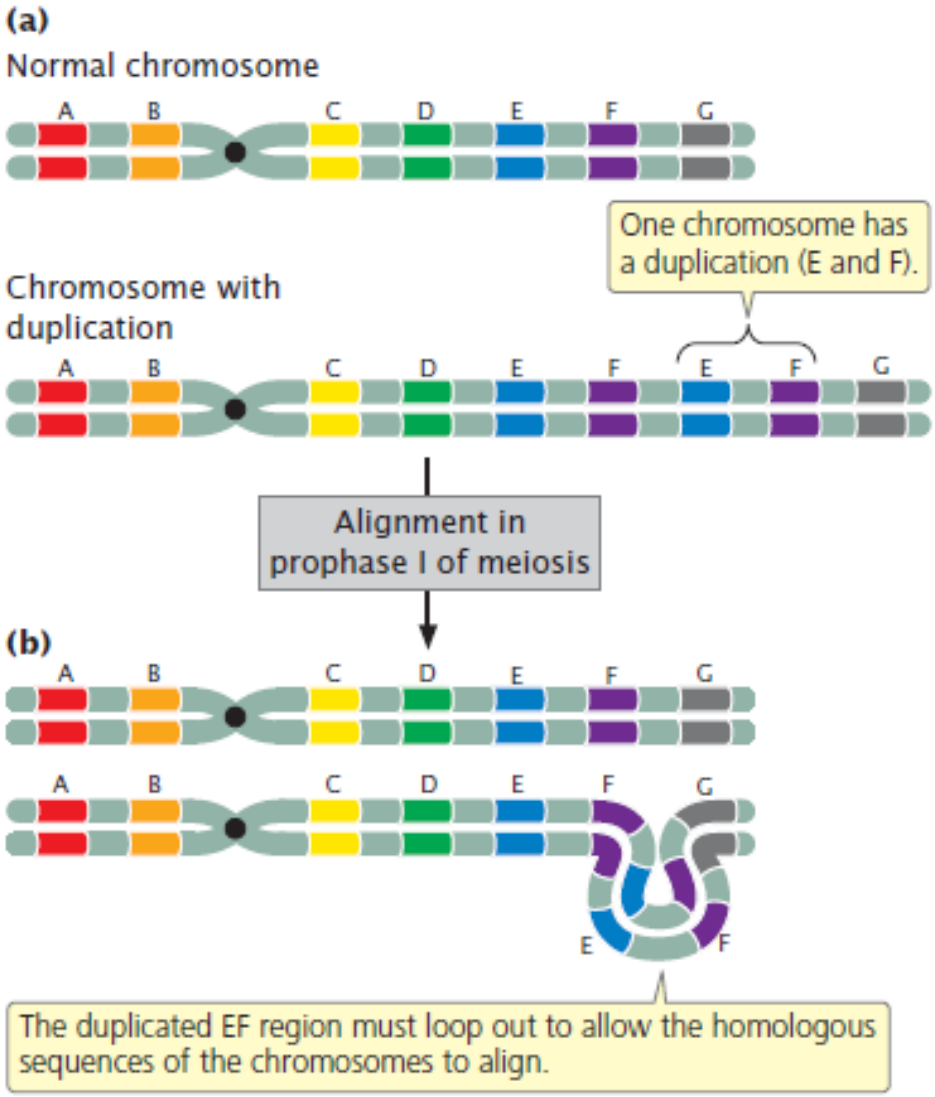


Duplication

1. Mispairing- unequal cross-over results in chromosome segment repeats
2. Tandem , displaced, reverse

ABC.DEFGH
ABC.DEFEFGH
ABC.DEFGHEF
ABC.DEFFEGH

Duplication



Question?

How does a chromosome duplication alter the phenotype?

Answer

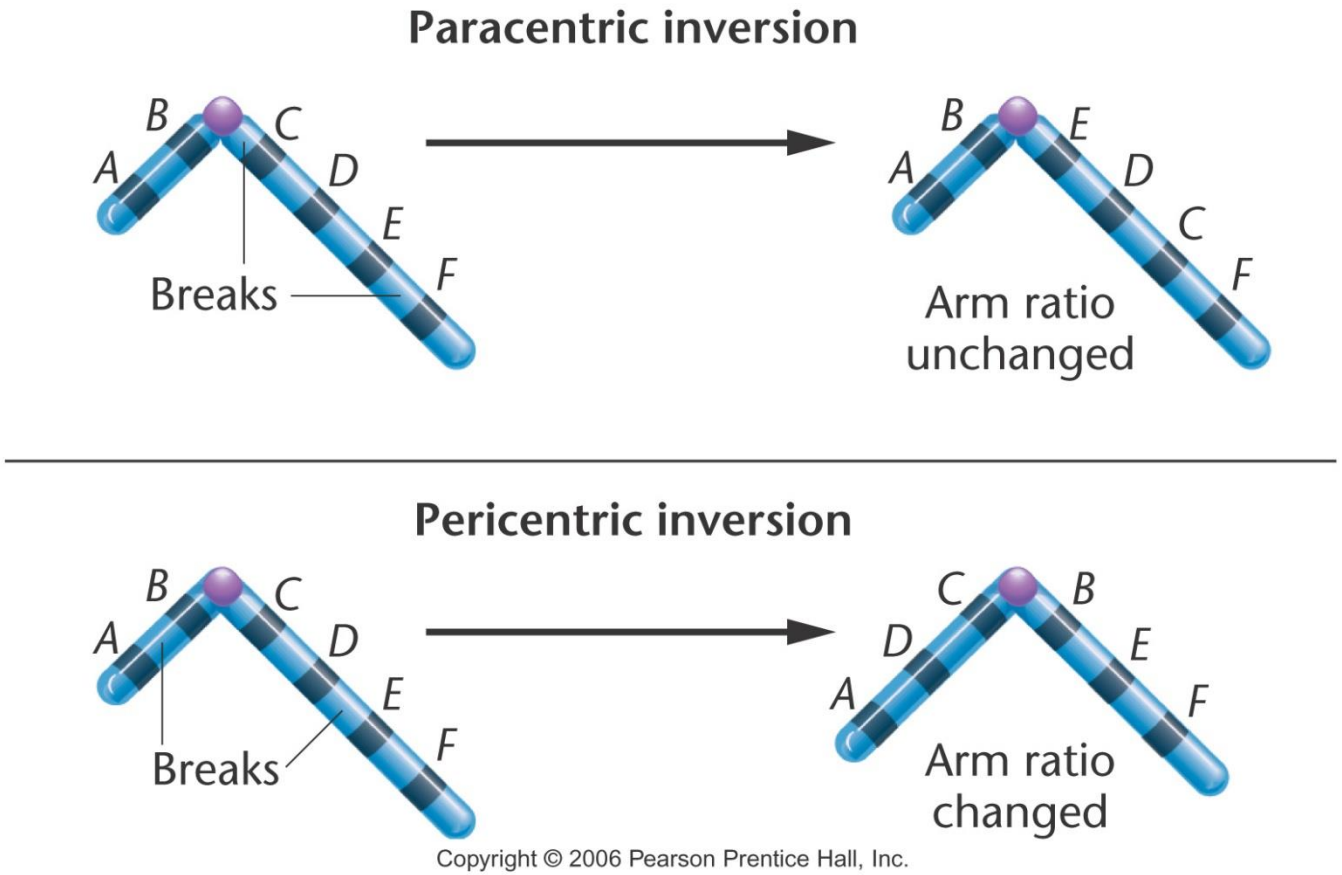
Unbalanced gene dosage= developmental abnormalities.

an individual organism with three functional copies of a gene often produces 1.5
times as much of the protein encoded by that gene as that produced by an individual with two copies. Because developmental processes require the interaction of many proteins, they often depend critically on proper gene dosage

Inversion

1. Chromosome segment breaks apart
2. Rejoins in reversed direction, turned 180^{o}
3. Same genes present, but sequence of genes is reversed
4. **position effect:** may be expressed at inappropriate times or in inappropriate tissues.

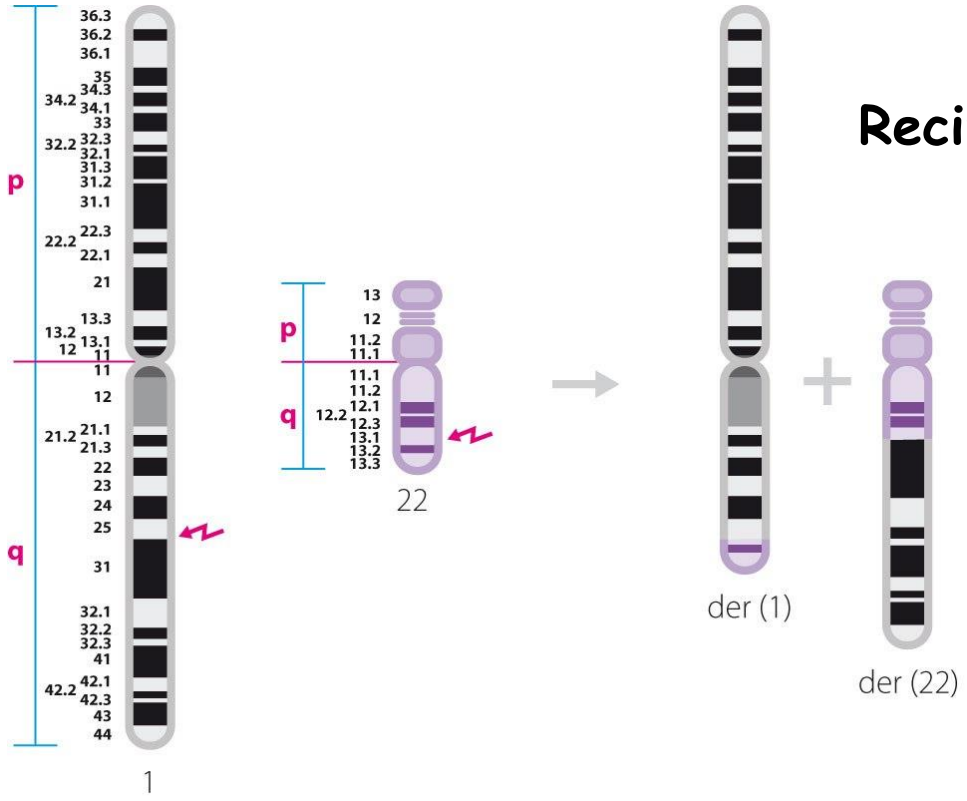
Chromosomal Inversions



Translocation

-1. Movement of segment from one chromosome to another **non**homologous chromosomes

-3-4% of Down syndrome (familial) result of translocation between chromosomes 21 and 14 (a segment of chr. 21 detaches and fuses with chr. 14= fused chr.=14/21)

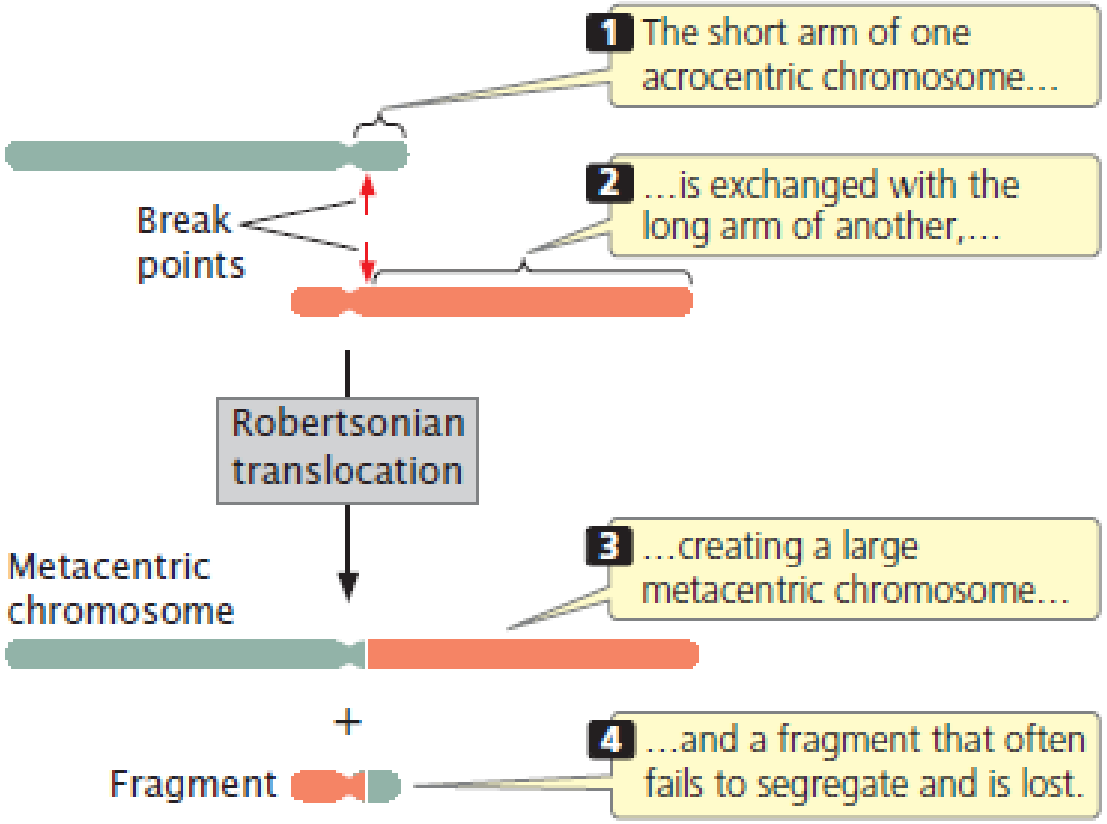


Reciprocal translocation

How the 1;22 translocation originated

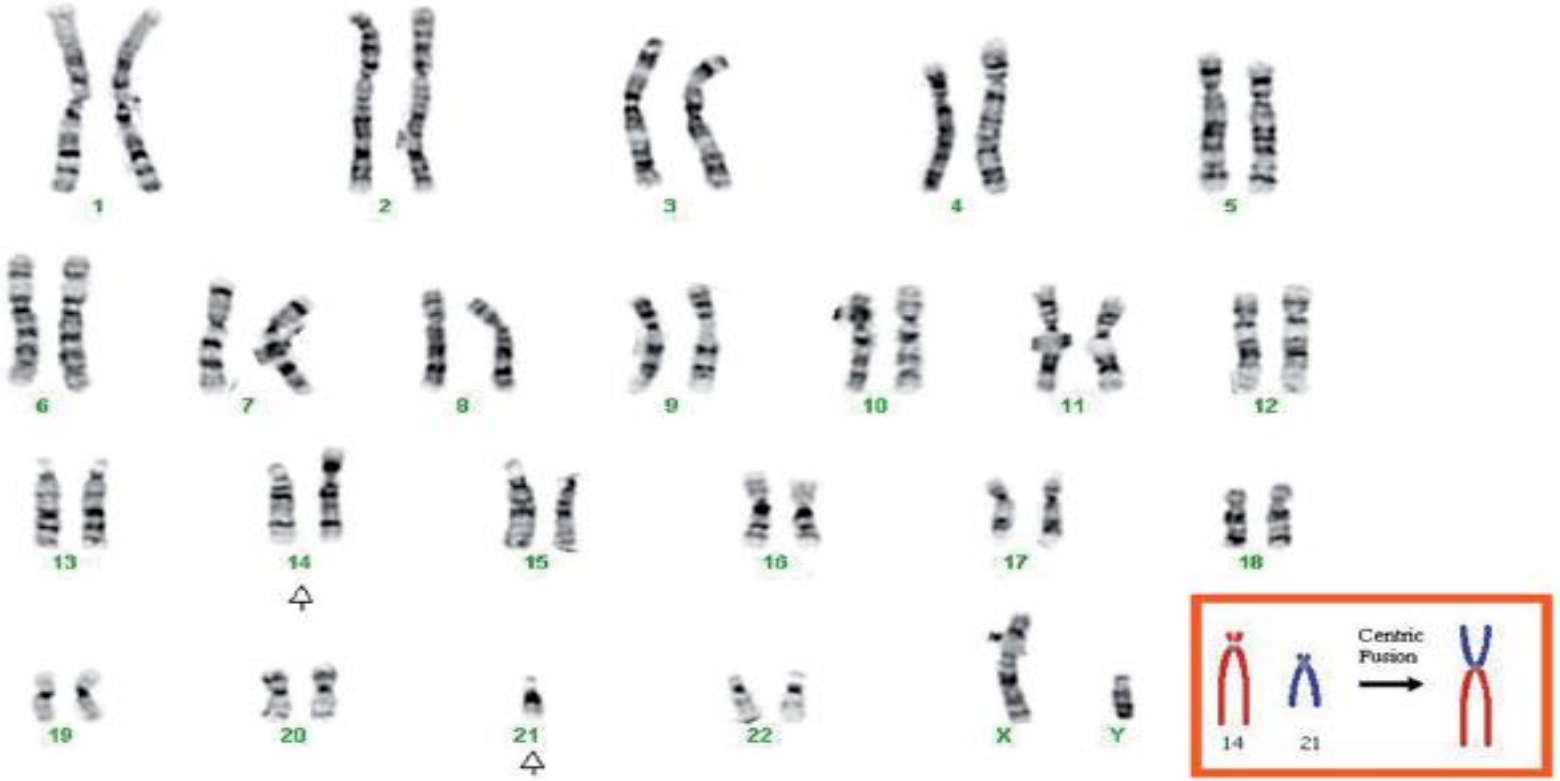
Chromosome 1 and 22 broke at the positions indicated by the arrows, and the cell's DNA repair machinery rejoined the ends to form the two derivative chromosomes as shown. The derivative chromosomes are labelled der(1) and der(22).

Robertsonian translocation: centric fusion



9.15 In a Robertsonian translocation, the short arm of one acrocentric chromosome is exchanged with the long arm of another.

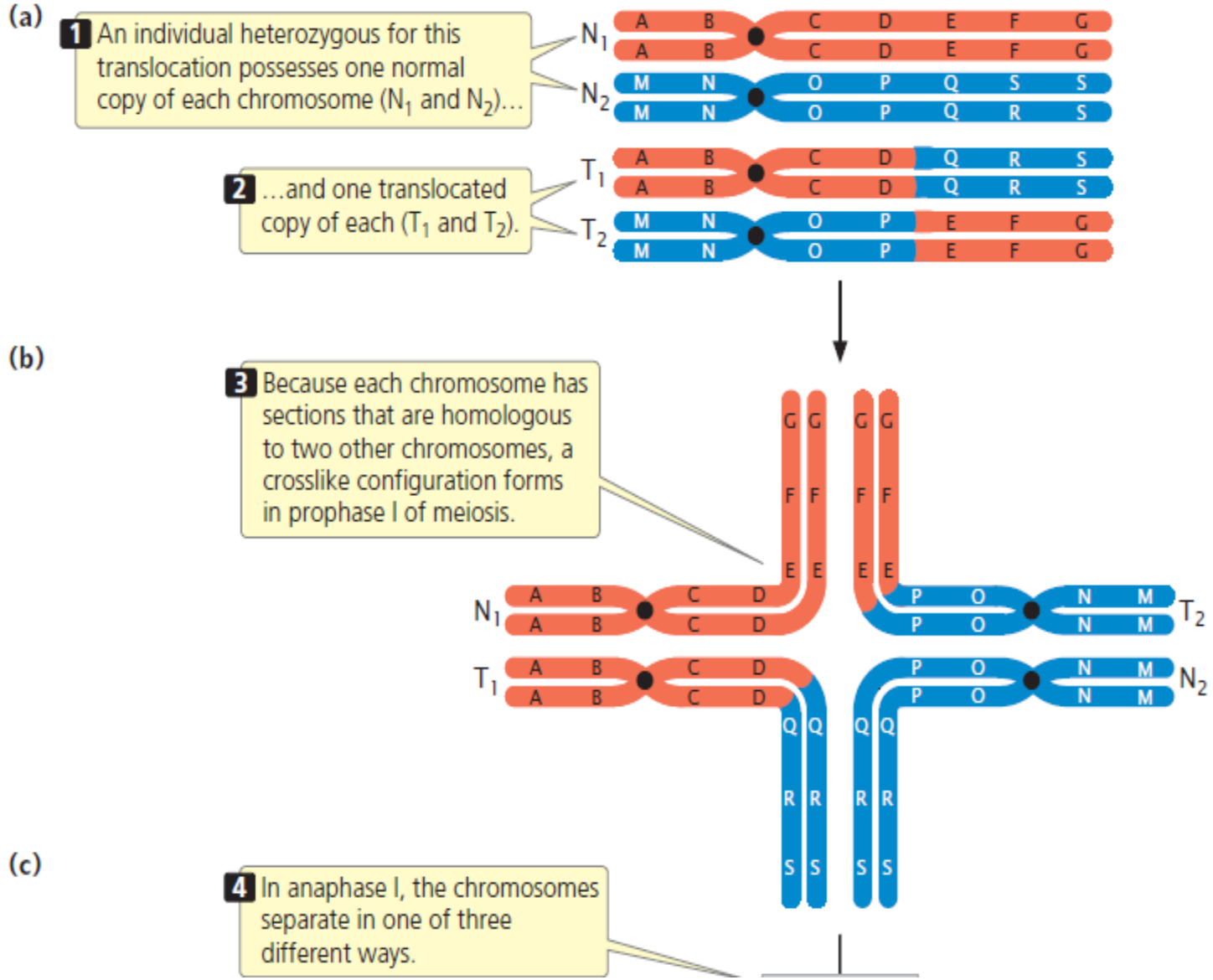
A centric fusion is a translocation in which the centromeres of two acrocentric chromosomes fuse to generate one large metacentric chromosome

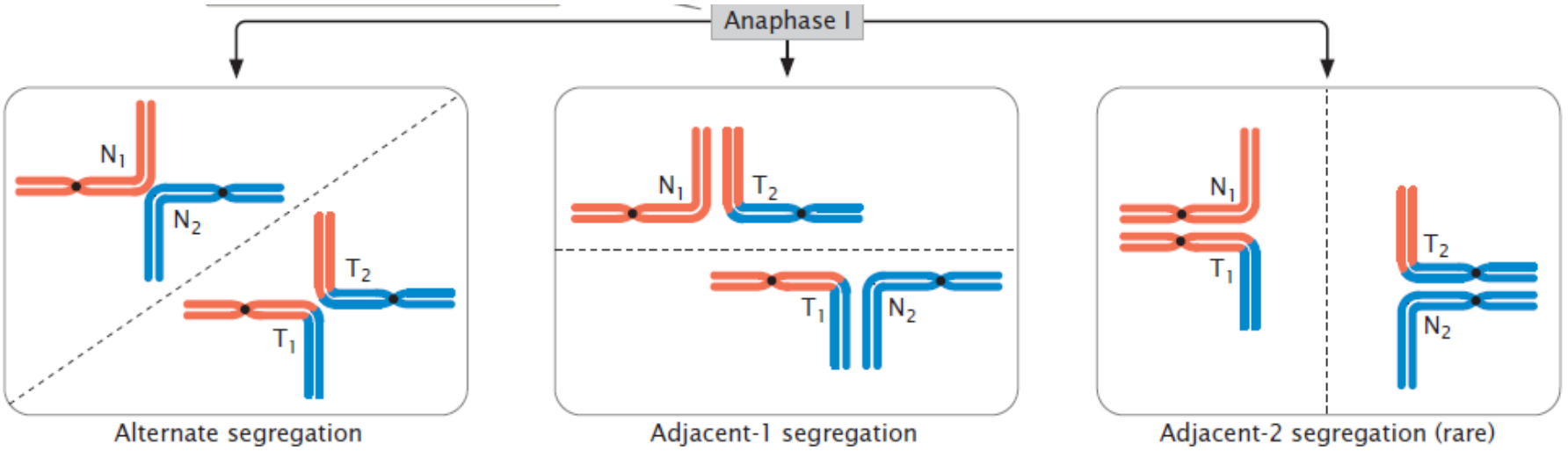


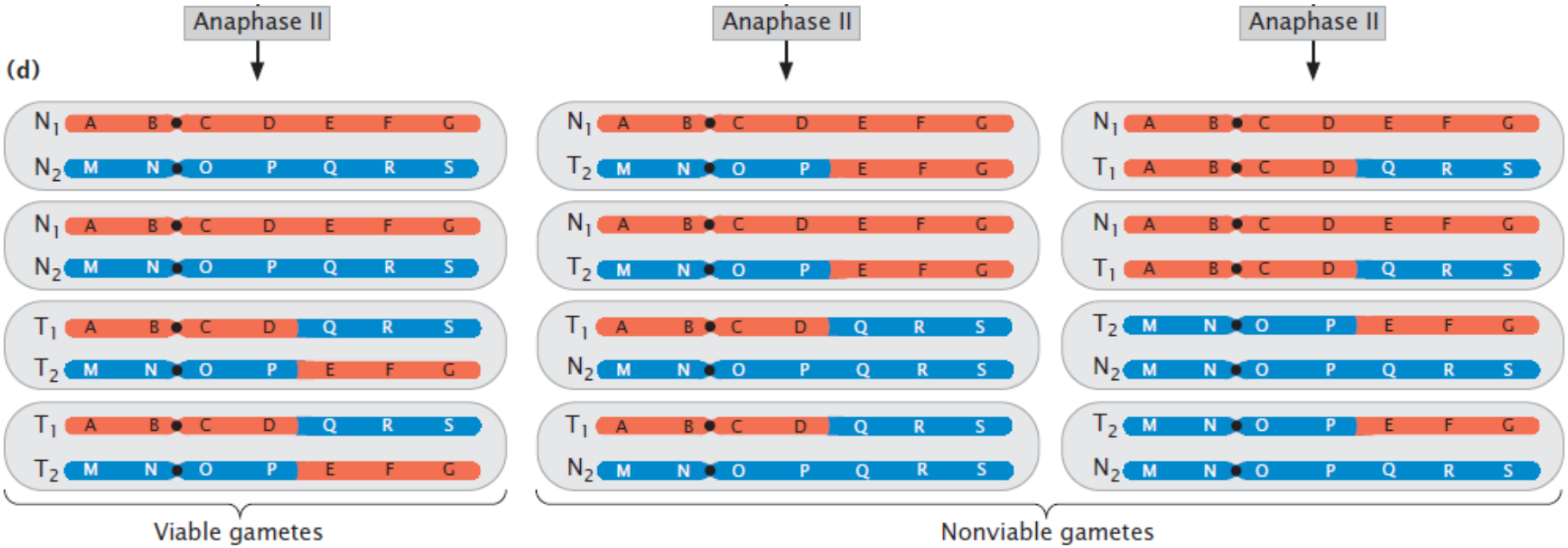
A Robertsonian translocation

The inset shows how this common type of chromosome abnormality arises. The short arms of all the acrocentric chromosomes (13, 14, 15, 21, 22) contain similar DNA. Inappropriate recombination between two non-homologous chromosomes produces the fusion chromosome, which functions as a normal single chromosome in mitosis. The small acentric fragment comprising the two distal short arms is lost.

Translocation in Meiosis: cross like structure

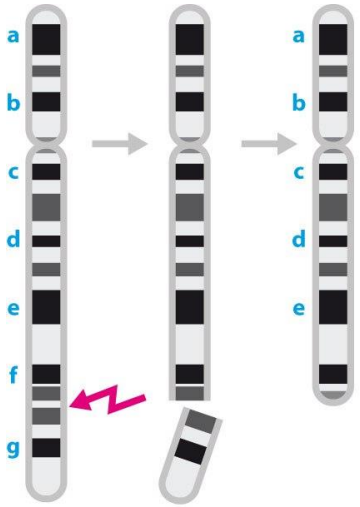



Anaphase I
N1
N2
T2
T1
Alternate segregation
N1
T2
T1
N2
Adjacent-1 segregation
N1
T1
T2
N2
Adjacent-2 segregation (rare)



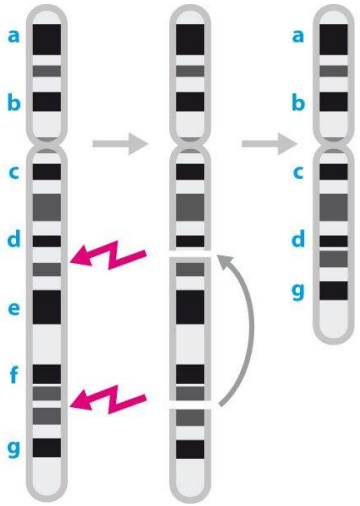
Conclusion: Gametes resulting from adjacent-I and adjacent-2 segregation are nonviable because some genes are present in two copies, whereas others are missing.

you can imagine …

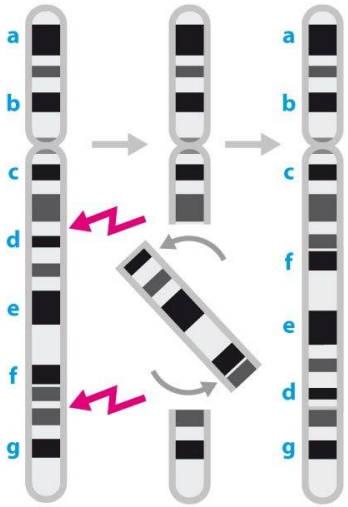


N.B. to be stable a terminal deletion must be capped by a telomere

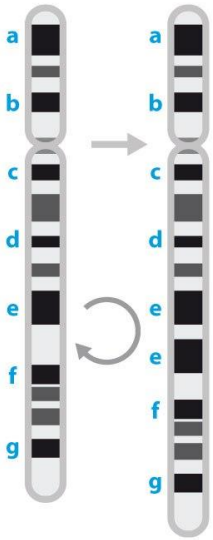
A TERMINAL DELETION



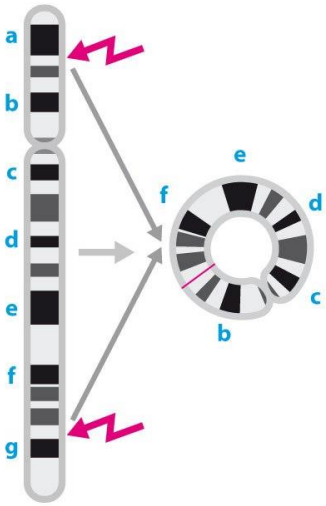
AN INTERSTITIAL DELETION



AN INVERSION



A DUPLICATION



A RING CHROMOSOME

Most frequent numerical anomalies in live born

Autosomes

Down syndrome (trisomy 21: 47,XX,+21)

Edwards syndrome (trisomy 18: 47,XX,+18)

Patau syndrome (trisomy 13: 47,XX+13)

Sex chromosomes

Turner syndrome 45,X

Klinefelter syndrome 47,XXY

VARIATIONS ON SEX CHROMOSOME NUMBERS

- Klinefelter syndrom . (47,XXY)
- Genital and internal ducts are present as in males. Their testes are underdeveloped and fail to produce sperms.
- They have enlarged breast.
- Mentally retarded.
- Feminine sexual development is not entirely suppressed.

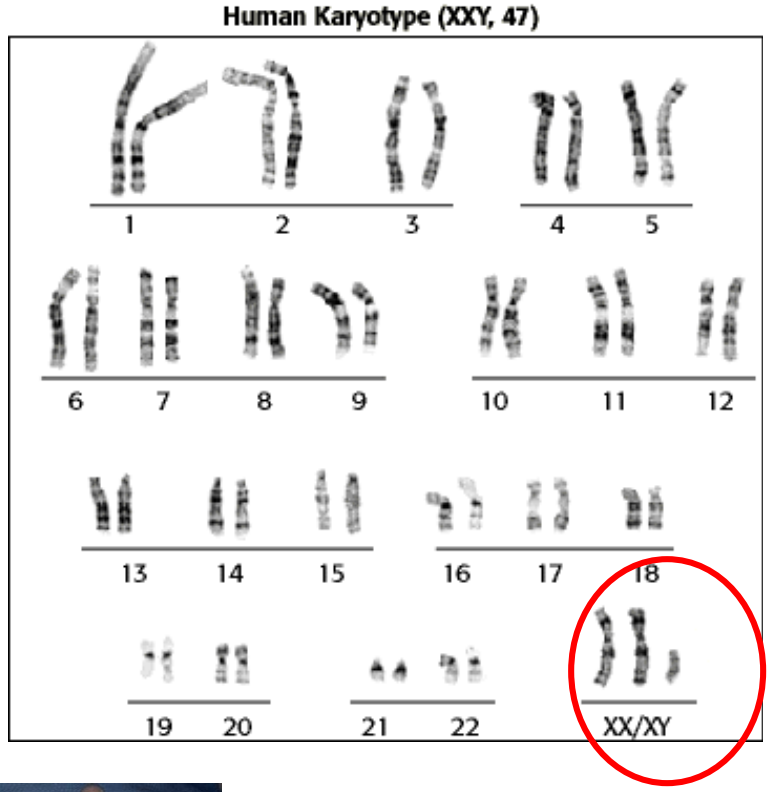
Klinefelter Syndrome

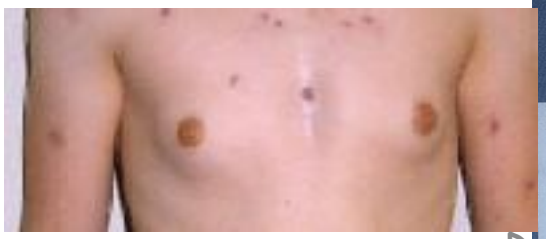
1 in 1,100 births

47 chromosomes
XXY only

#23 Trisomy
Nondisjunction

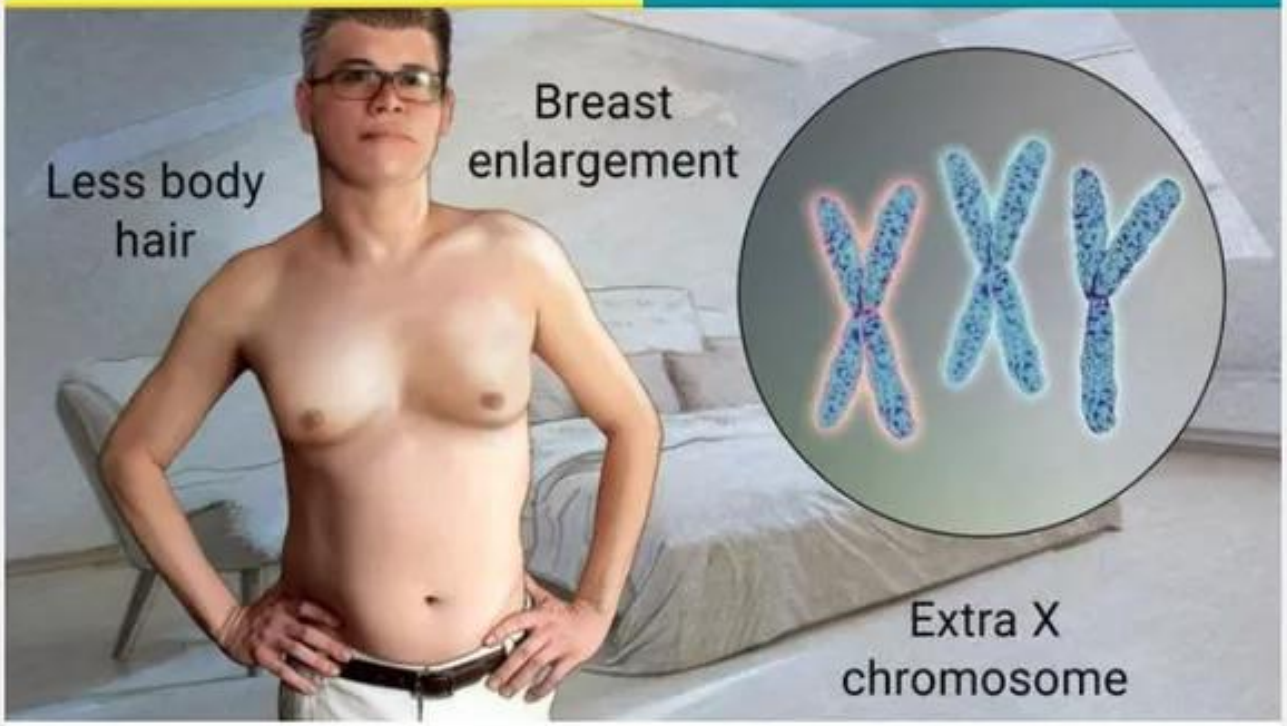
No facial hair
Longer fingers and arms
Sterile
Low mental ability
Normal lifespan





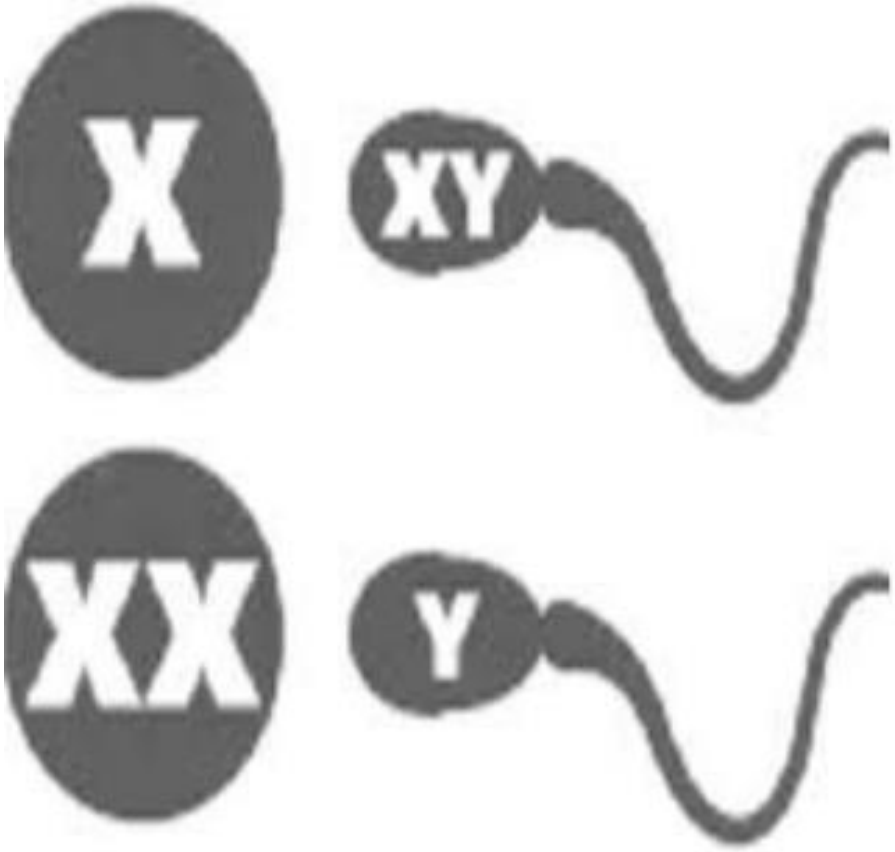
Klinefelter syndrome
Also called: XXY syndrome

ABOUT SYMPTOMS



Wide hip and feminine fat distribution

How it happens.



- Kline Felter Syndrome is caused by an error in the mother's and father's sex chromosomes during cell division.

Turner syndrome XO

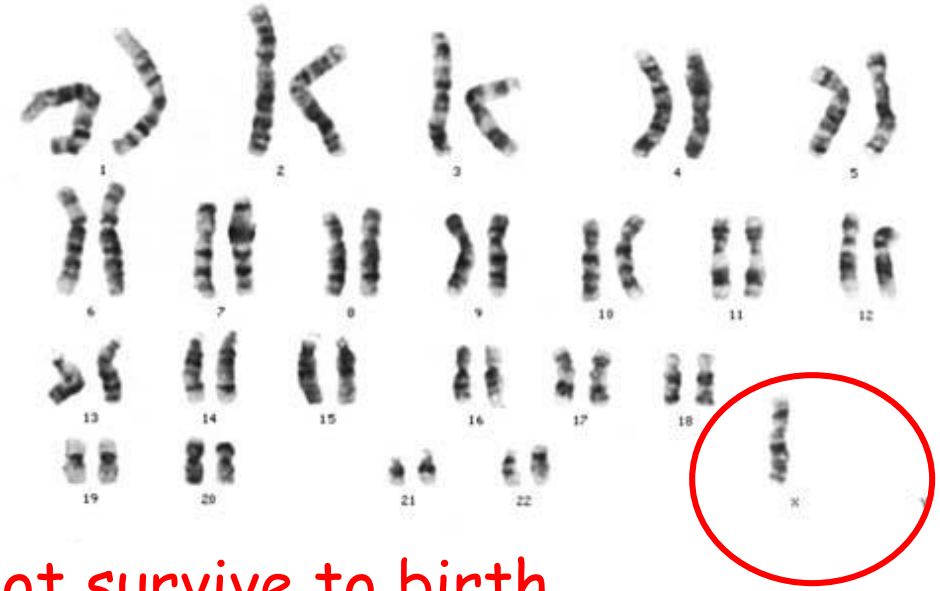
- (45,X).
- Female external genetelia, and internal ducts, but ovaries are redundant.
- Short status. Under 5 feets.

Turners Syndrome

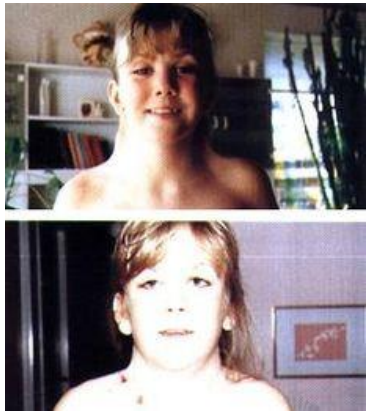
1 in 5,000 births

45 chromosomes X only

#23 Monosomy
Nondisjunction



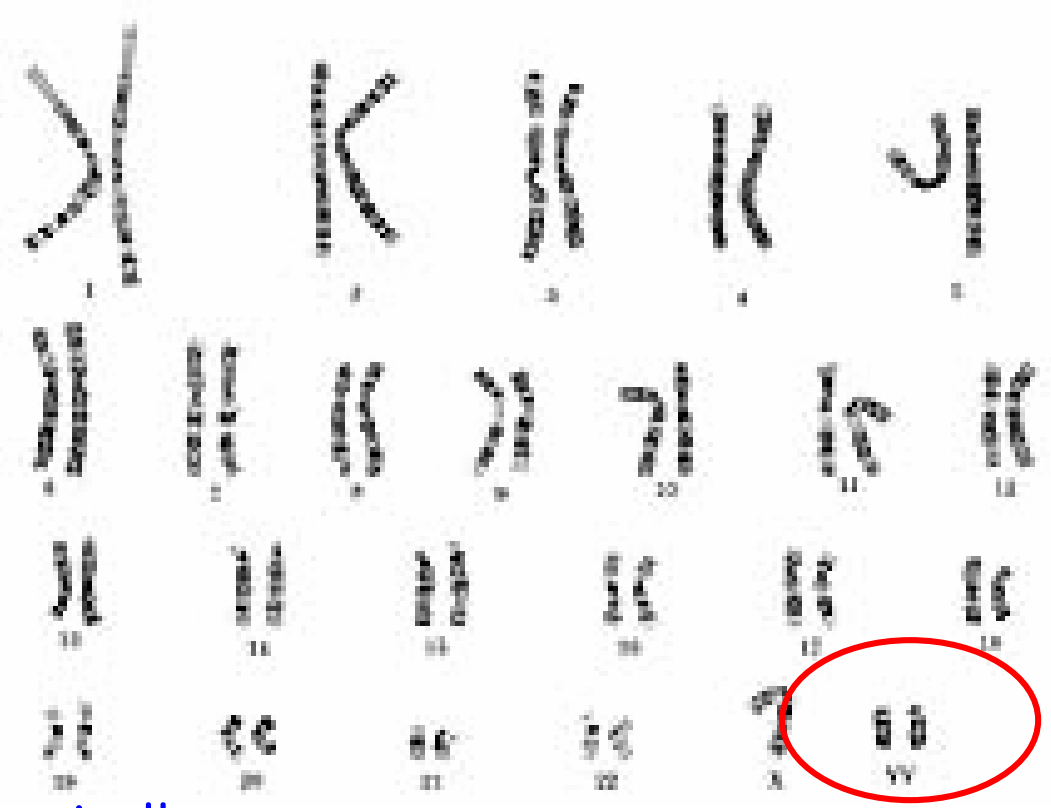
96-98% do not survive to birth
No menstruation
No breast development
Narrow hips
Broad shoulders and neck
Learning difficulties in school



Webbed neck

Jacob's Syndrome

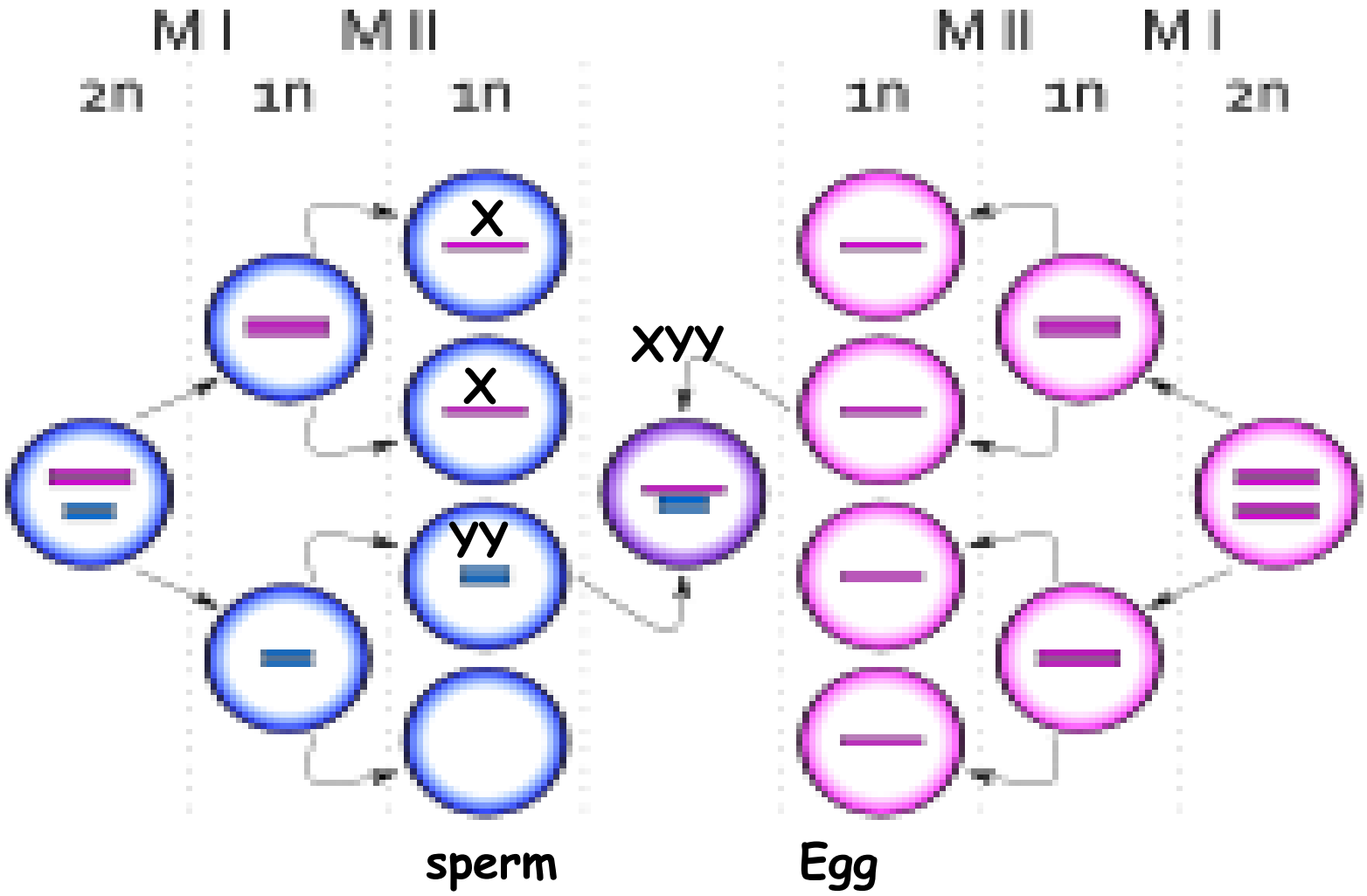
1 in 1,800 births
47 chromosomes
XYY only
#23 Trisomy
Nondisjunction



?

Normal physically
Normal mentally
normal sexual development.
Increase in testosterone
More aggressive
Normal lifespan

xyy

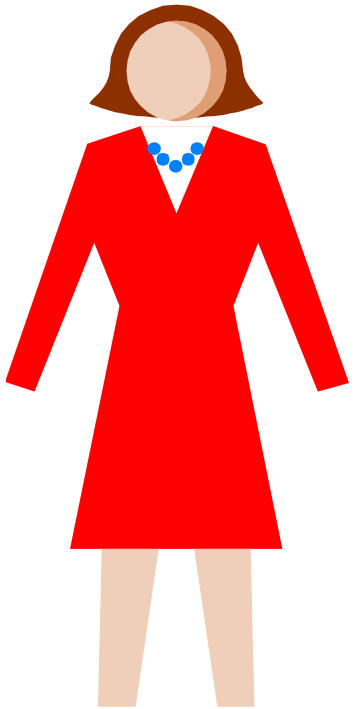


Triple X Syndrome

Normal physically
- Sometimes taller

Normal mentally

Fertile(menstrual irregularities)



If nondisjunction was mother

- P: $X^BX^b \times X^BY$

- c.

	X^B	Y
$X^B X^b$	$X^BX^BX^b$ Super female	X^BX^bY Klinefelter
0	X^B0 Turner	0Y Lethal

If nondisjunction was father

P: X^BX^b x X^BY

	X^BY	0
X^B	X^BX^BY Klinefelter	X^B0 Turner
X^b	X^BX^bY Klinefelter	X^b0 Turner

Dosage Compensation

- **Shouldn't XX females produce twice the amount of X-linked gene products (proteins) as XY males?**

- **No, because XX females "compensate" by inactivating one of their X chromosomes to make a single "dosage" of X-linked genes.**

Inconsistencies between syndromes and X inactivation

If normal XX female has one X inactivated, why is a X Turner female not normal?

Similarly, if XXY male has one X inactivated, why does he have Klinefelter syndrome?

Random inactivation
Perhaps not complete inactivation
Or inactivation does not happen immediately,
Then some overexpression of X-linked genes

Trisomy:

In general, more viable than monosomy

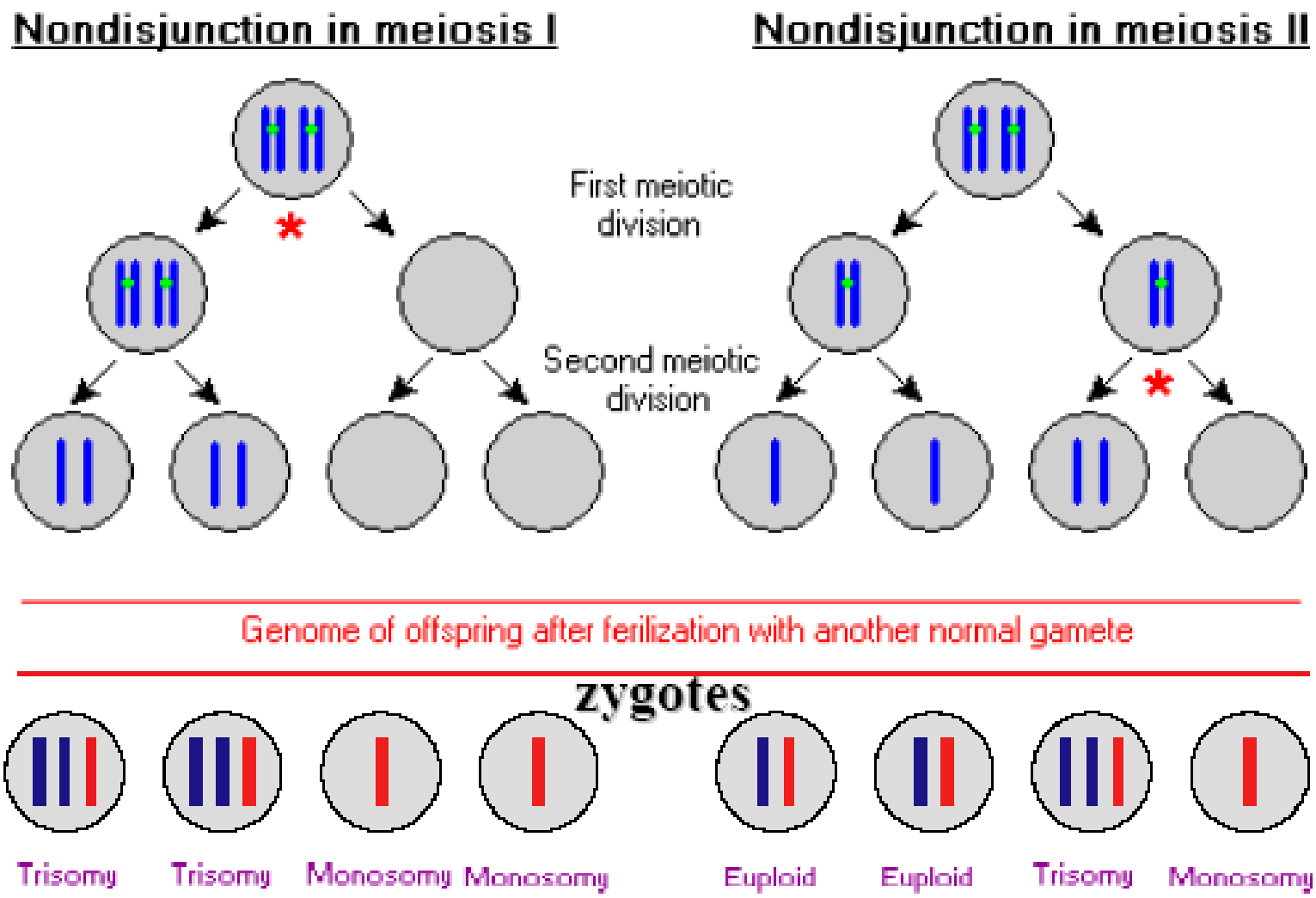
<u>Down Syndrome (47, xx +21)</u>

- **Characteristic facial patterning (flattened)**
- **1 / 800 live births**

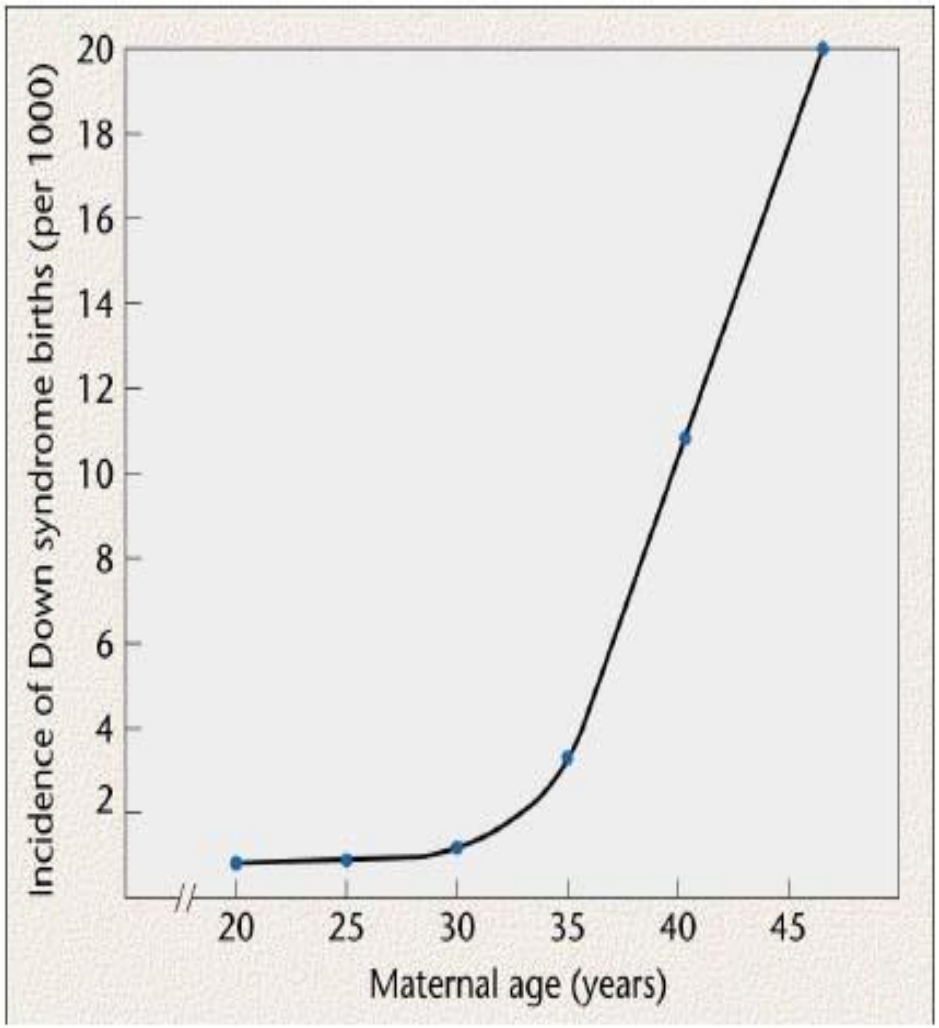
Down Syndrome, Mongolism Characteristics

- **Most often occurs by nondisjunction of chr. 21 during meiosis; in theory could occur in either mom or dad, but 95% of these trisomies have defective egg as source.**
- **Prone to respiratory diseases, etc.**
- **About 30% of all cases of mental retardation in U.S.**
- **1/25 can read; 1/50 can write**

Nondisjunction



Incidence of Down Syndrome Increases with Maternal Age



All eggs are formed by birth and arrested in meiosis; is the correlation of increased age and the syndrome due to more non-disjunction in older eggs?

Familial Down Syndrome

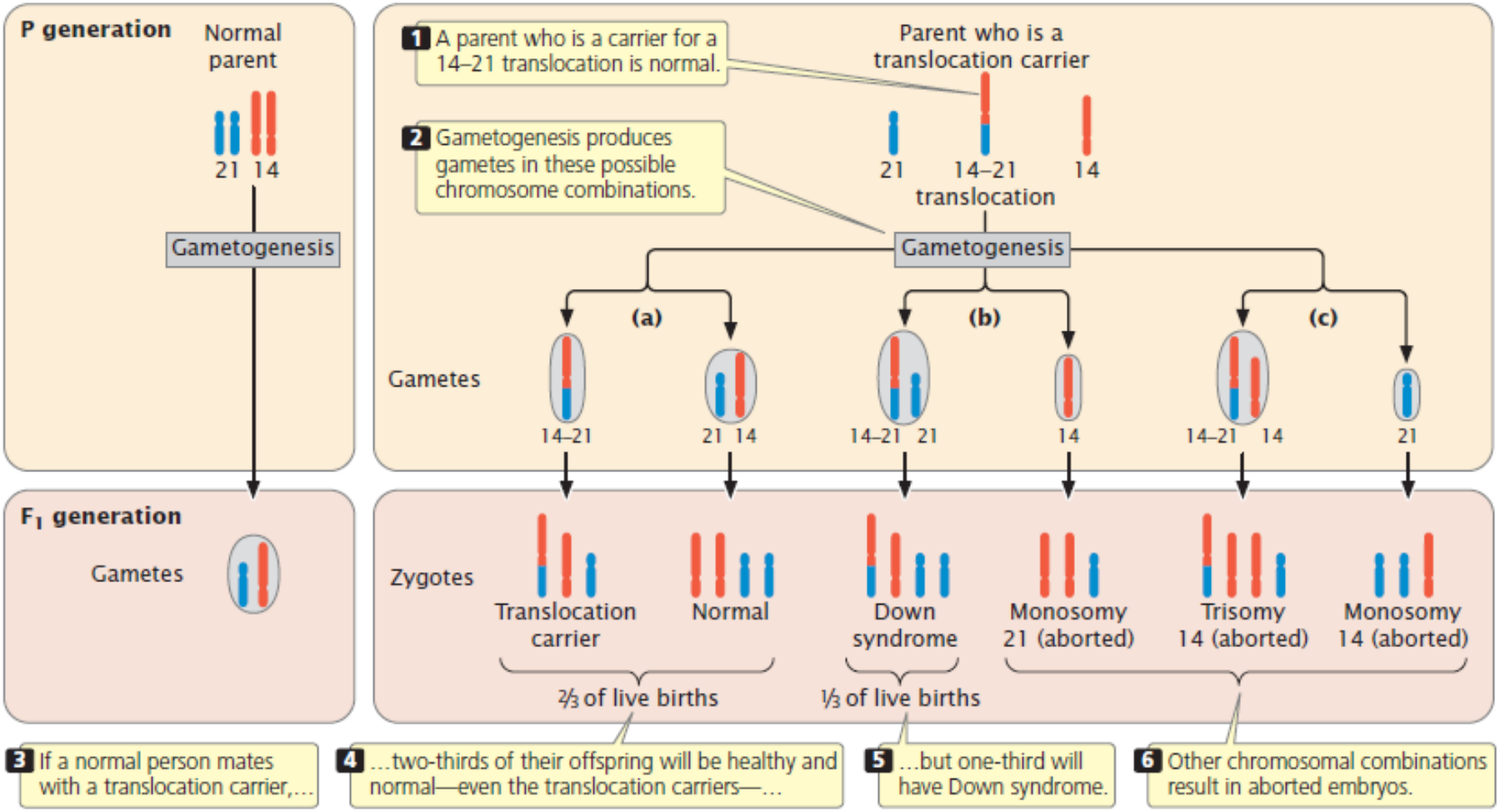
1 in 31,000 births

46 chromosomes

XY=97%

XX=3%

#14/21 Translocation



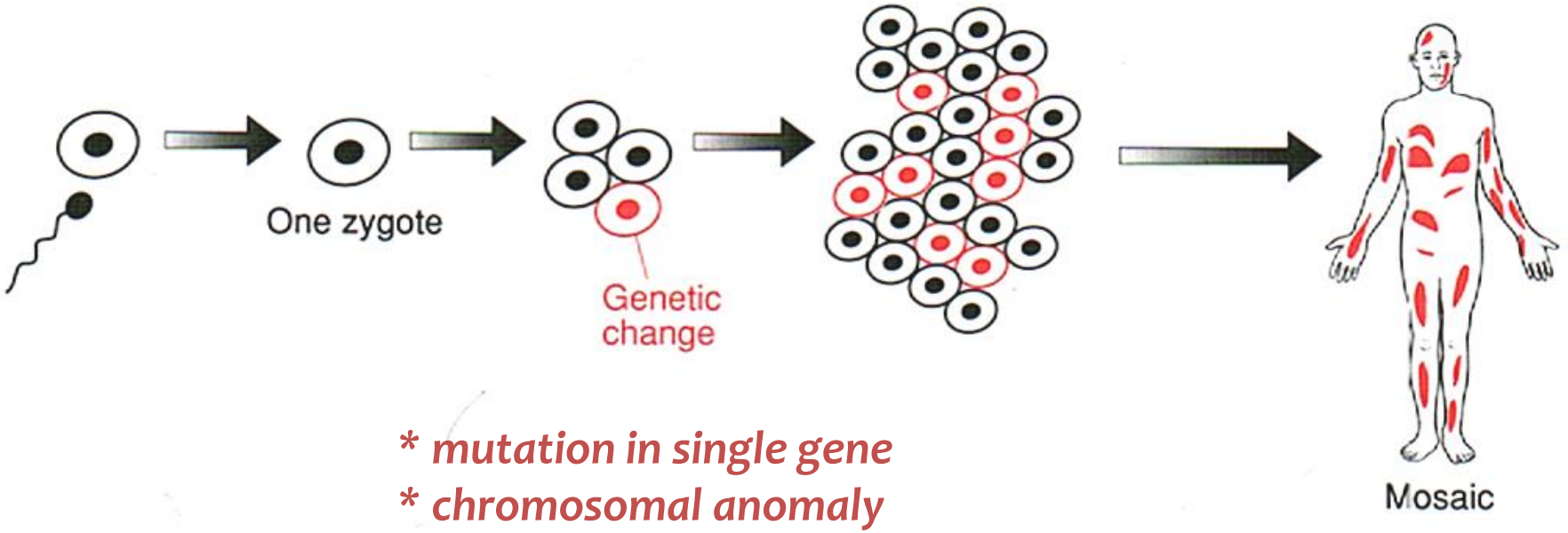
9.23 Translocation carriers are at increased risk for producing children with Down syndrome.

Nondisjunction syndrome frequencies

Syndrome	Description	Chromosomes	Incidences (newborns)
Down	Mental retardation; wide, flat face with upper eyelid fold, short stature; abnormal palm creases	Trisomy 21	1/800
Patau	Malformed internal organs, face, and head; extra digits; mental retardation	Trisomy 13	1/15,000
Edward	Malformed internal organs, face, and head; extreme muscle tone	Trisomy 18	1/6,000
Turner	Short stature; webbed neck; broad chest; no sexual maturity	XO	1/6,000
Klinefelter	Breast development possible; testes underdeveloped; no facial hair	XXY (or XXXY)	1/1,500
Triplo-X	Tall and thin with menstrual irregularities	XXX (or XXXX)	1/1,500
Jacob	Taller than average; persistent acne; speech and learning problems possible	XYY	1/1,000

b. From Robert F. Weaver and Philip W. Hedrick, *Genetics*, *2nd ed.* Copyright 1992 WCB.

Mosaicism

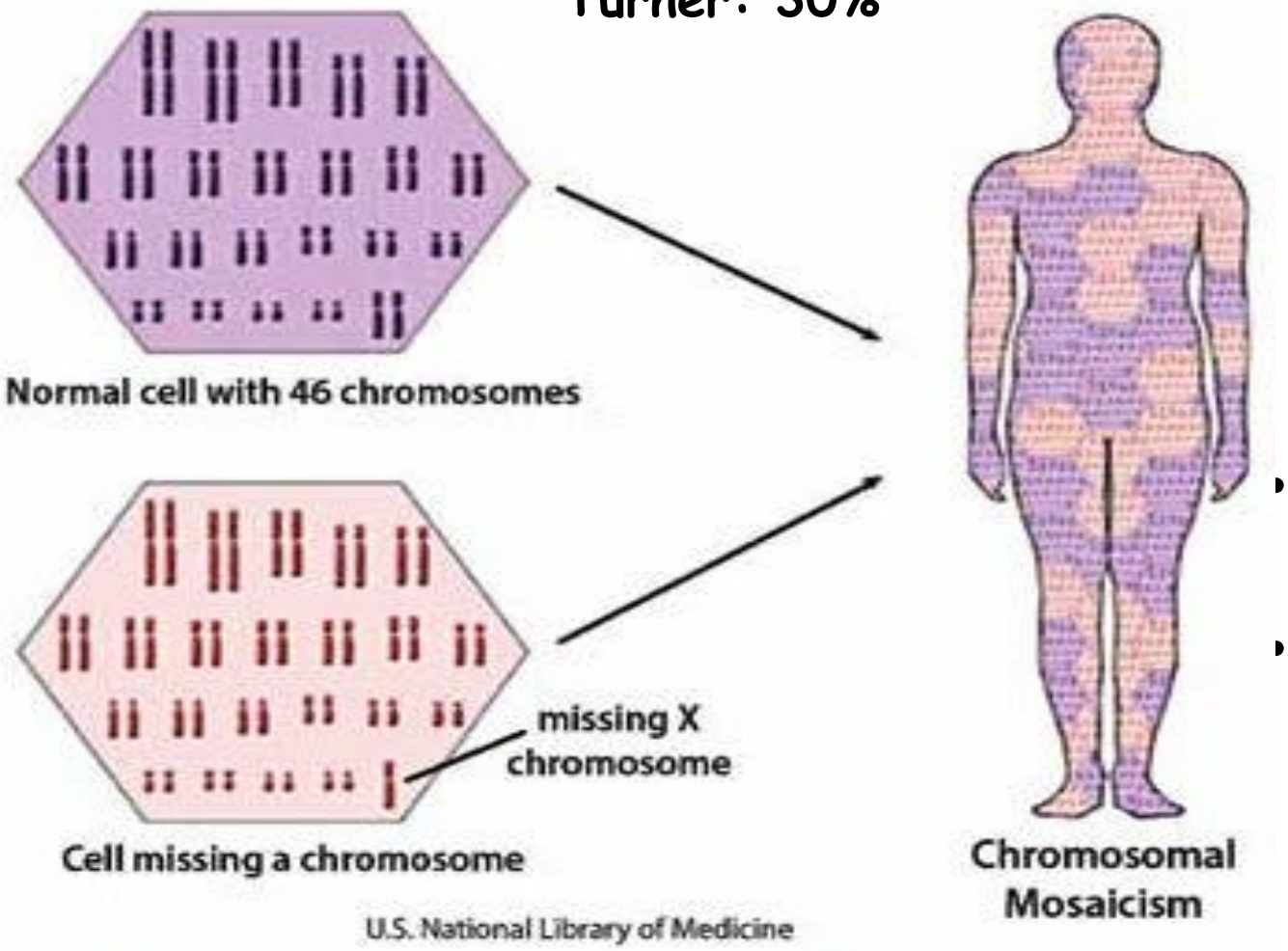


** mutation in single gene*
** chromosomal anomaly*

Mosaicism can be:

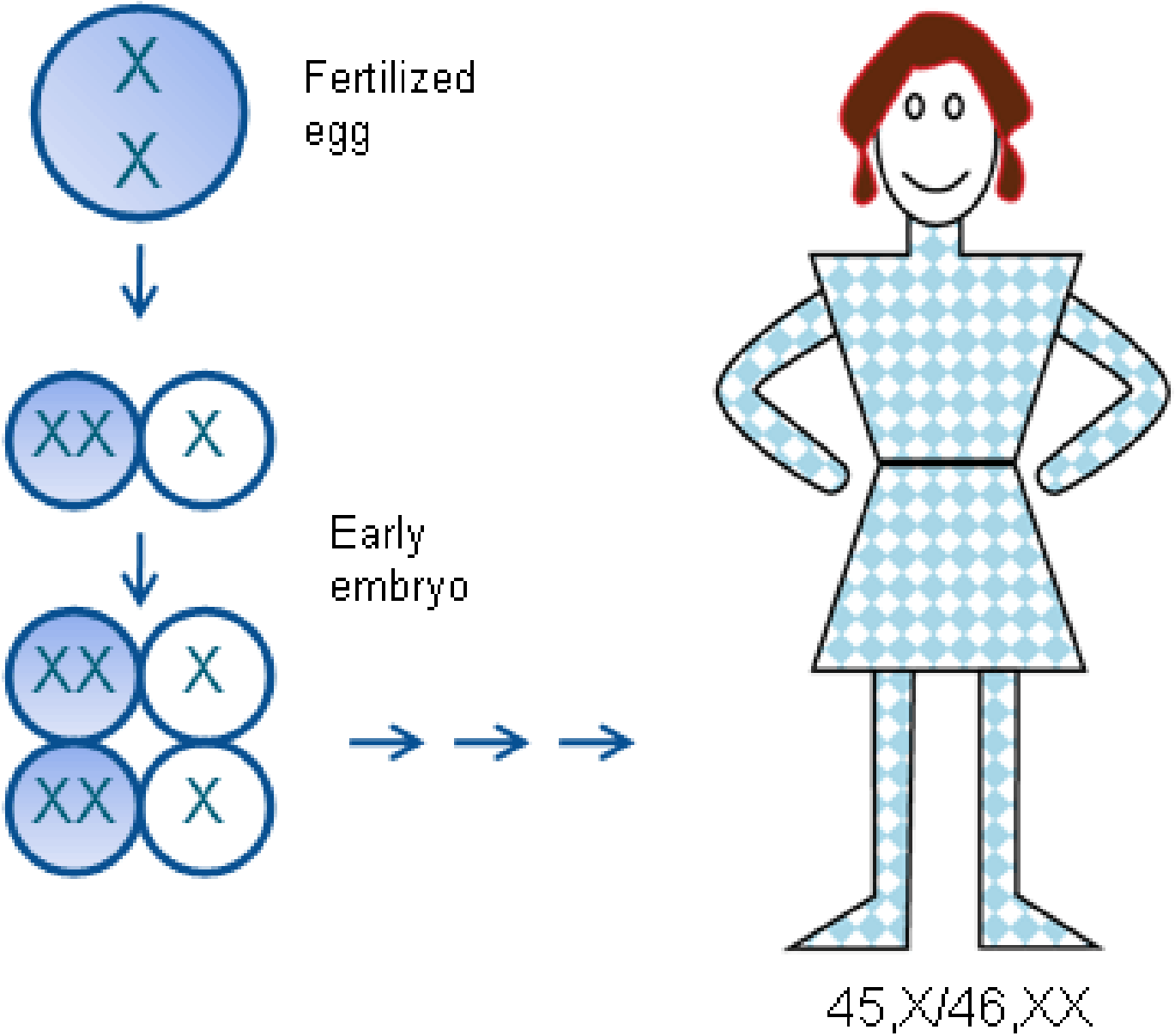
- **somatic (ie in most body cells) or**
- **gonadal (confined solely to the gonads).**

Turner: 30%

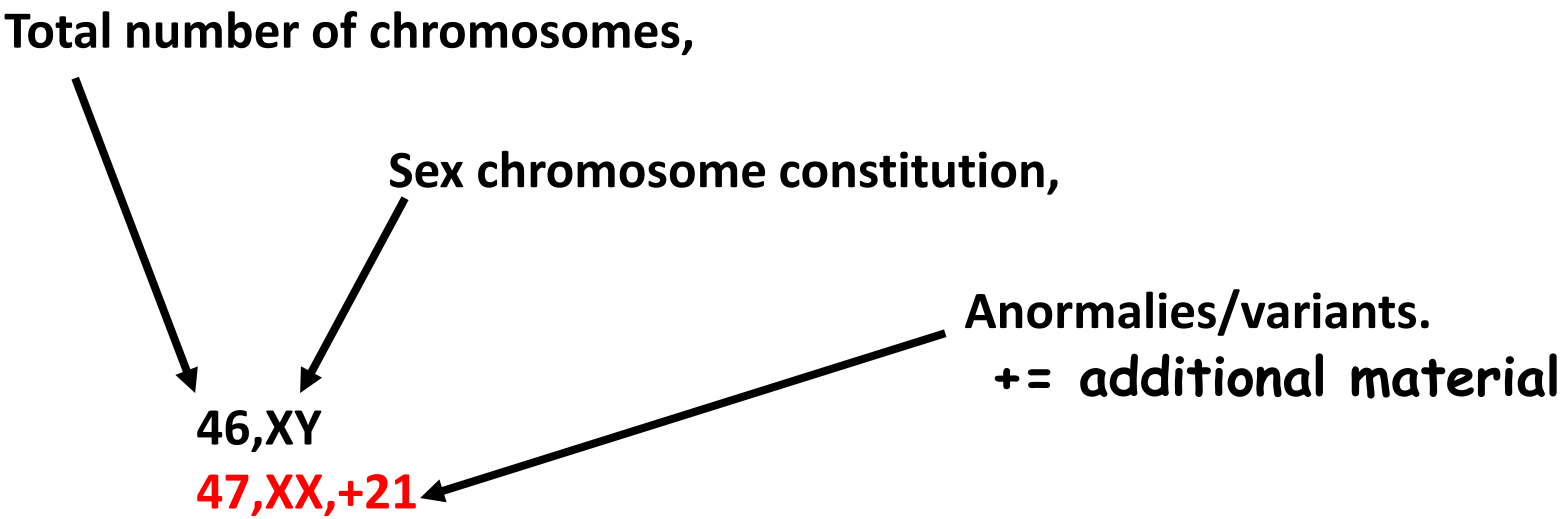


- Reduced fertility
- Delayed or absent periods

Figure 2. Schematic of chromosomal mosaicism, which exists in a large percentage of individuals with Turner Syndrome, contributing to phenotypic variability. (From U.S. National Library of Medicine)


X
X
Fertilized egg
XX
X
Early embryo
XX
X
XX
X
45,X/46,XX

The Karyotype: an international description



The Karyotype: an international description

46,XY	**Normal**
47,XX,+21	***Trisomy 21 (Down syndrome)***
47,XXX	***Triple X syndrome***
69,XXY	***Triploidy***
45,XX,der(22)	***chromosome derived from ch22 -contains its cent.***
46,XY,t(2;4)(p12;q12)	***Reciprocal translocation***
46,XX,del(5)(p25)	***Deletion tip of chromosome 5***
46,XX,dup(2)(p22)	***Duplication of part of short arm Chr 2***
46,XY,inv(11)(p15q14)	***Pericentric inversion chromosome 11***
46,XY/47,XXY	***Mosaicism normal/Klinefelter syndrome***
46,xx/45,x	***Mosaicism normal/ Turner syndrome***

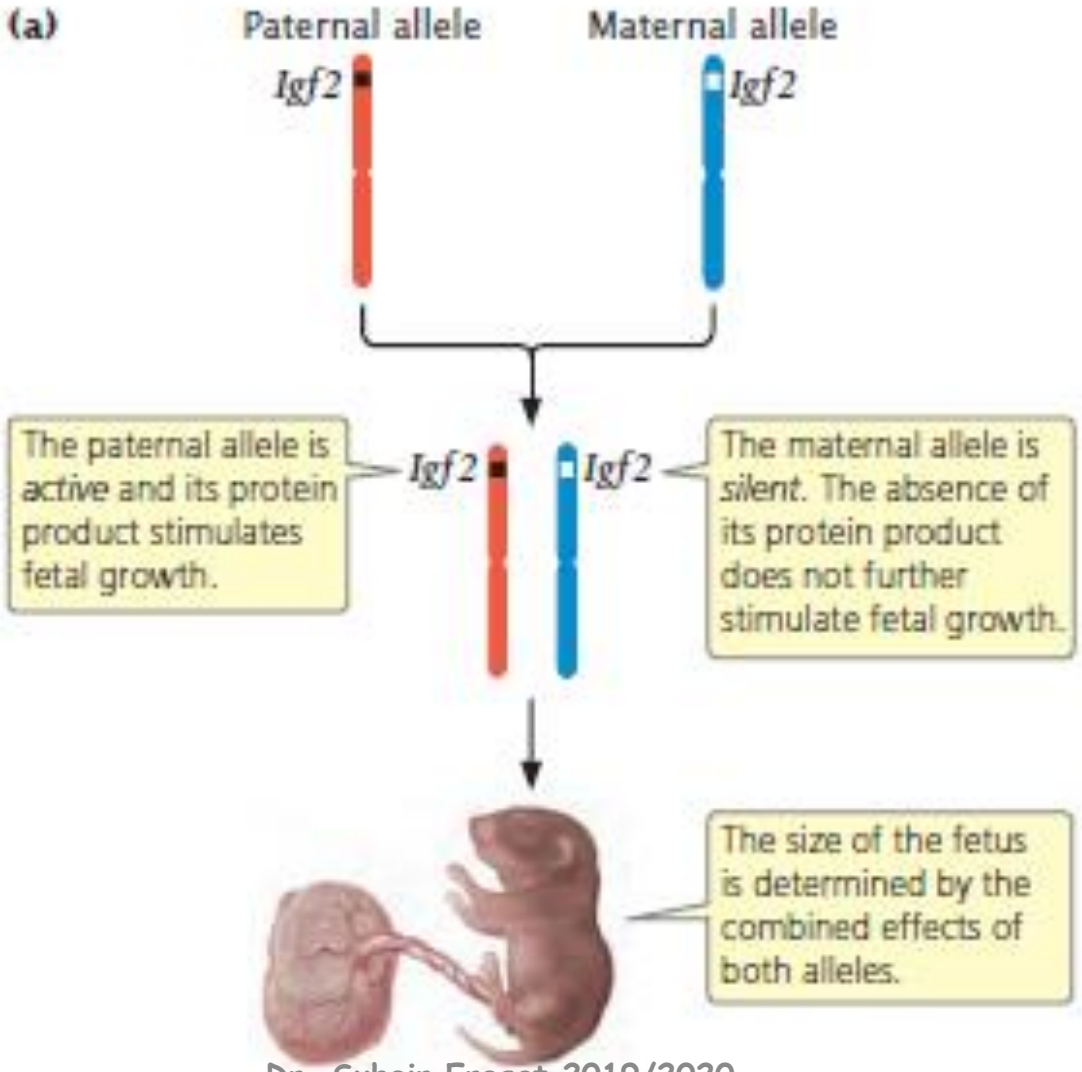
Epigenetics:Genomic imprinting

Some genes are expressed only from the maternal genome and some only from the paternal genome

It is estimated that about 40 genes are imprinted and they can be found on several different chromosomes

For example - Insulin-like growth factor (*Igf2*) gene

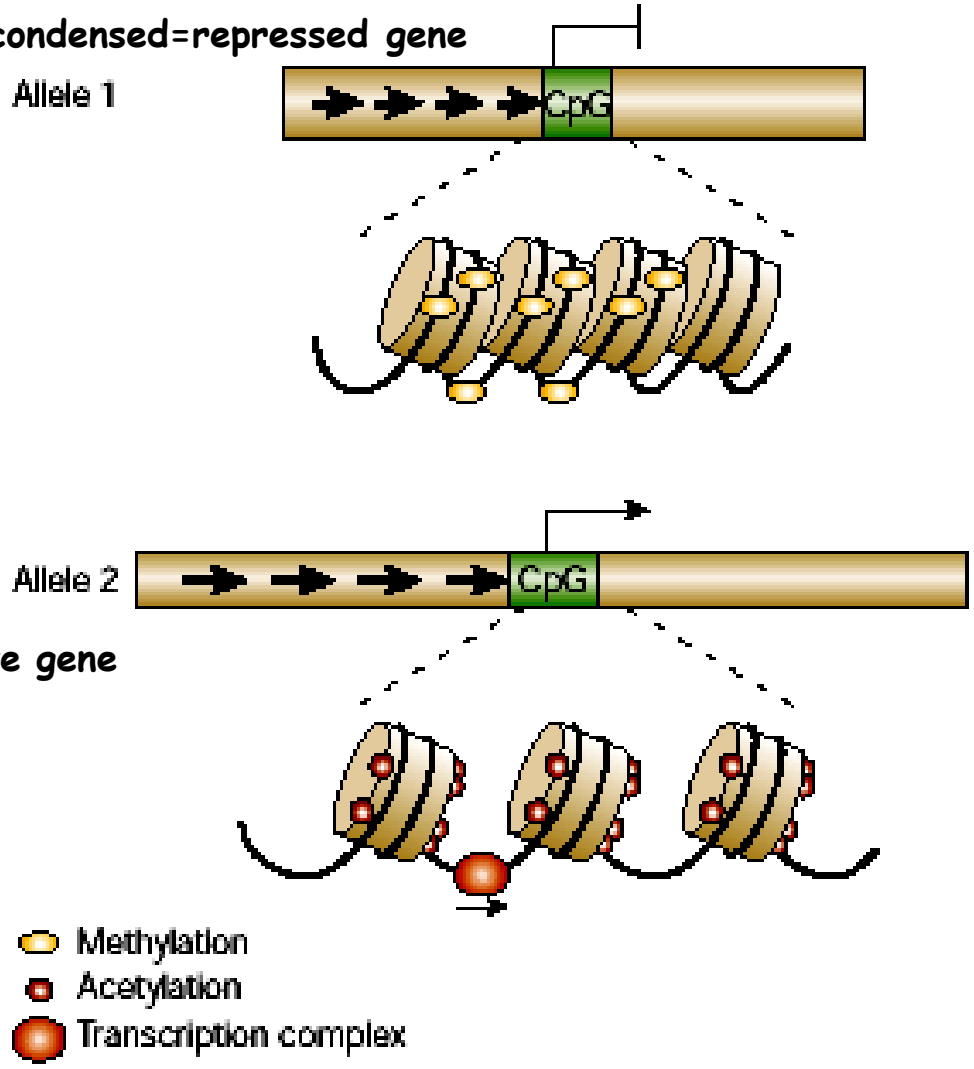
insulin like growth factor2



Imprinting is maintained by DNA methylation

Chromatin remodeling=dynamic modification of chromatin = control gene expression

Heterochromatin=more condensed=repressed gene



Euchromatin=loose=active gene

Angelman Syndrome

Developmental delay
Functionally severe Speech impairment
frequent laughter/smileing;
apparent happy demeanor;
easily excitable personality

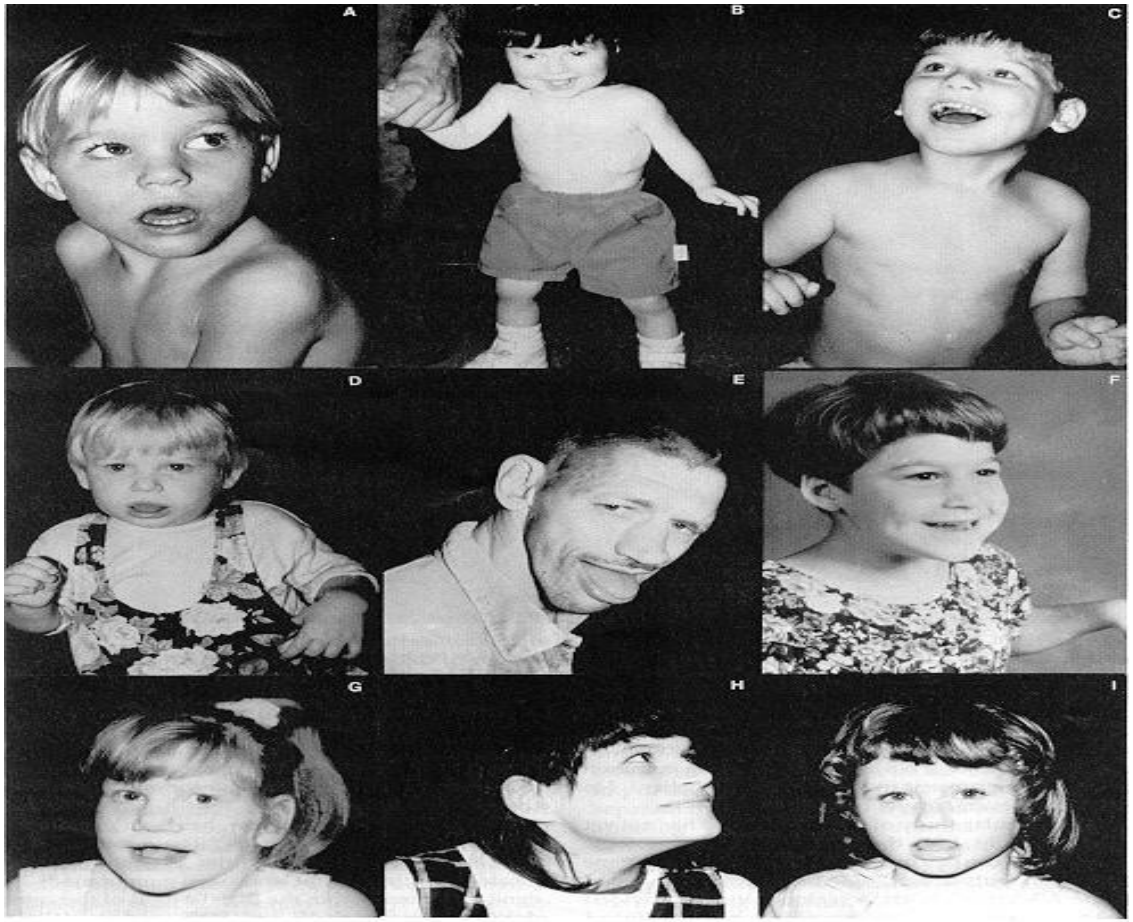
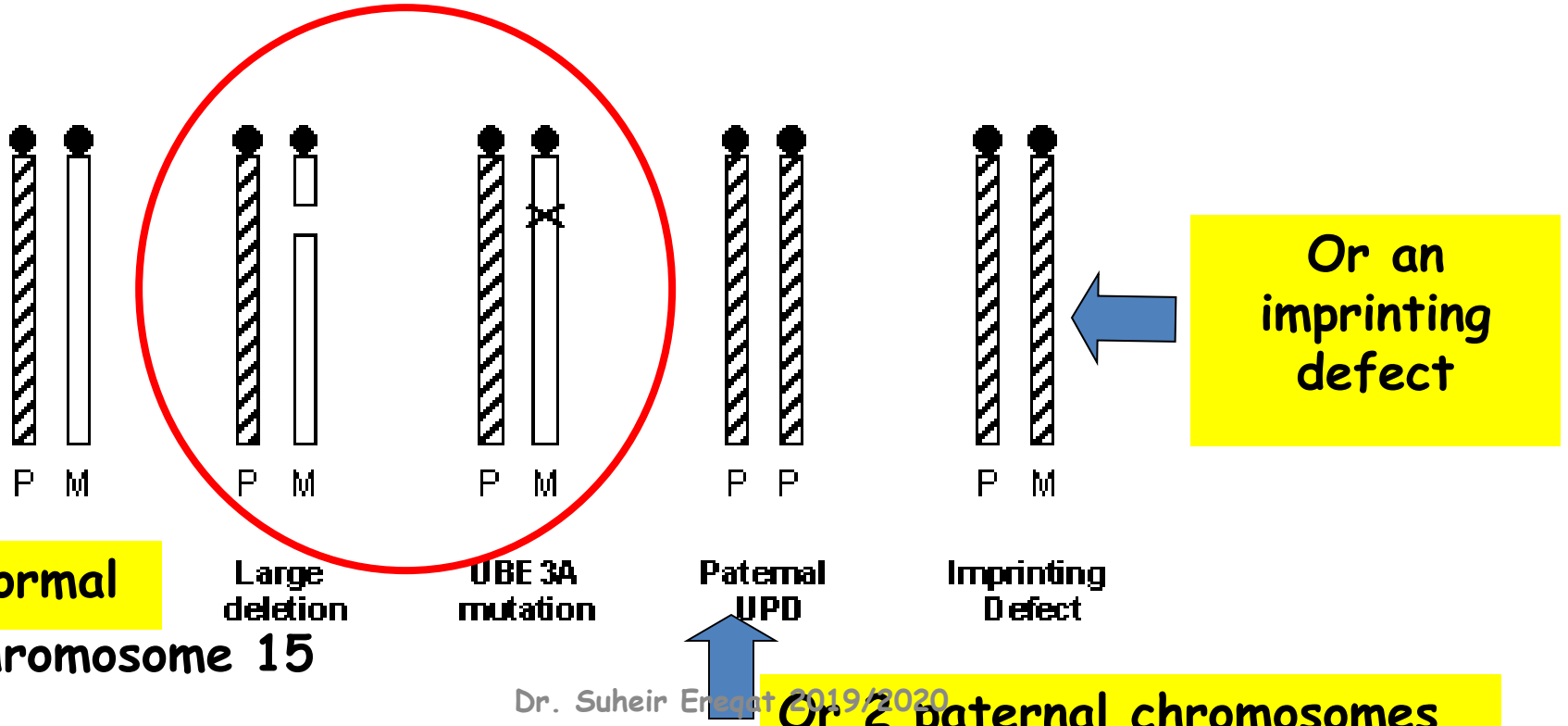


FIGURE 1. Composite of unrelated individuals with AS illustrating some typical behavioral and facial appearances. All individuals except C have typical large deletions of 15q11-13. Individual C has no abnormality yet detected of his chromosomes 15. See text for details.

Angelman Syndrome

-Angelman Syndrome- maternal chromosome deletion

Genetic Mechanisms Leading to AS



Prader-Willi Syndrome

Poor weight gain in infancy
Excessive or rapid weight gain between 1 and 6
Delayed sexual maturity
Mild to moderate mental retardation
Obsession with food (hyperphagia)-
Diabetes

For the genes affected in PWS, paternal copy of this gene is deleted and the maternal copy that is usually imprinted (and thus is silenced)