Incidence of Chromosomal Abnormalities in Newborns

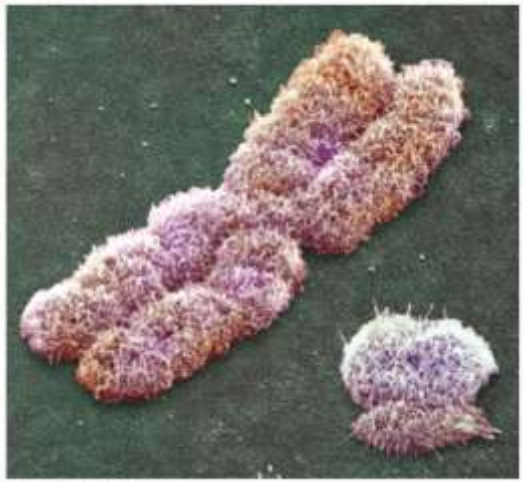
Type of Abnormality	Prevalence at Birth
Sex Chromosome Aneuploidy	
Males (43,612 newborns)	
47,XXY	1/1000
47,XYY	1/1000
Females (24,547 newborns)	
45,X	1/5000
47,XXX	1/1000
Autosomal Aneuploidy (68,159 newborns)	
Trisomy 21	1/800
Trisomy 18	1/6000
Trisomy 13	1/10,000
Structural Abnormalities (68,159 newborns)	
(Sex chromosomes and autosomes)	
Balanced rearrangements	
Robertsonian	1/1000
Other (reciprocal and others)	1/885
Unbalanced rearrangements	1/17,000
All Chromosome Abnormalities	
Autosomal disorders and unbalanced rearrangements	1/230
Balanced rearrangements	1/500
Total	1/154

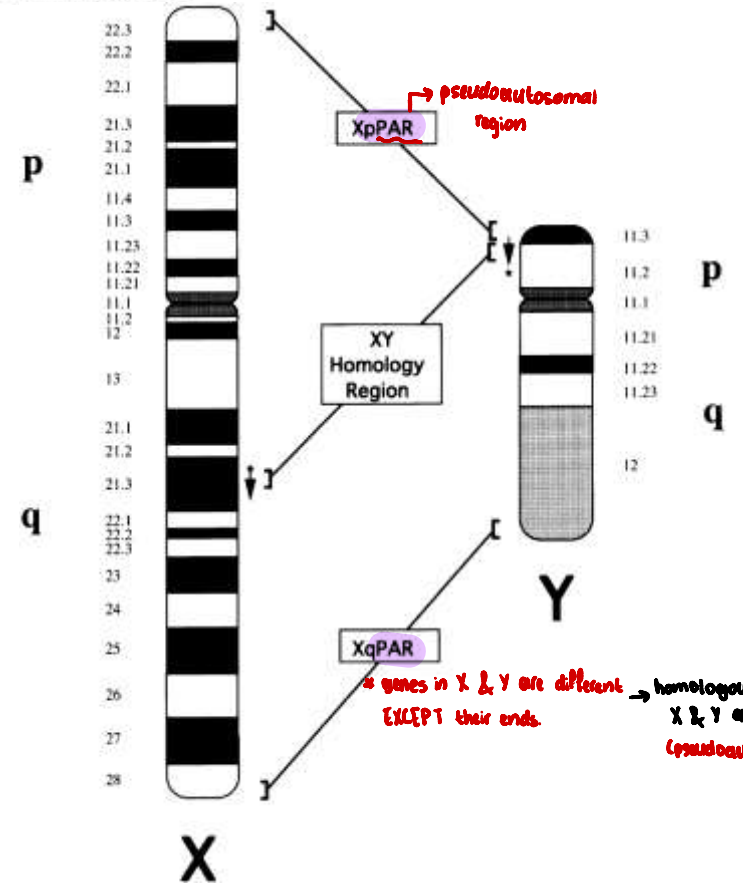
Data from Hsu LYF (1998) Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A (ed.), *Genetic Disorders and the Fetus*, 4th edition, Johns Hopkins University Press, Baltimore, pp. 179-248.

The Chromosomal Basis of Sex

- In humans and other mammals, there are two varieties of sex chromosomes: a larger X chromosome and a smaller Y chromosome
- Only the **ends of the Y** chromosome have regions that are **homologous** with corresponding regions of the X chromosome
- The ***SRY*** gene on the Y chromosome codes for a protein that **directs the development of male anatomical features**

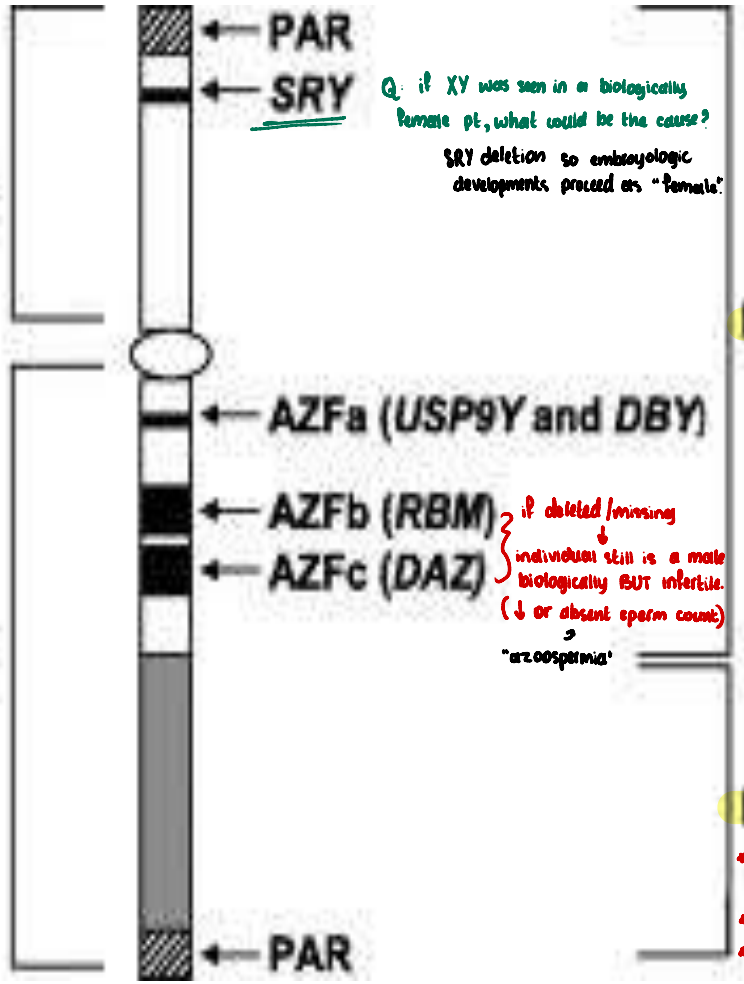
Figure 15.5





→ pseudoautosomal region

* genes in X & Y are different EXCEPT their ends. → homologous region between X & Y are the end. (pseudoautosomal region)



Q: if XY was seen in a biologically female pt, what could be the cause?

SRY deletion so embryologic developments proceed as "female"

Euchromatin

if deleted/missing ↓ individual still is a male biologically BUT infertile. (↓ or absent sperm count) → "azoospermia"

Heterochromatin

- does NOT carry clinically significant genes
- if deleted → X clinical consequences.
- size of this region is variable between males.

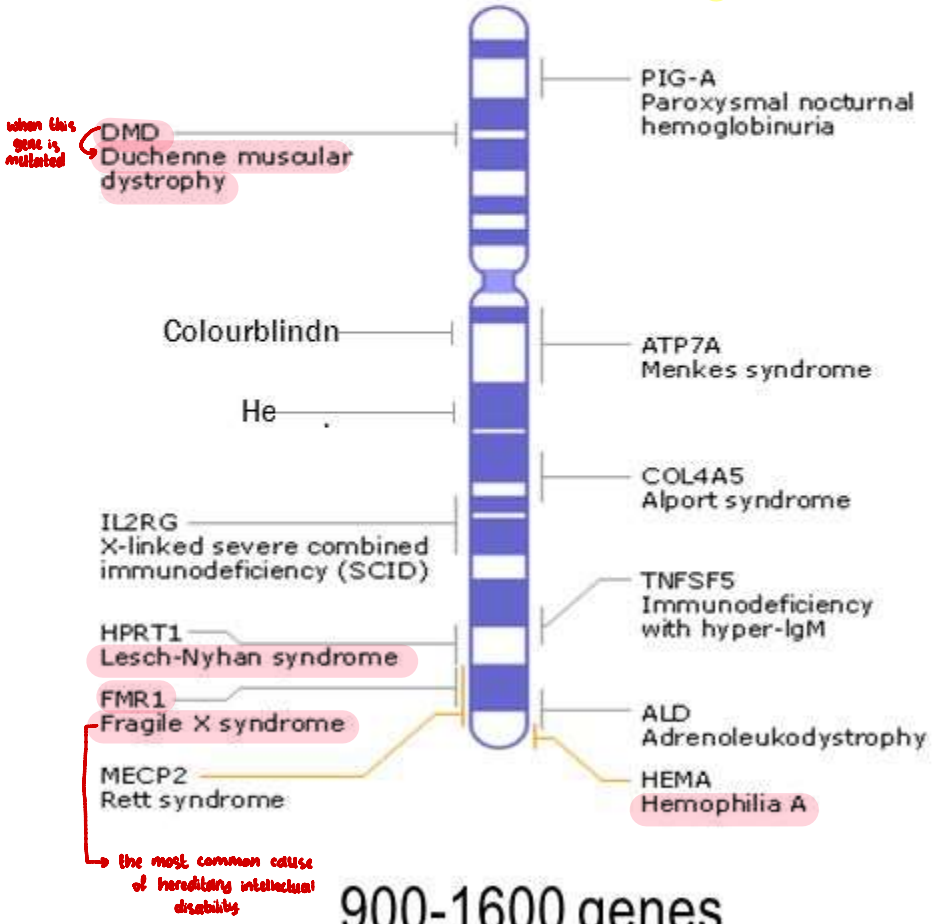
SRY (Sex-determining region Y)

↳ found distally on the p arm of ch.Y → induces development of male.

* default embryonic/fetal development is female unless there was SRY which becomes a male

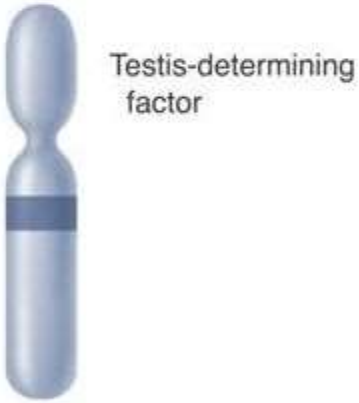
Sex Chromosomes

X chromosome



900-1600 genes

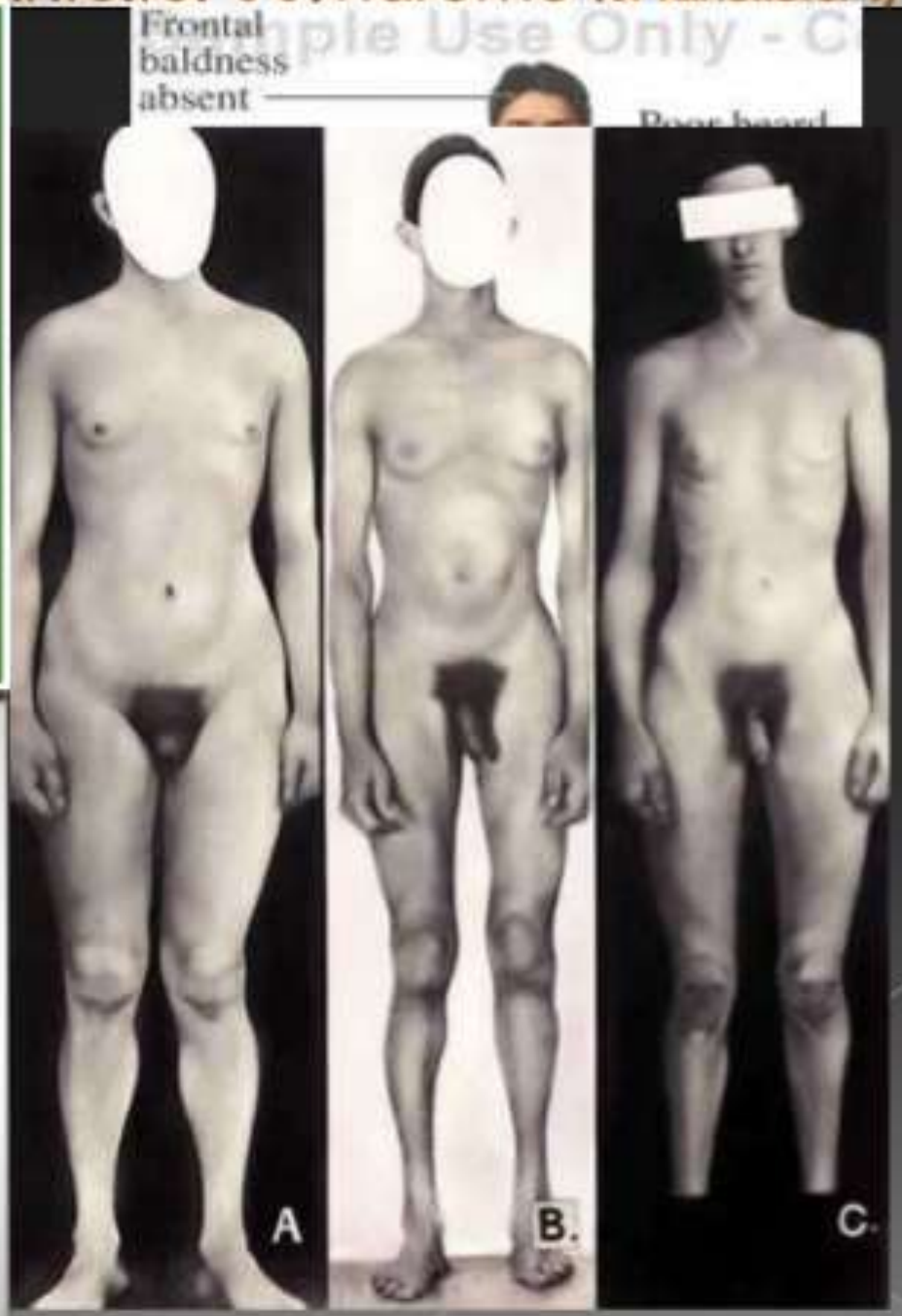
Y chromosome

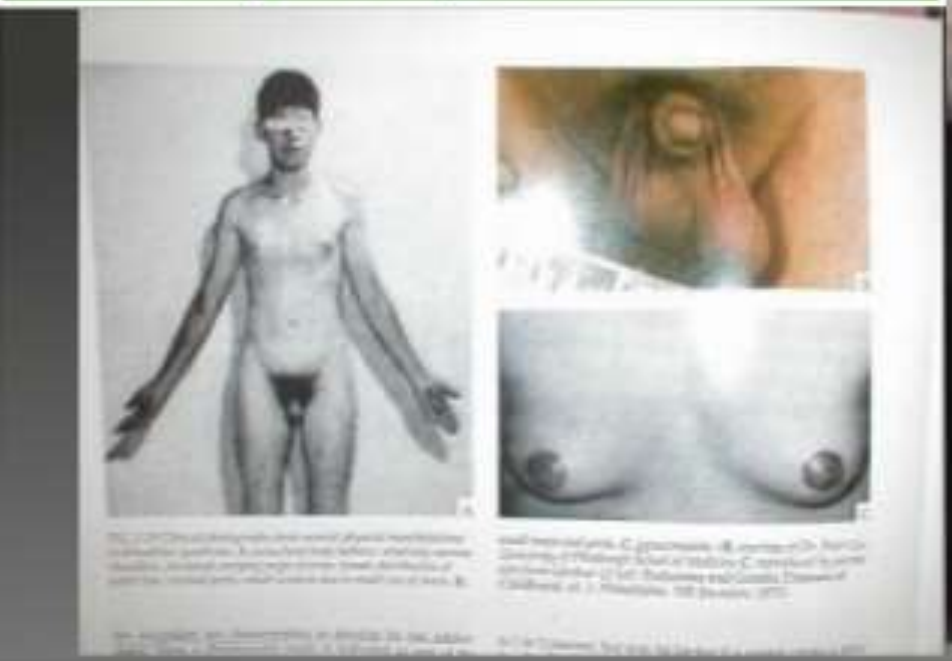


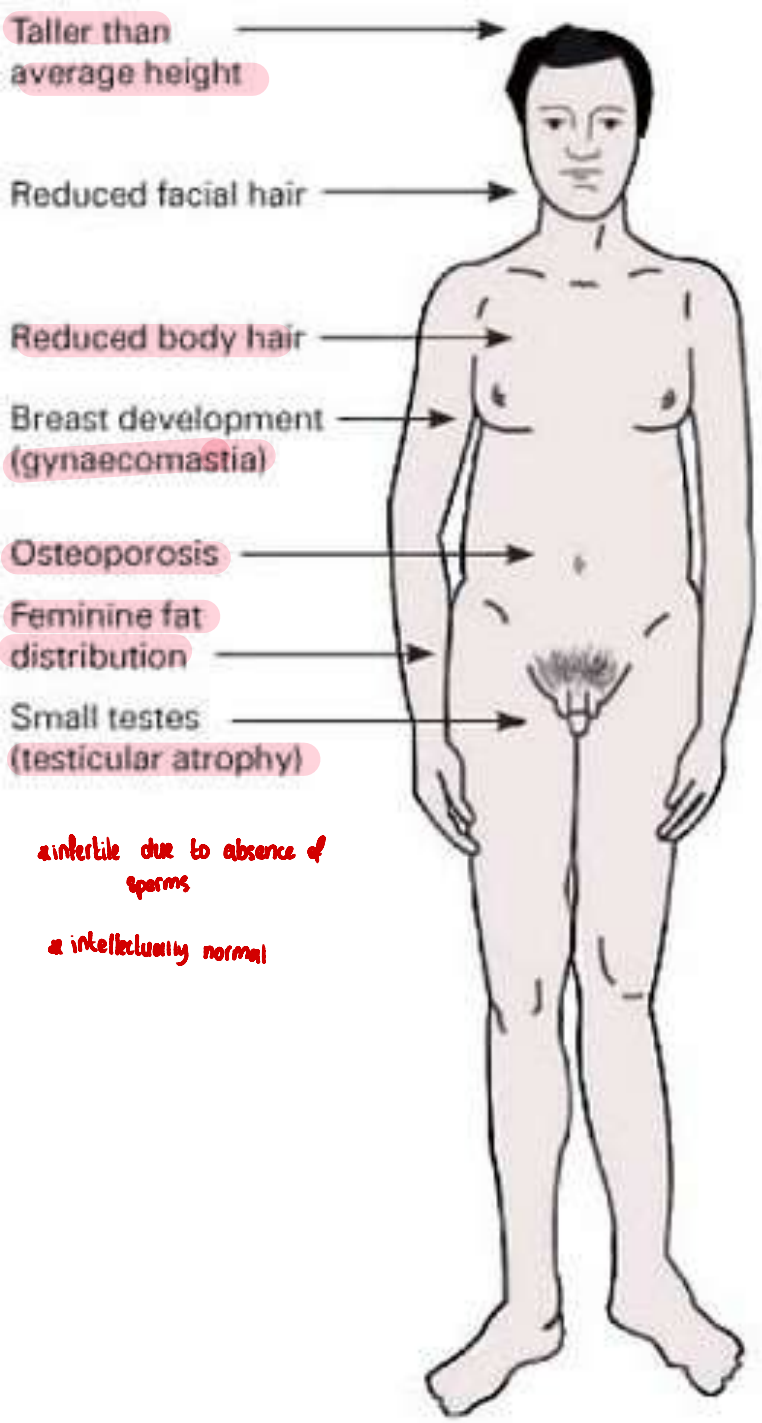
70-200 genes

Kleinfelter's syndrome (or Klinefleter's)

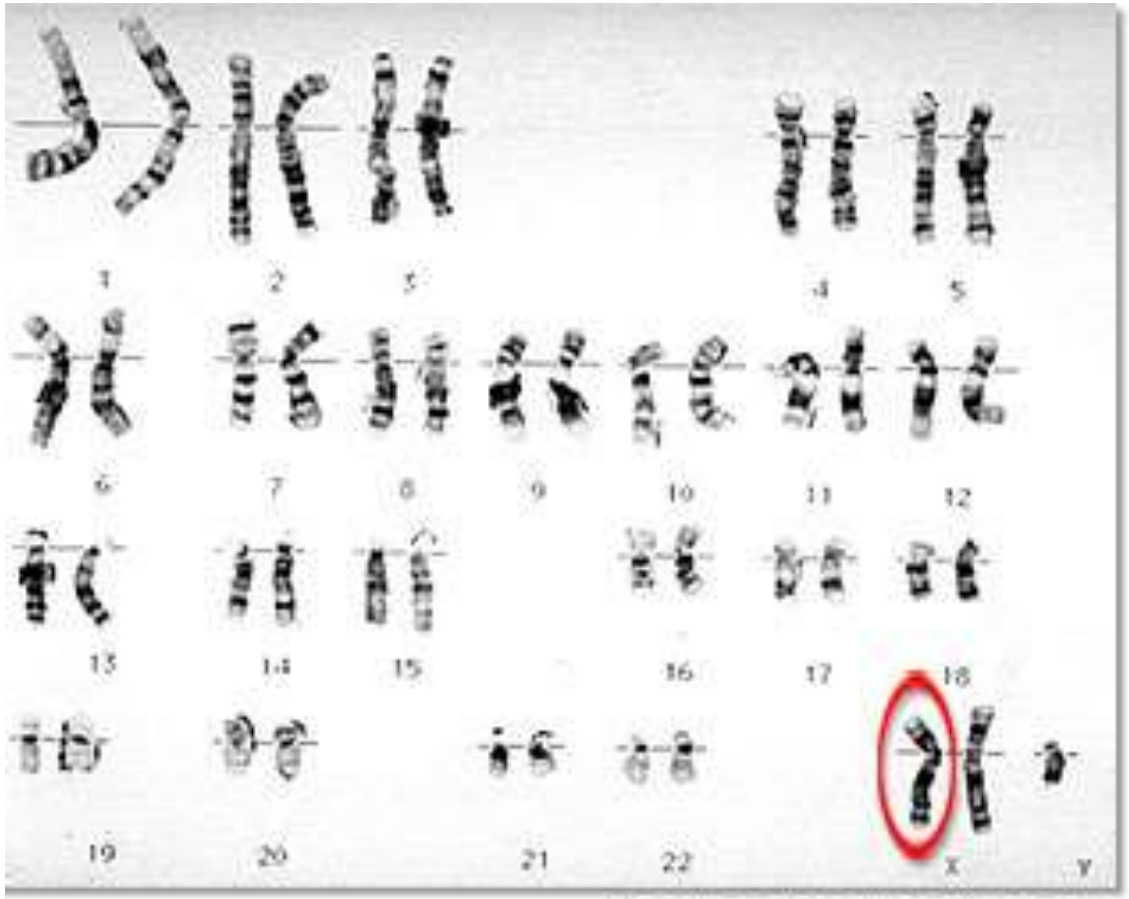
- Males with some development of breast tissue normally seen in females.
- Little body hair is present, and such person are typically tall, have small testes.
- Infertility results from absent sperm.
- Evidence of mental retardation may or may not be present.







- infertile due to absence of sperms
- intellectually normal

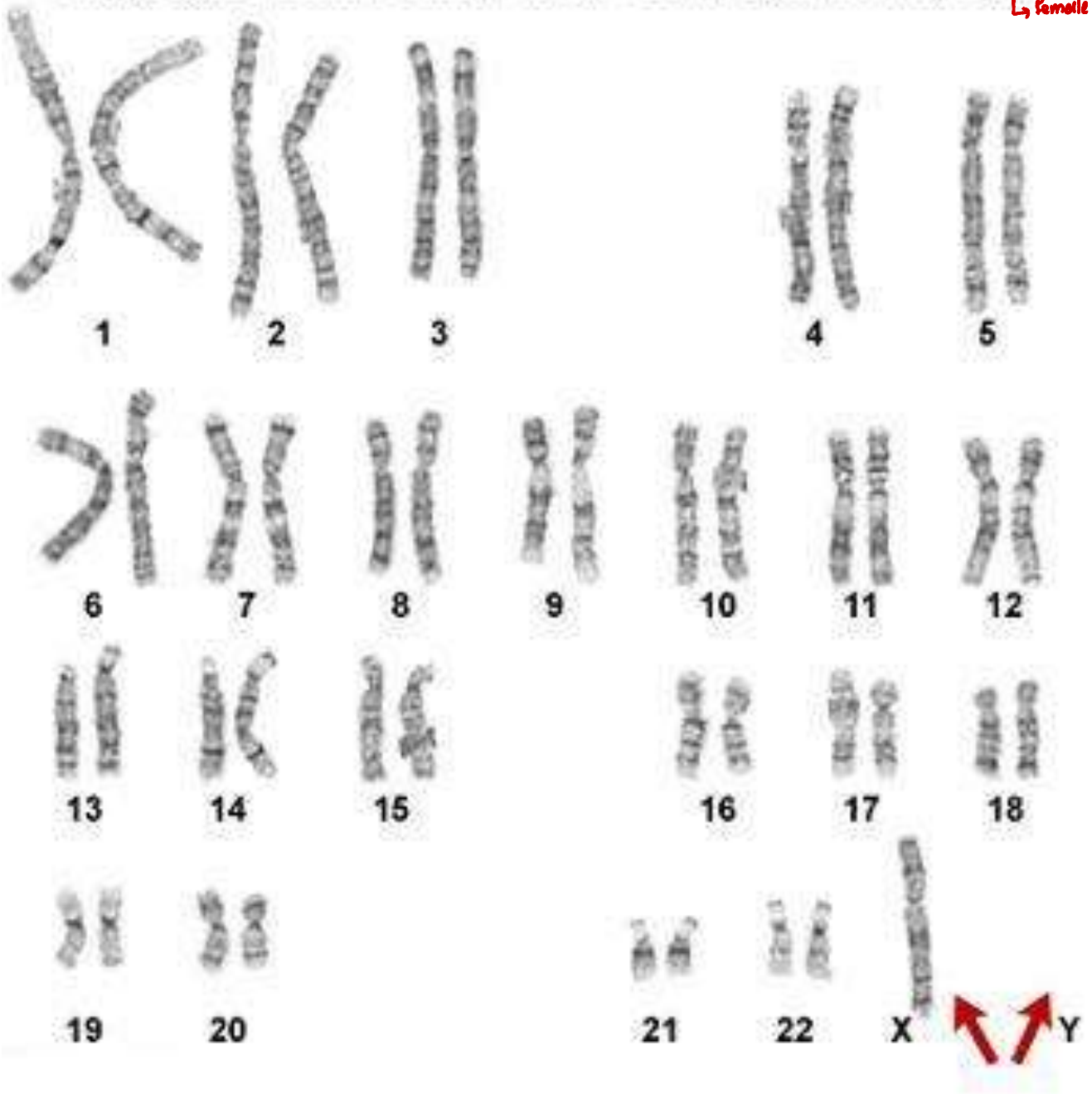


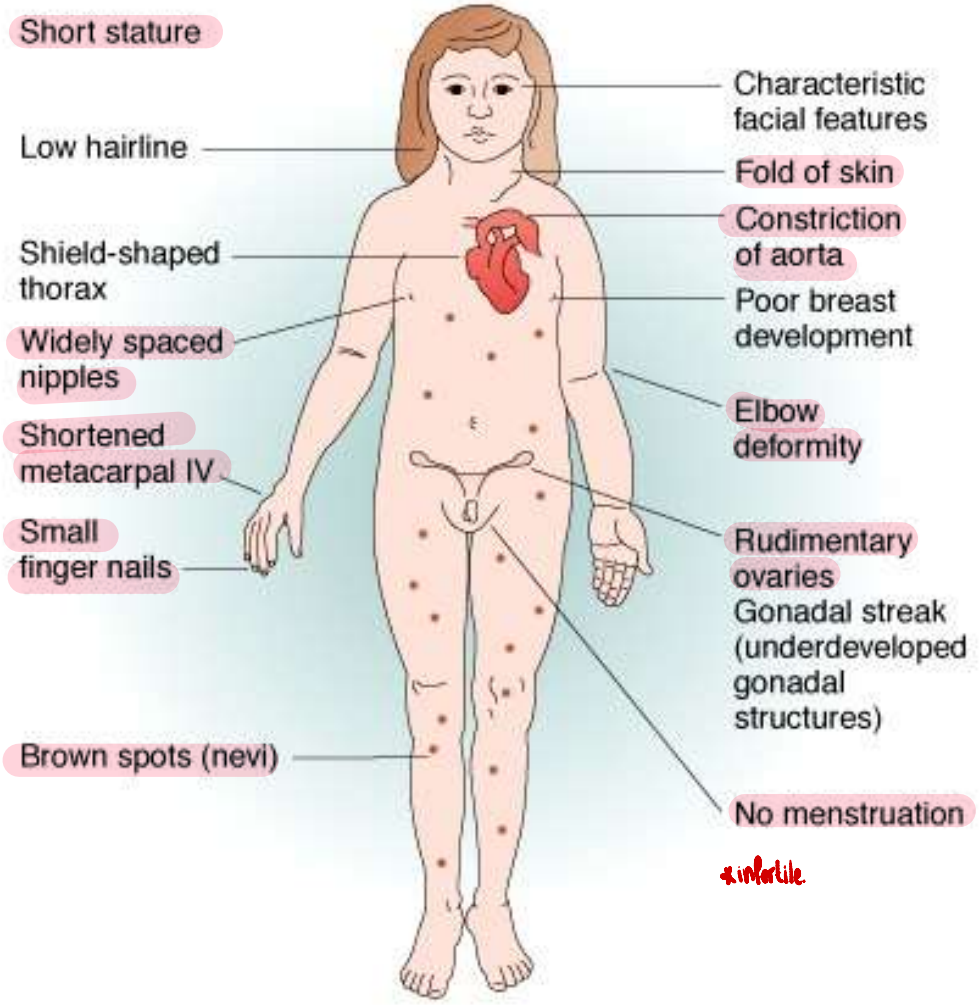
medgen.genetics.utah.edu

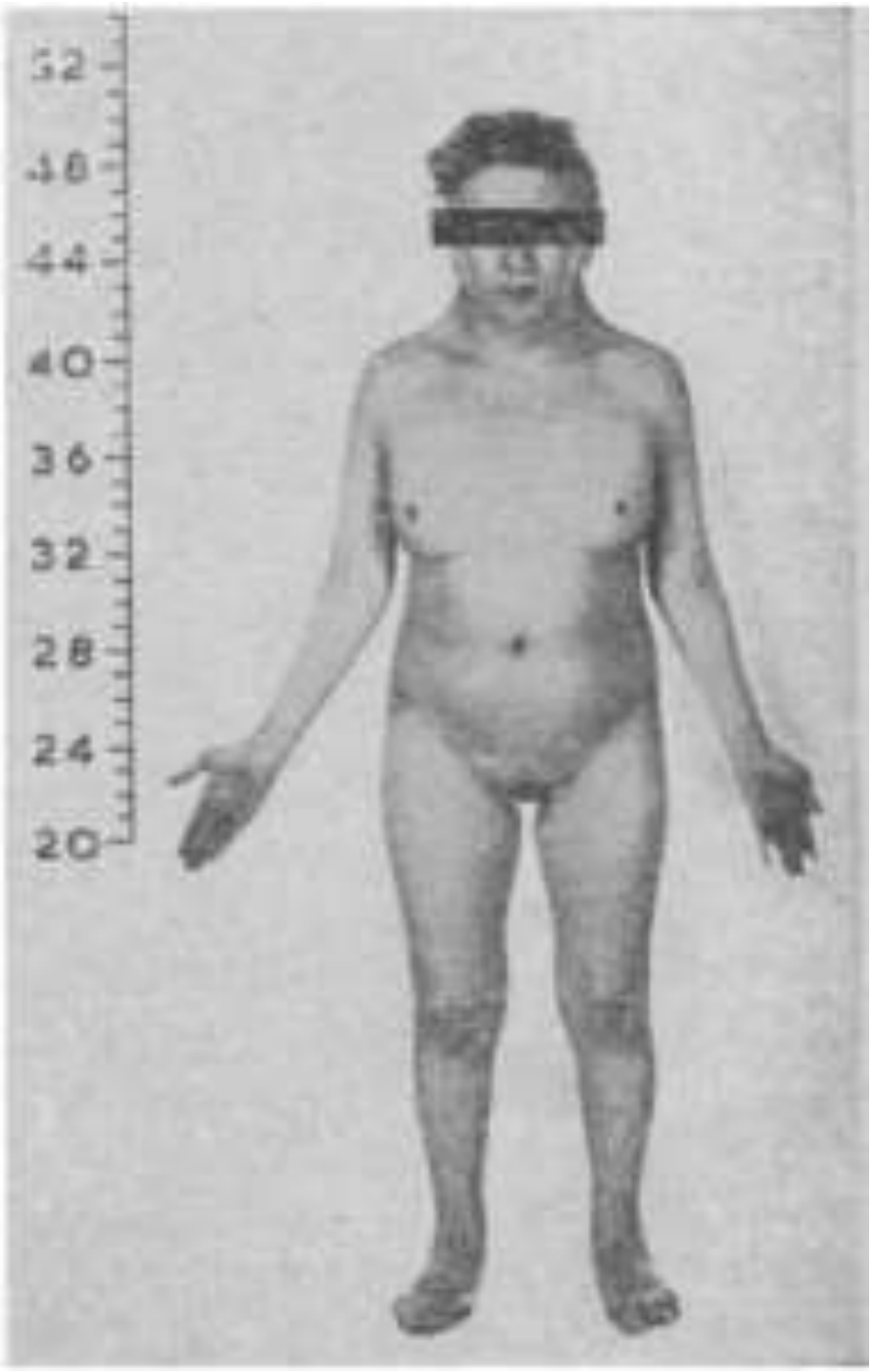
- karyotype : 47, XXY
  - Y → primary sexual organs are male.

Karyotype From a Female With Turner syndrome (45,X)

↳ female biology




Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small finger nails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation
infertile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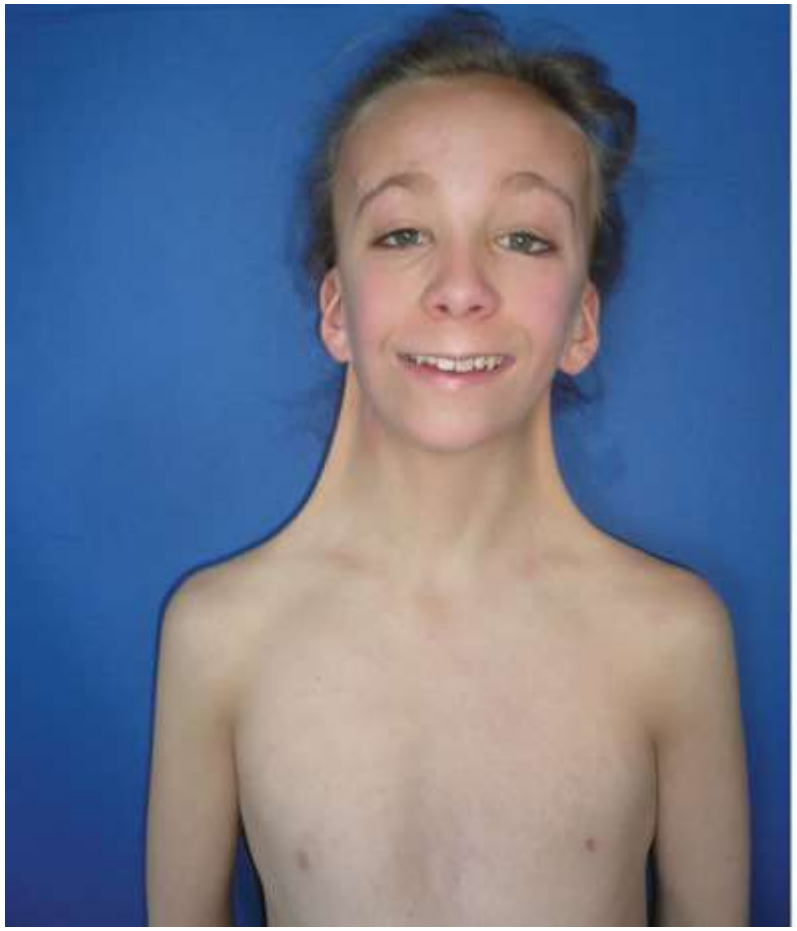
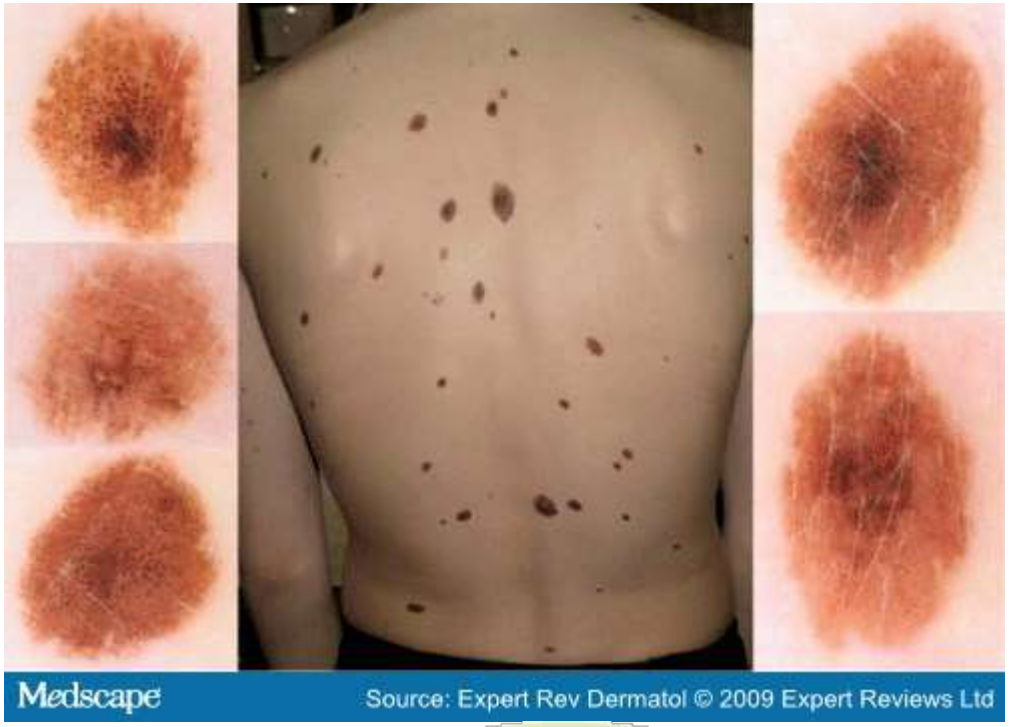
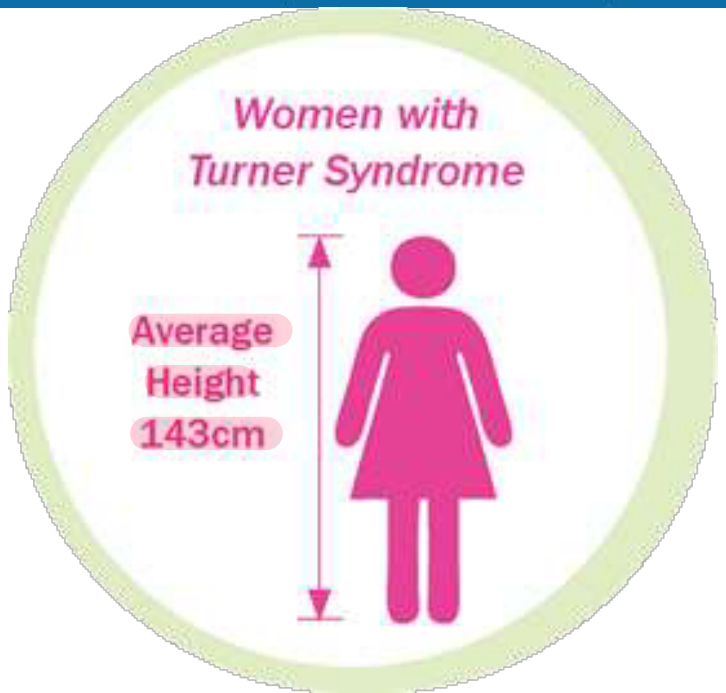
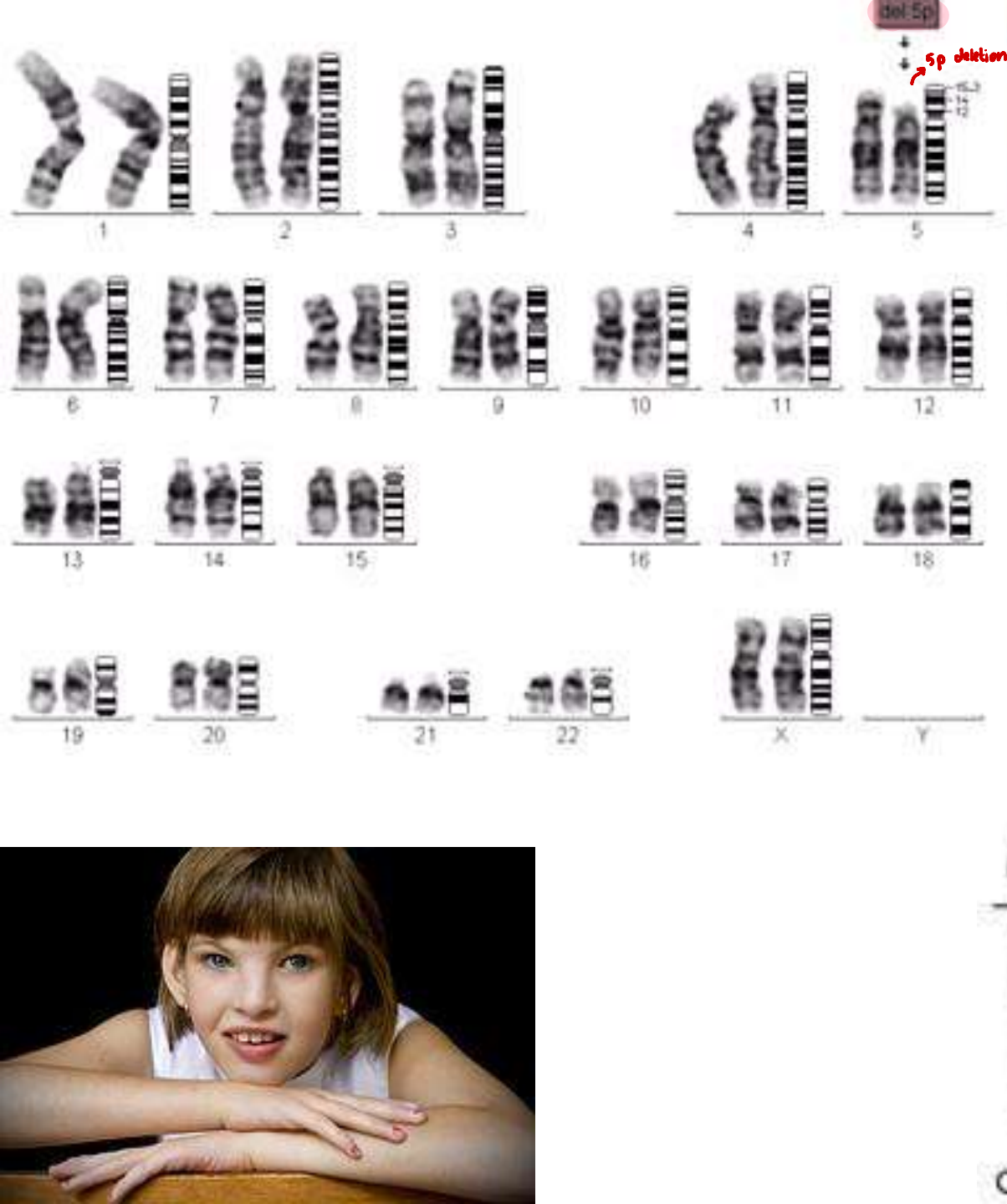


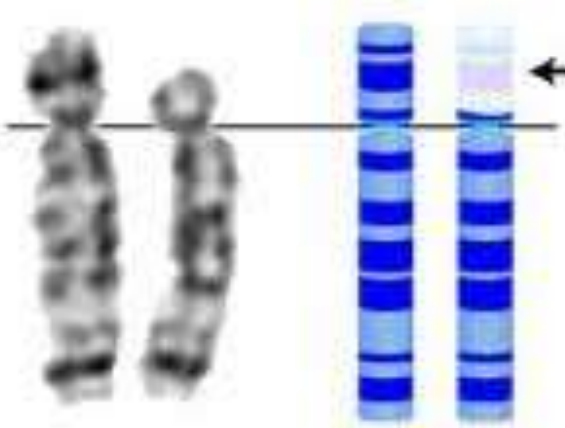

Medscape
Source: Expert Rev Dermatol © 2009 Expert Reviews Ltd


Women with
Turner Syndrome
Average
Height
143cm

Disorders Caused by Structurally Altered Chromosomes

- The syndrome *cri du chat* ("cry of the cat"), results from a specific deletion in chromosome 5
- A child born with this syndrome is mentally retarded and has a catlike cry; individuals usually die in infancy or early childhood
- Certain cancers, including *chronic myelogenous leukemia* (CML), are caused by translocations of chromosomes





Cri-du-chat Chromosome 5 pair

Symptoms of cri du chat syndrome are mostly those of looks. People who have this syndrome have very distinct looks. They have:

- Small heads (microcephaly)
- Unusually round face
- Small chin
- Eyes that are very far apart
- Folds of skin over their eyes
- Small nose bridge

Symptoms occur inside the body also. Heart defects, muscular/skeletal problems, hearing or sight problems, and poor muscle tone are all possible. When children diagnosed with Cri Du Chat grow, they usually have difficulty walking and talking correctly. They might have behavior problems like hyperactivity and aggression. Also, some may have severe mental retardation

Le opposite of Down Syndrome (benign/friendly)

Cri-du-chat Symptoms

- Approximately 75% of the patients with cri-du-chat syndrome die within the first few months of life and about 90% before they are aged 1 year. These figures are from an older study (1978), and decreased morbidity and mortality are most likely with contemporary interventions. Survival to adulthood is possible.
- Pneumonia, aspiration pneumonia, congenital heart defects, and respiratory distress syndrome are the most common causes of death.

Disorders Caused by Structurally Altered Chromosomes

- Certain cancers, including *chronic myelogenous leukemia* (CML), are caused by translocations of chromosomes

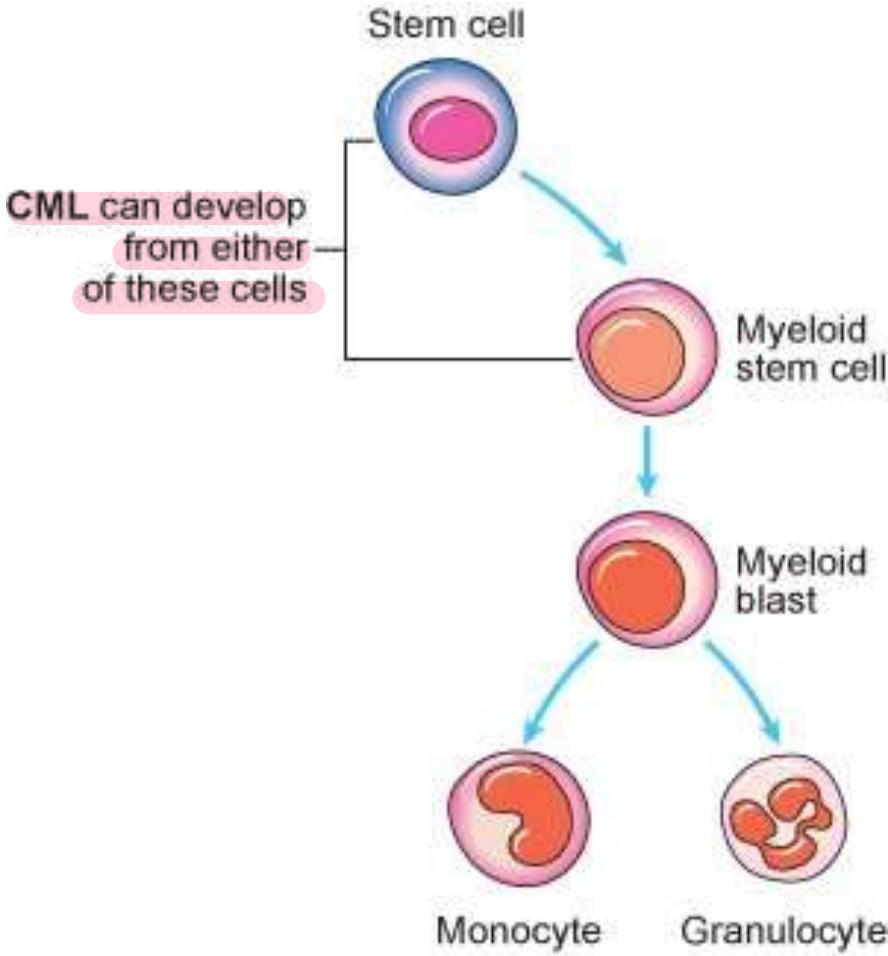
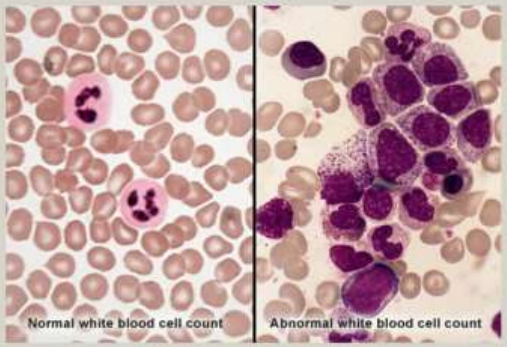


Diagram showing which cells CML can start in
© CancerHelp UK

What is leukemia?

A cancer found in the blood and bone marrow, caused by too many white blood cells in the body. The white blood cells don't let the body fight disease and prevent the body from making red blood cells and platelets.



4 types of leukemia

Acute lymphoblastic leukemia

Found in lymphoid cells
Grows quickly
Common in children
6,000 cases a year

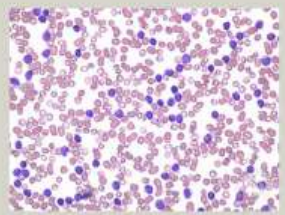
ALL is the m/c type of cancer in children

Acute myelogenous leukemia

Found in myeloid cells
Grows quickly
Common in adults and children
18,000 cases a year

Chronic lymphoblastic leukemia

Found in lymphoid cells
Grows slowly
Common in adults 55+
15,000 cases a year



Chronic myelogenous leukemia

Found in myeloid cells
Grows slowly
Common in adults
6,000 cases a year

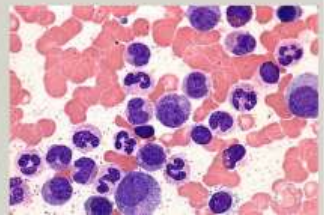
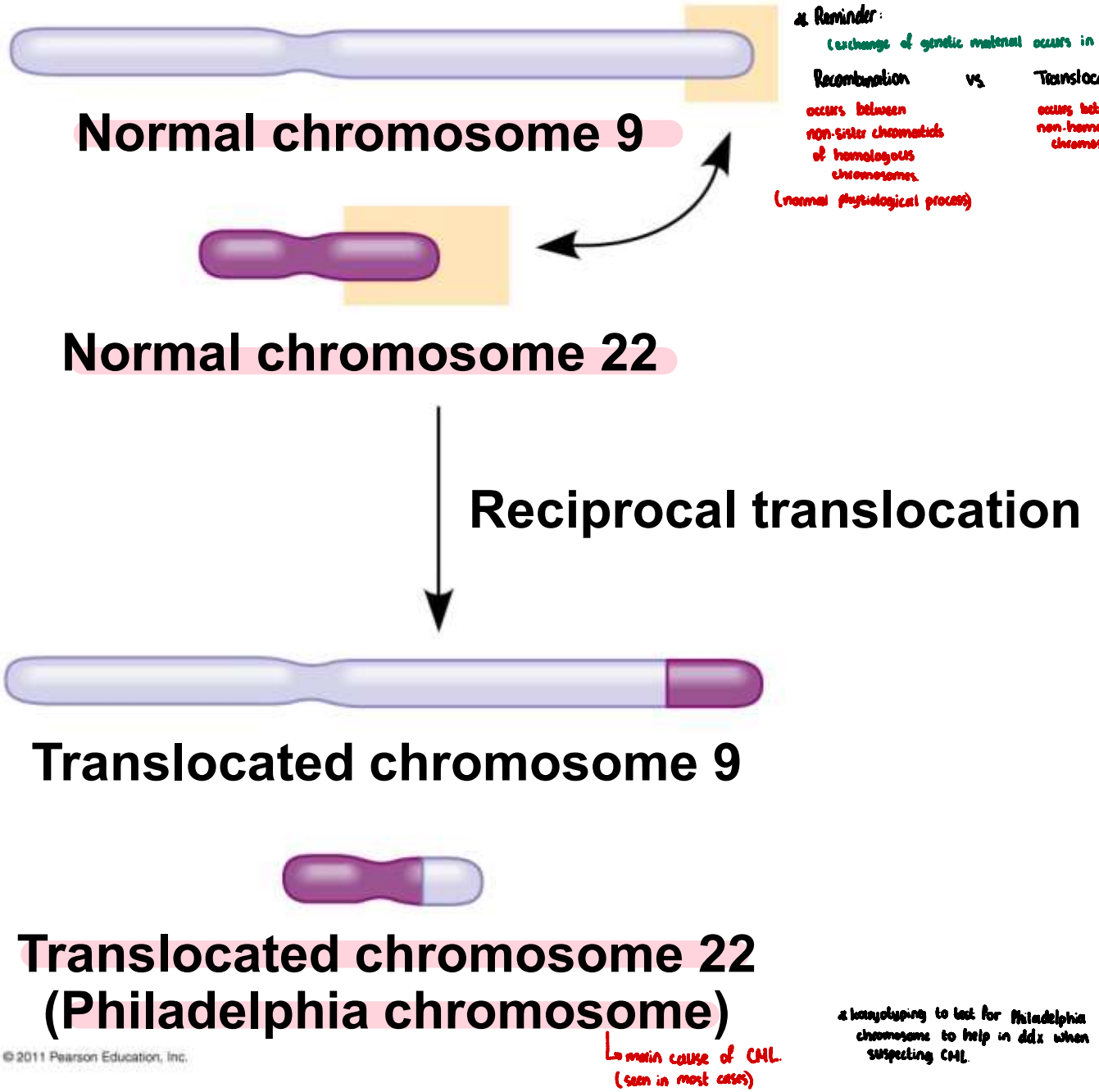


Figure 15.16



✍ Reminder:
(exchange of genetic material occurs in BOTH)

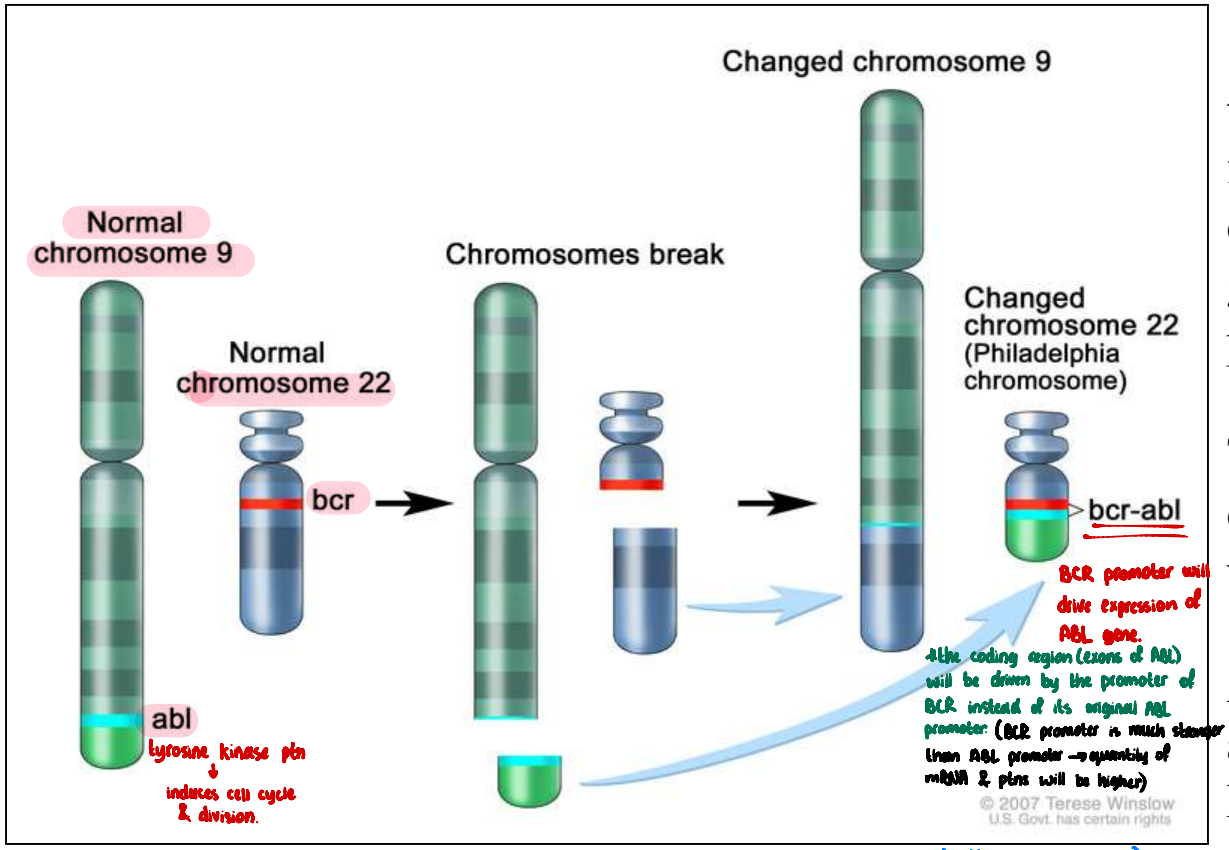
Recombination vs. Translocation

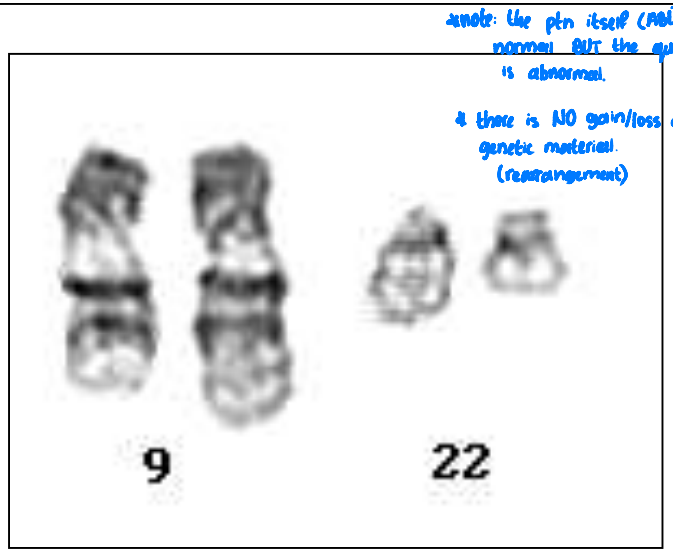
Recombination: occurs between non-sister chromatids of homologous chromosomes (normal physiological process)

Translocation: occurs between non-homologous chromosomes.

↳ main cause of CML (seen in most cases)

✍ karyotyping to test for Philadelphia chromosome to help in ddx when suspecting CML





result of the translocation is the oncogenic BCR-ABL gene fusion, located on the shorter derivative 22 chromosome. This gene encodes the Bcr-abl fusion protein

The ABL tyrosine kinase activity of *BCR-Abl* is elevated relative to wild-type ABL

Abl gene expresses a membrane-associated protein, a tyrosine kinase, the BCR-Abl transcript is also translated into a tyrosine kinase. The activity of tyrosine kinases is typically controlled by other molecules, but the mutant tyrosine kinase encoded by the BCR-Abl transcript results in a protein that is "always on" or continuously activated, which results in unregulated cell division (i.e. cancer)

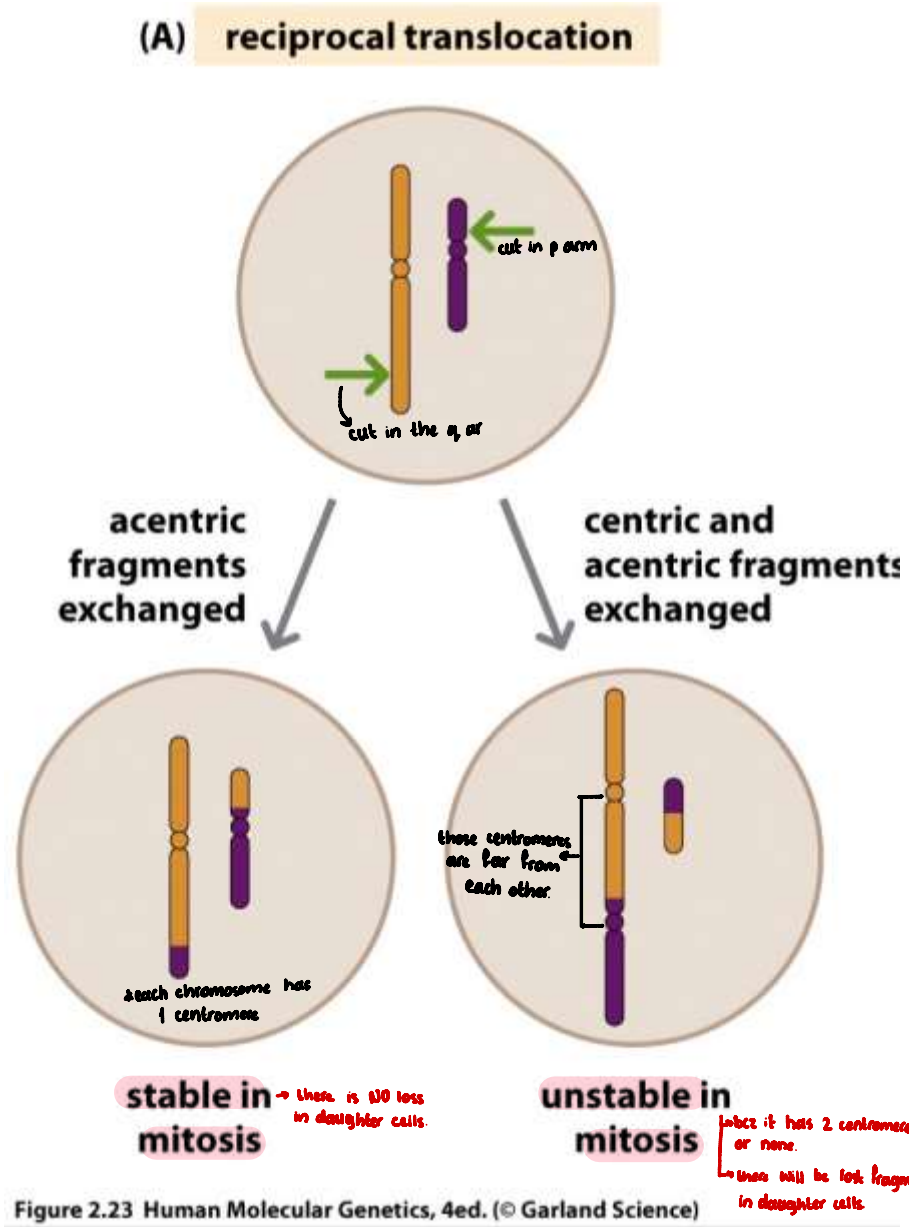


Figure 2.23 Human Molecular Genetics, 4ed. (© Garland Science)

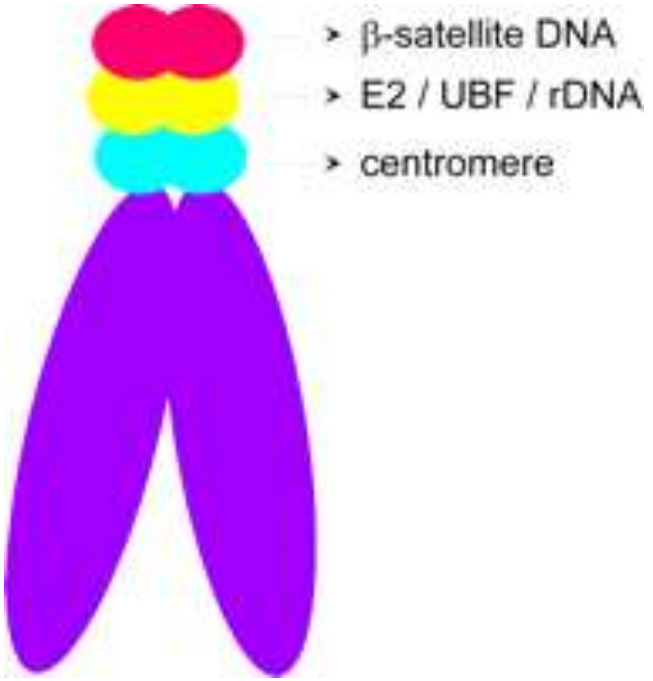
(A) Reciprocal translocation. The derivative chromosomes are stable in mitosis when one acentric fragment is exchanged for another; when a centric fragment is exchanged for an acentric fragment, unstable acentric and dicentric chromosomes are produced.

If an acentric fragment from one chromosome is exchanged for an acentric fragment from another, the products are stable in mitosis, however exchange of an acentric fragment for a centric fragment results in acentric and dicentric chromosomes that are unstable in mitosis.

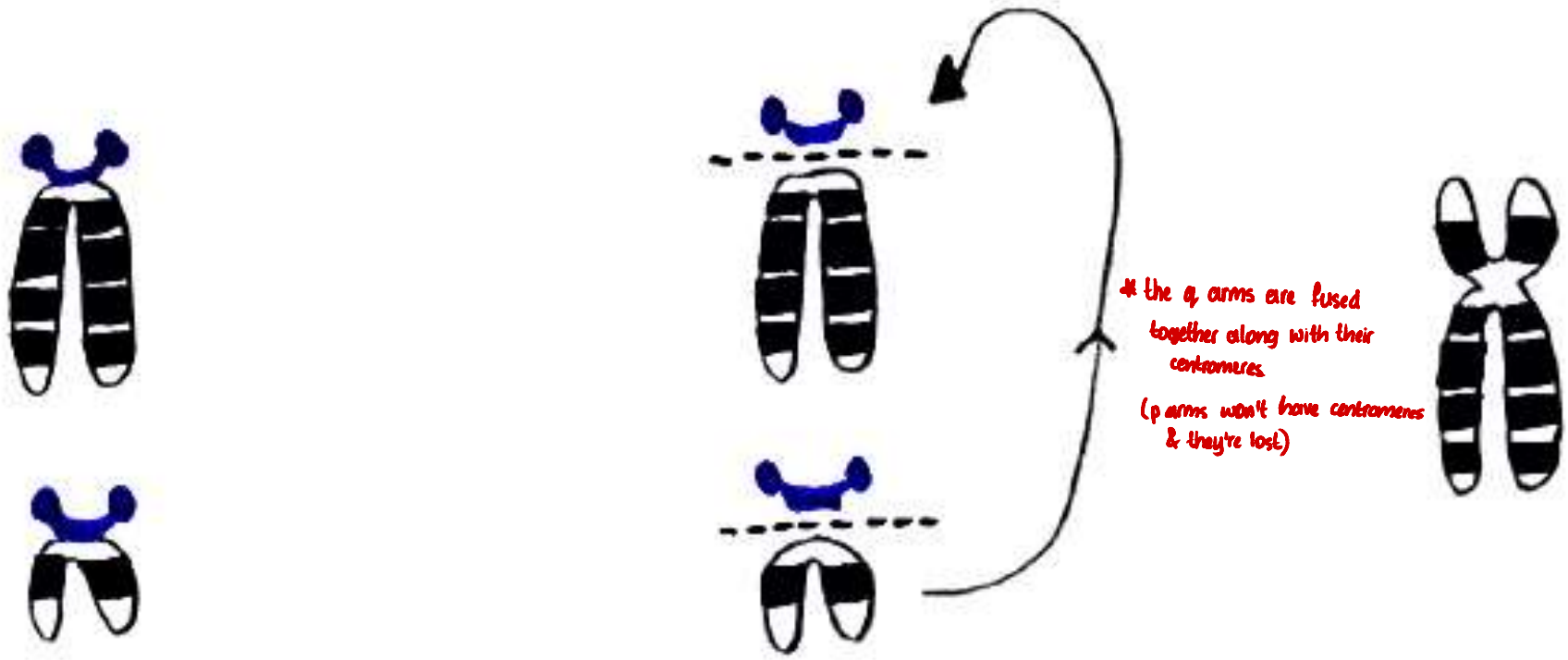
→ 2 acrocentric chromosomes give rise to 1 translocated chromosome that encompasses each q arm of these chromosomes (p arm is lost)

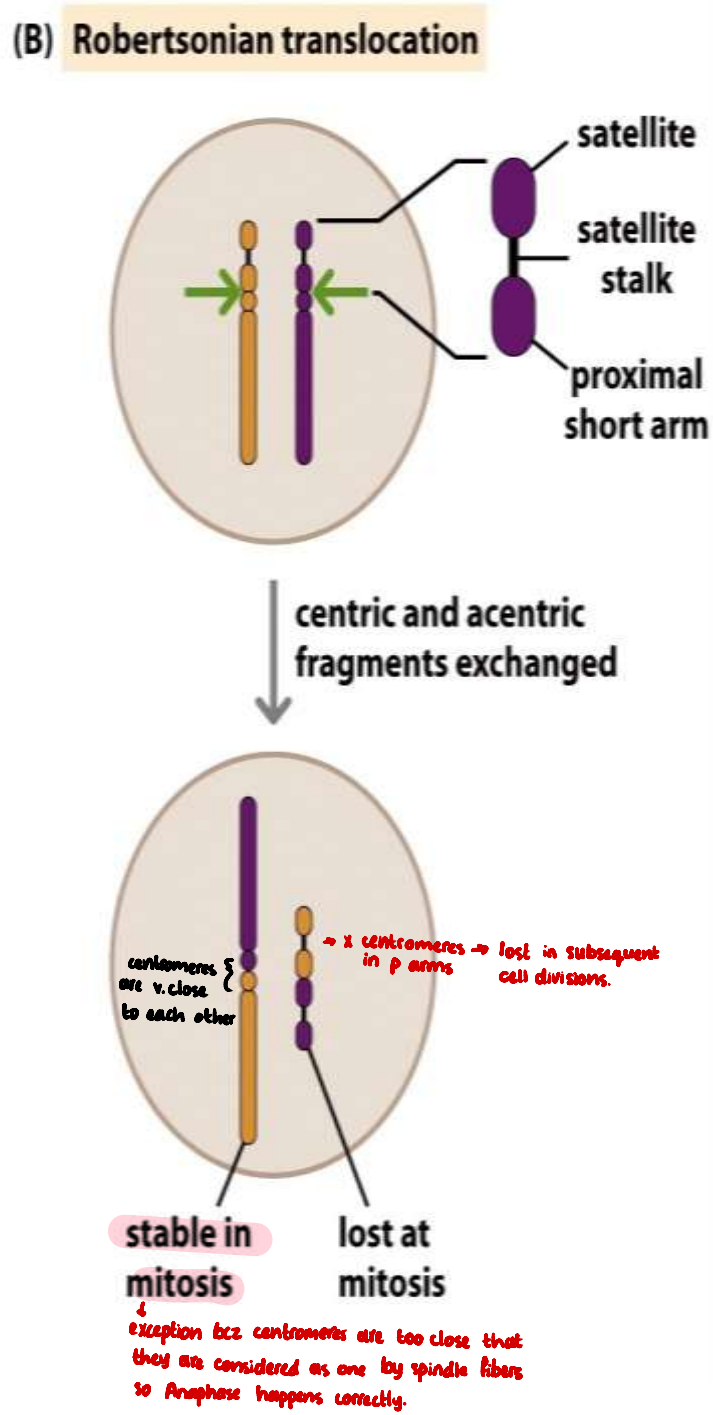
- **A robertsonian translocation** is a specialized type of translocation between two of the five types of **acrocentric** chromosome in human (13,14,15,21,and 22) the short arm is very small and very similar in DNA content ,each contains **1-2Mb** of tandemly repeated rRNA genes sandwiched between two blocks of heterochromatic DNA

4 p arm is common in acrocentric centromeres & contains ribosomal DNA genes & β-satellite



Robertsonian translocation (both chromosomes are acrocentric)
(with chromosome #14 and chromosome #21)





(B) Robertsonian translocation. This is a highly specialized reciprocal translocation in which exchange of centric and acentric fragments produces a **dicentric chromosome** that is nevertheless stable in mitosis, plus an acentric chromosome that is lost in mitosis without any effect on the phenotype. It occurs exclusively after breaks in the short arms of the human acrocentric chromosomes 13, 14, 15, 21, and 22.

The short arm of the acrocentric chromosomes consists of three regions: a proximal heterochromatic region (composed of highly repetitive noncoding DNA), a distal heterochromatic region (called a chromosome satellite), and a thin connecting region of euchromatin (the satellite stalk) composed of tandem rRNA genes. Breaks that occur close to the centromere can result in a dicentric chromosome in which the **two centromeres** are so **close** that they can function as a **single centromere**. The loss of the small acentric fragment has no phenotypic consequences because the only genes lost are rRNA genes that are also present in large copy number on the other acrocentric chromosomes

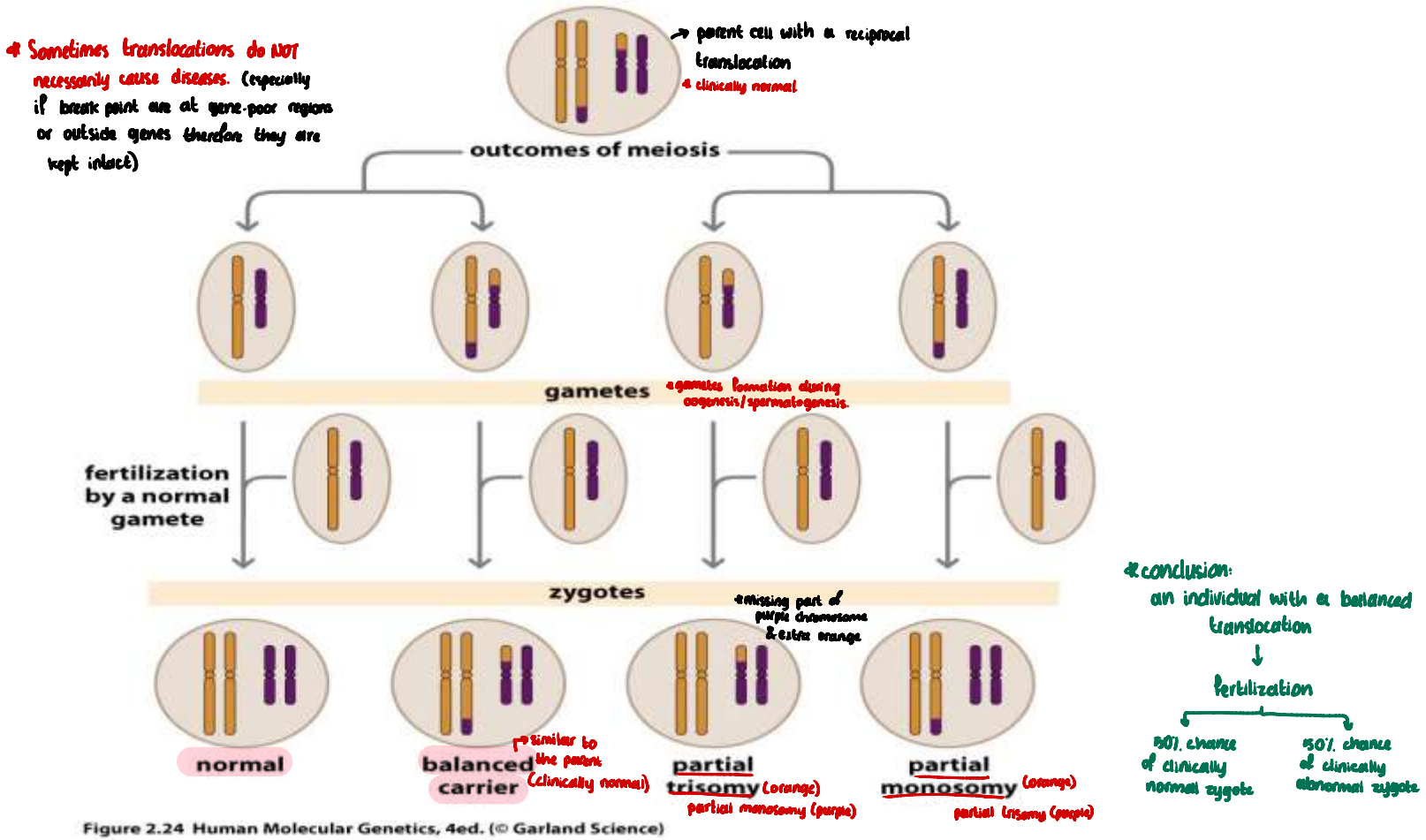


Figure 2.24 Possible outcomes of meiosis in a carrier of a balanced reciprocal translocation. Other modes of segregation are also possible, for example 3:1 segregation.

The relative frequency of each possible gamete is not readily predicted.

The risk of a carrier having a child with each of the possible outcomes depends on its frequency in the gametes and also on the likelihood of a conceptus with that abnormality developing to term.

➢A carrier of a balanced Robertsonian translocation can produce gametes that after fertilization give rise to an entirely normal child ,a phenotypically normal balanced carrier , or a conceptus with full trisomy or full monosomy for one of the chromosomes involved

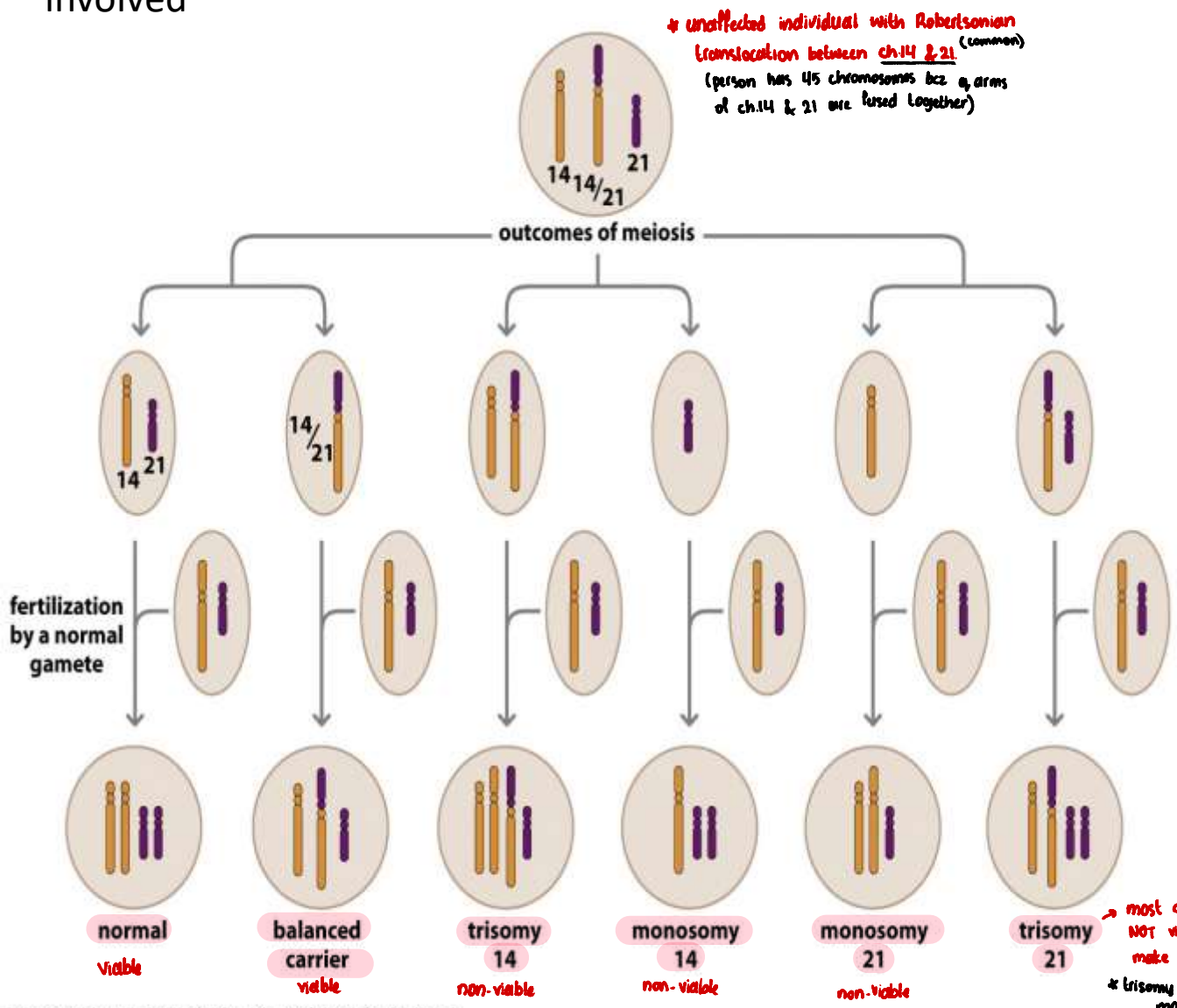


Figure 2.25 Possible outcomes of meiosis in a carrier of a Robertsonian translocation.
Carriers are asymptomatic but often produce unbalanced gametes that can result in a monosomic or trisomic zygote. The two monosomic zygotes and the trisomy 14 zygote in this example would not be expected to develop to term.

Figure 2.25 Human Molecular Genetics, 4ed. (© Garland Science)

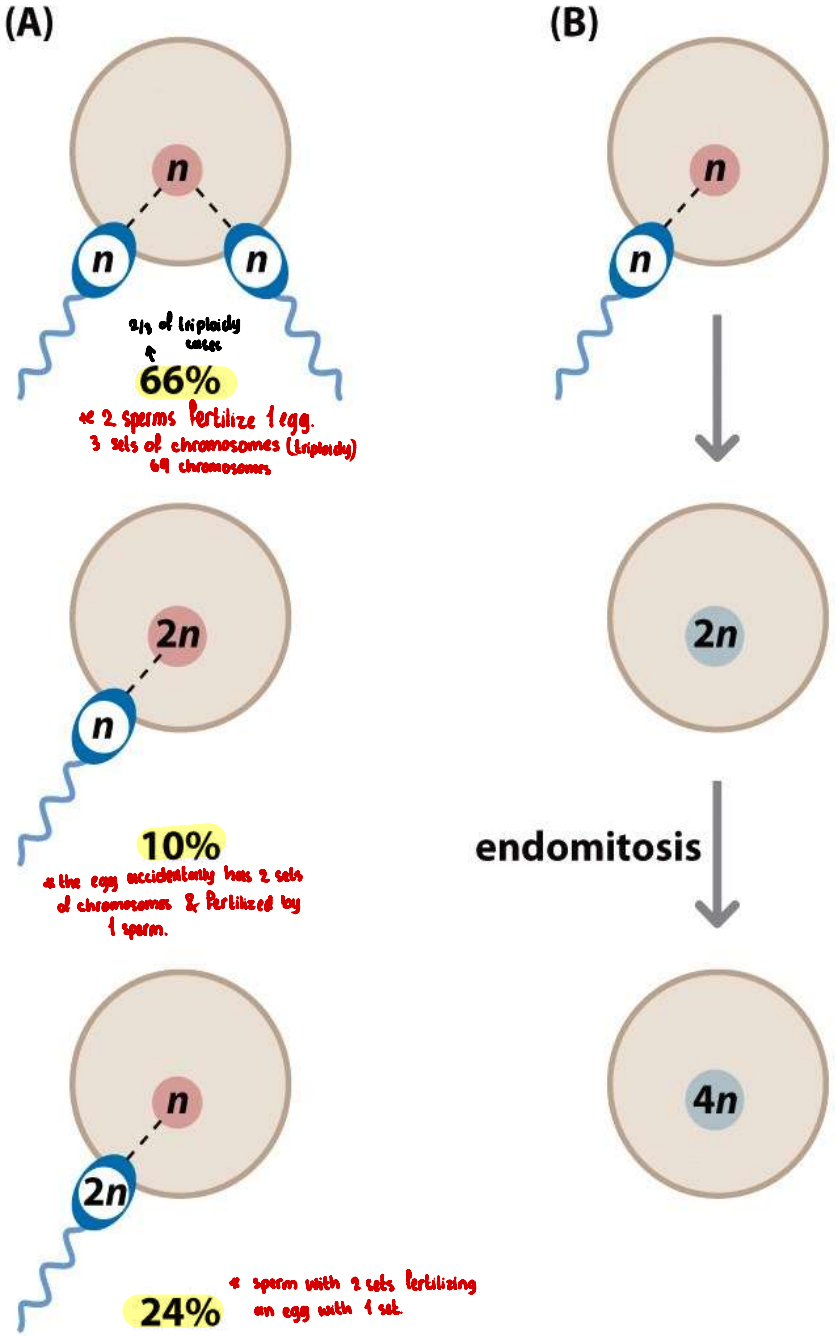


Figure 2.21 Human Molecular Genetics, 4ed. (© Garland Science)

Origins of triploidy and tetraploidy.

(A) Origins of human triploidy. **Dispermy** is the principal cause, accounting for 66% of cases. Triploidy is also caused by **diploid gametes** that arise by occasional faults in meiosis; fertilization of a diploid ovum and fertilization by a diploid sperm account for 10% and 24% of cases, respectively.

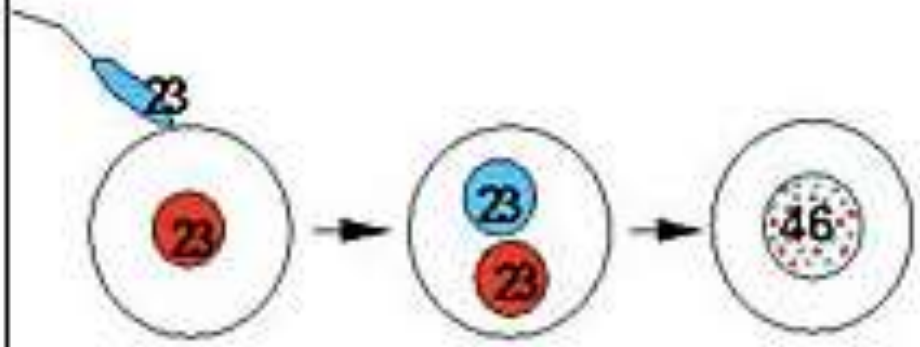
(B) **Tetraploidy** involves normal fertilization and fusion of gametes to give a normal zygote. Subsequently, however, tetraploidy arises by endomitosis when DNA replicates without subsequent cell division.

* a normal zygote forms then undergoes massive rounds of mitotic division.

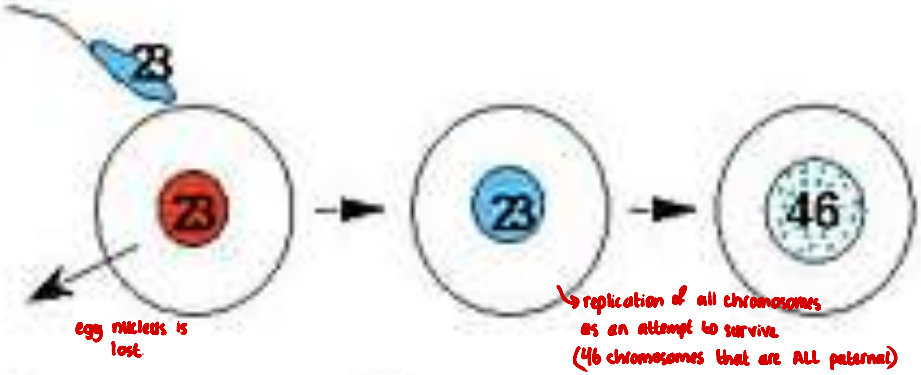
* Reminder:
  - the only viable autosomal aneuploidies: trisomy 13, 18, & 21.
  - " " " sex ch. aneuploidies: Turner, Klinefelter (not only these)

* in endomitosis, sister chromatids are NOT separated into 2 daughter cells, cytokinesis occurs abnormally in an area of no chromosomes.
↓
entire chromosomes are duplicated & remain in the same cell (4n)

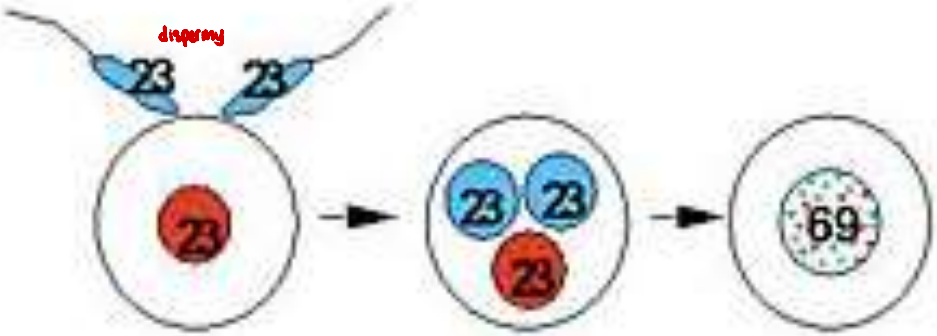
Genetic status in normal conception and molar pregnancy



- **Normal conception**
- 2 sets of genes
- 1 paternal
- 1 maternal
- Viable foetus



- **Complete Mole** either is pregnancy & growth but no fetus (molar pregnancy)
- 2 sets of paternal genes
- no maternal genes
- No foetus



- **Partial mole** ← there is a fetus BUT it's non-viable.
- 3 sets of genes
- 1 maternal
- 2 paternal
- non-viable foetus

Triploidy is the presence of an additional haploid set of chromosomes, is the cause of 20% of spontaneous abortions, premature births and perinatal deaths.

Triploidy syndrome is a rare syndrome and is estimated to occur in about 2 per cent of conceptuses. Triploidy occurs when there is double fertilization of an ovum (dispermy). The result may be 69, XXX or 69, XXY or 69, XYY. The extra set of paternal chromosomes predisposes to formation of a partial mole, features of which may or may not be grossly or microscopically apparent.

- 69,XXX triploidy
- 69,XXY triploidy
- 69,XYY triploidy

Triploidy - stillbirth at 39 weeks (69,XXX) - note the appearance of the hands

Physiopathology

Triploidy is constituted by an extra haploid set of chromosomes for a total of 69 chromosomes in humans. A "parent-of-origin" effect has been demonstrated by analysis of cytogenetic polymorphisms of triploidy pregnancies. Two distinct phenotypes of human triploid fetuses have been recognized according to the parental origin of the extra haploid set.

The first one or triploidy of diandric type occurs when the extra haploid set of chromosomes arises from the father, the second one or triploidy of digynic type occurs when the extra haploid set of chromosomes arises from the mother. Diandric fetuses appear relatively well grown with a large placenta, while digynic fetuses show intrauterine growth retardation with a small placenta.

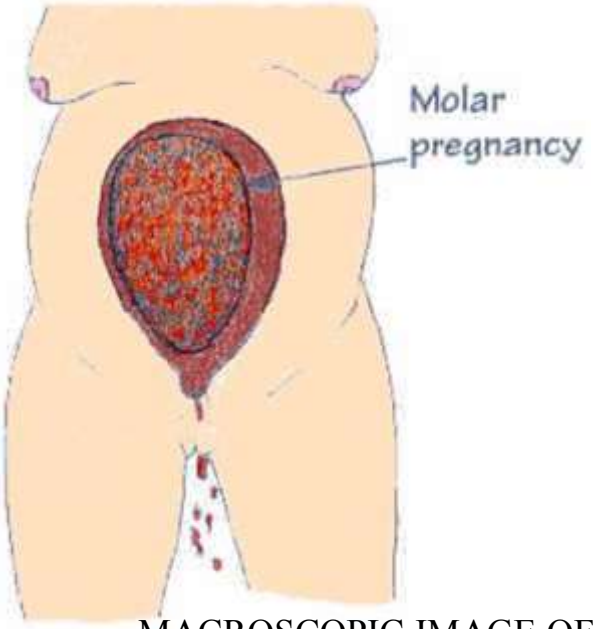
Types

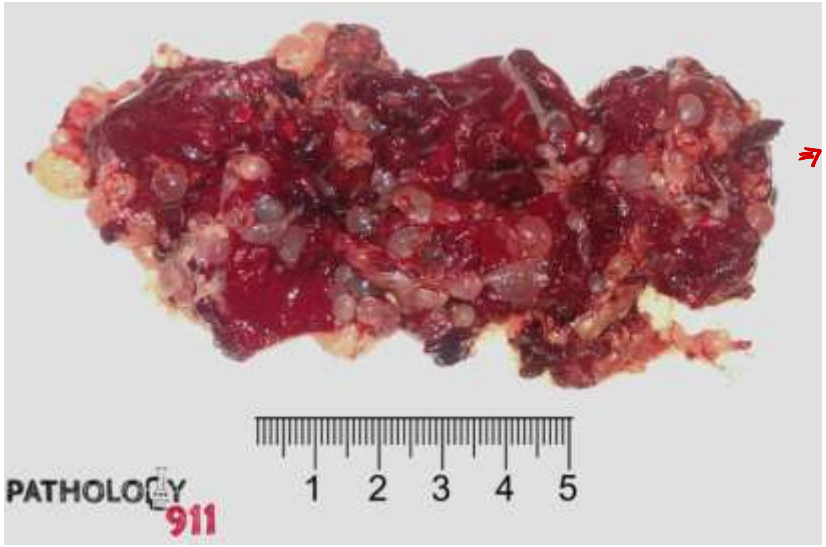
- maternal triploidy (triploidy by digyny)
- paternal triploidy (diandry or dispermy)

Synopsis

The most common clinical signs of triploidy are: severe intrauterine growth retardation, macrocephaly, total syndactyly of third and fourth fingers and CNS, heart and renal defects.

Hydatidiform mole, one of the characteristic features of pure triploidy, is found in more than 90% of cases.





MACROSCOPIC IMAGE OF A COMPLETE HYDATIDIFORM MOLE, SHOWING THE CHARACTERISTIC VESICULAR, OR 'BUNCHES OF GRAPES' APPEARANCE OF THE CHORIONIC VILLI.

PARTIAL MOLE

- The oocyte has an intact set of maternal DNA
- Option A: Fertilised by one sperm – reduplicates its own DNA
- Option B: Fertilised by two sperm
- Karyotype: Triploid – 69 chromosomes (69 XXY – an extra set of paternal DNA)

COMPLETE MOLE

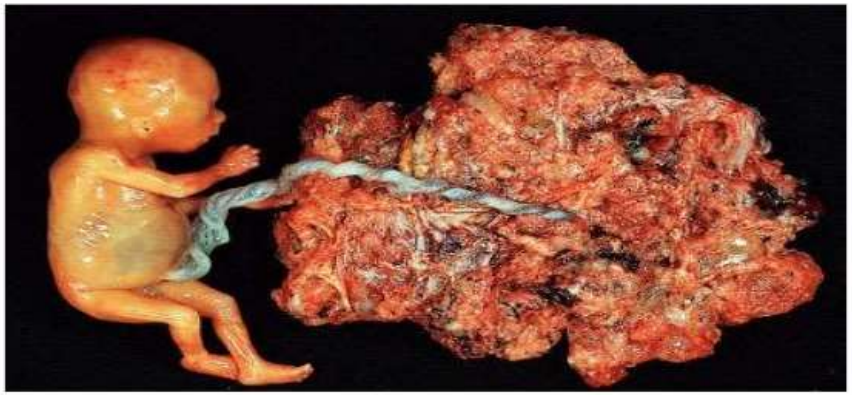
- The oocyte has somehow lost its DNA – it is 'empty' of DNA
- Option A: Fertilised by one sperm – reduplicates its own DNA = *homozygous*
- Option B: Fertilised by two sperm = *heterozygous*
- Karyotype: Diploid – 46 chromosomes (46XX or 46XY – the 46YYs are not viable)

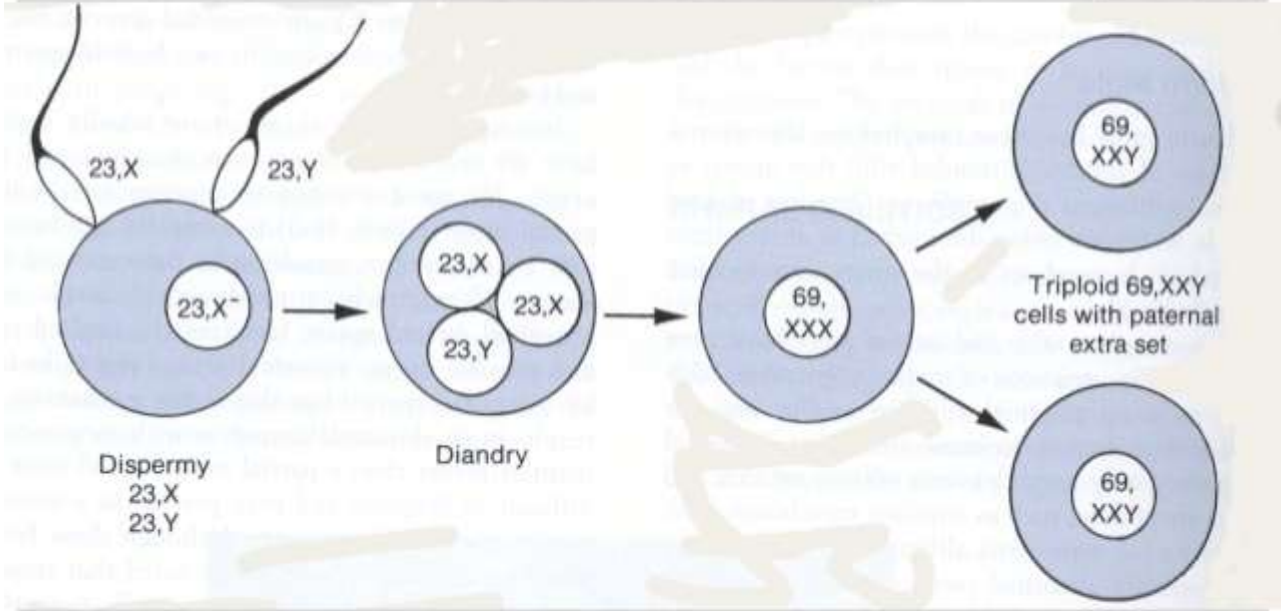
Note: (*all paternal DNA* – no maternal DNA – i.e. androgenetic)

Extra Q:

- why is complete mole (i.e: 46XX, 46XY) non-compatible with life?
  - due to "imprinting" which is genetic modifications that do NOT alter the sequence of DNA, it rather impacts methylation patterns (epigenetic)
  - There are different regions in the egg & the sperm that are methylated so a specific pattern is required from both to have a viable pregnancy

Partial mole



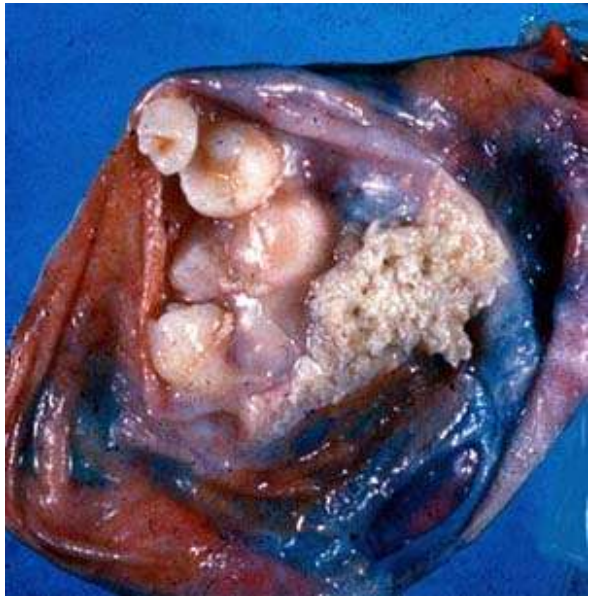


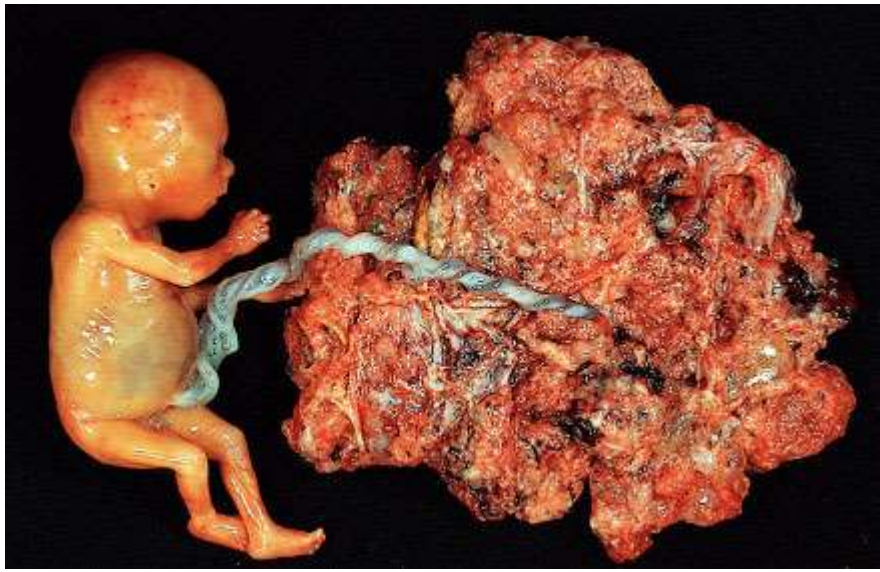
Diandric triploidy

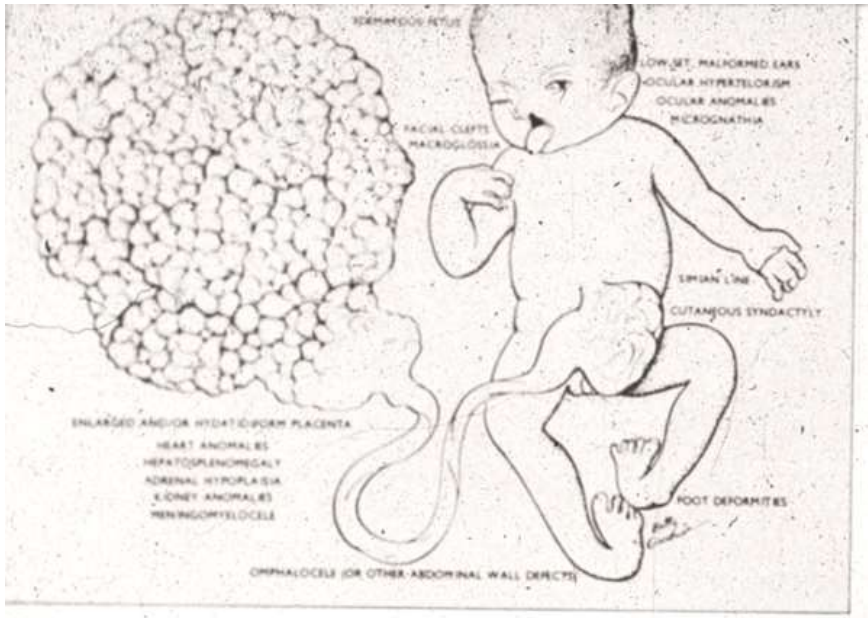
Uniparental diploidy changes the balance between the embryo or fetus and its supporting membranes

- **Paternal uniparental diploidy** produces hydatidiform moles, abnormal conspectuses that develop to show widespread hyperplasia (overgrowth)of the trophoblast but no fetal parts, they may transform into choriocarcinoma.

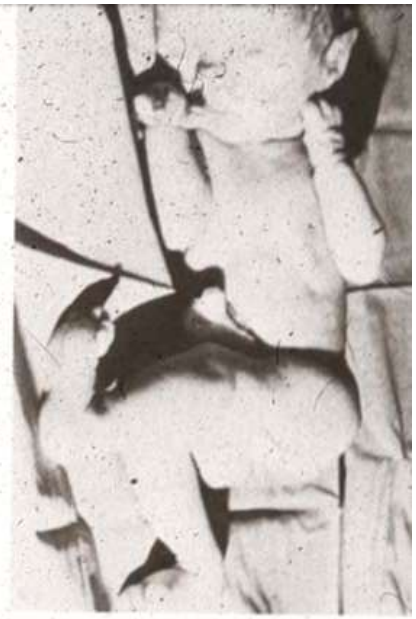
- **Maternal uniparental diploidy** results in ovarian teratomas , rare benign tumors of the ovary which consist of disorganized embryonic tissue but are lacking in vital extra-embryonic membranes.





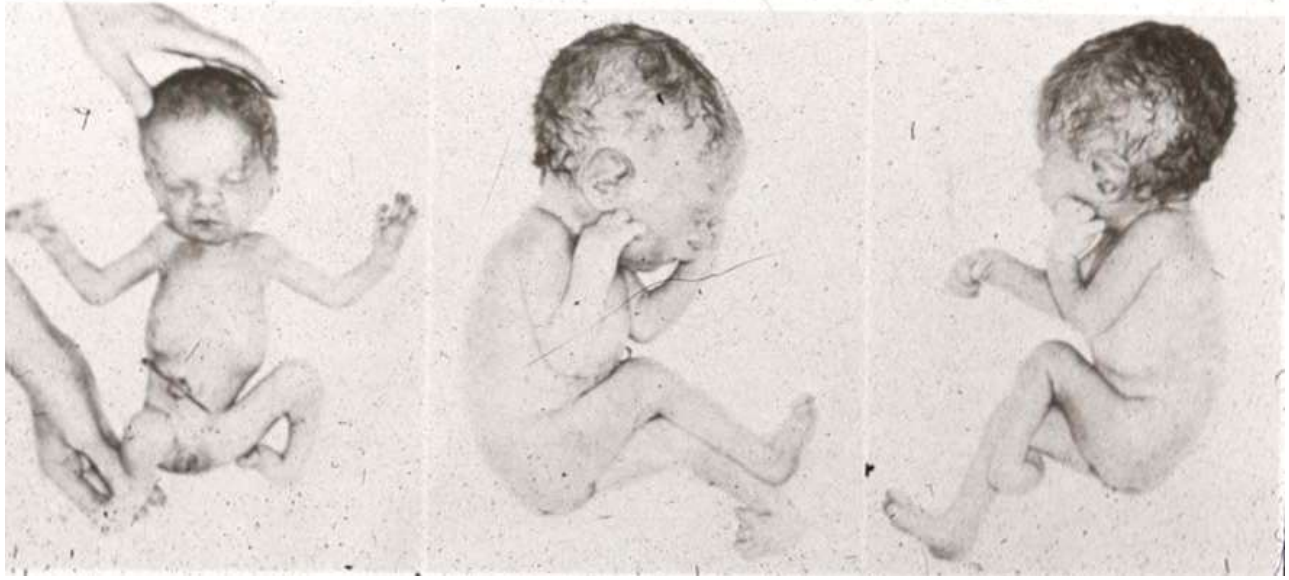


4.1



24.2

24.3



Triploidy

Findings:
CHD
Kidney anomalies
Low-set, malformed ears
Hypertelorism (↑ distance between the eyes)
Foot deformities
Abdominal wall defects

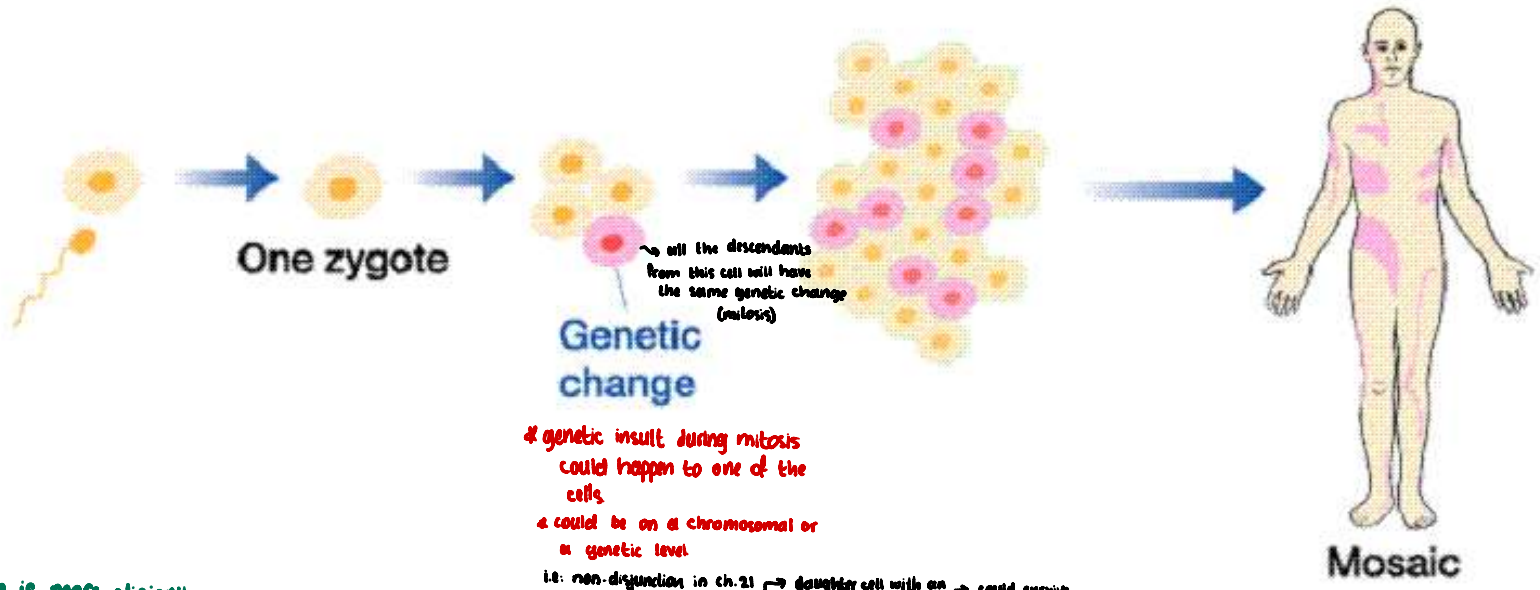
Diandric
Enlarged placenta
Cyst-like placenta
Well-formed fetus with or without microcephaly

Digynic
Macrocephaly
Severe intrauterine growth retardation

Mosaicism

⇒ an individual with >1 population of cells

Two or more distinct cell lines from single zygote differing because of mutation or nondisjunction.



* genetic insult during mitosis could happen to one of the cells
* could be on a chromosomal or a genetic level
i.e: non-disjunction in ch.21 → daughter cell with an extra ch.21 → could survive.
→ daughter cell with a missing ch.21 → dies.

* Result: 2 cell lines from a zygote
→ group of cells w/o a genetic mutation.
→ " - " with an anomaly

* Q: Which case is more clinically deleterious?

A. pt with Down Syndrome bcz the sperm had an extra ch.21 (100% Down)

B. pt with Down Syndrome bcz of non-disjunction during mitosis. (Mosaic Down)

(A) is more deleterious bcz all cells are genetically abnormal.

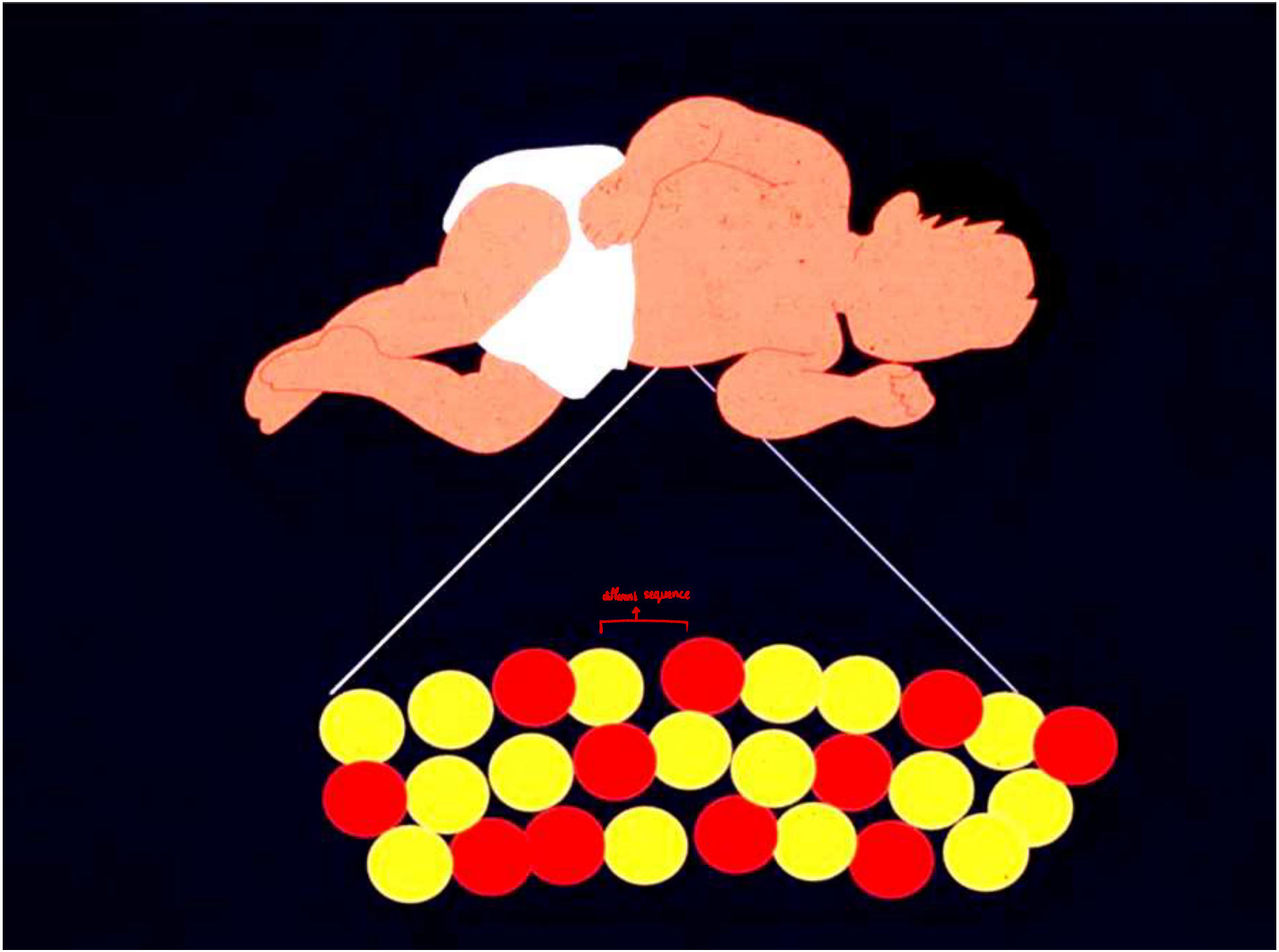
* Q: Which is clinically worse/more deleterious?

A. Mosaic individual with a genetic change in 1st trimester.

B. Mosaic " " "
" " in 3rd trimester.

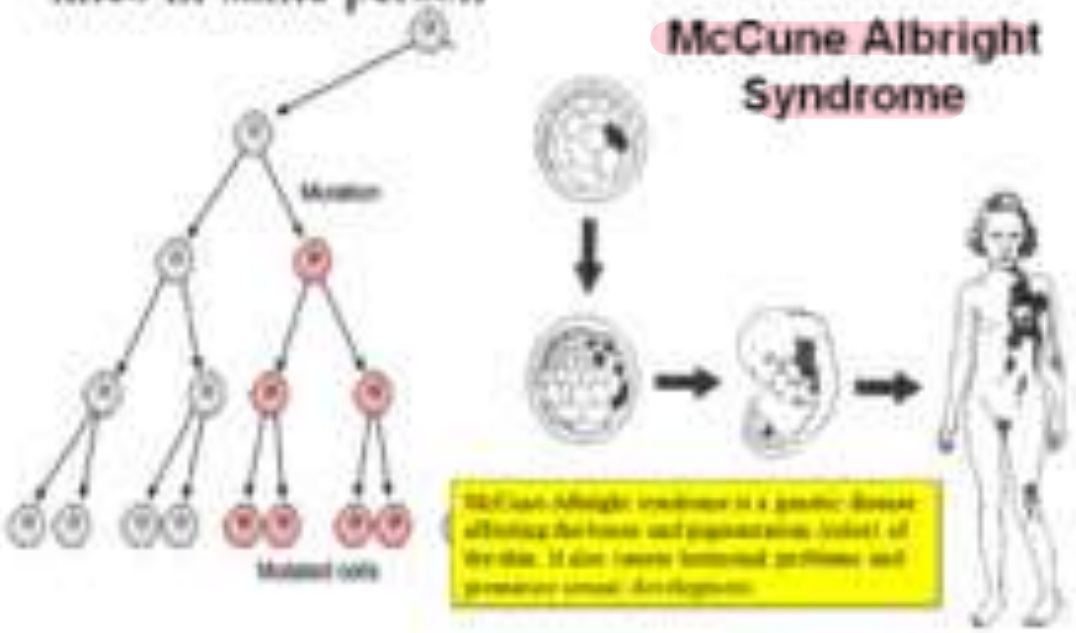
(A) bcz more cells will have the genetic anomaly.

* note:
earlier genetic anomaly = larger # of cells affected

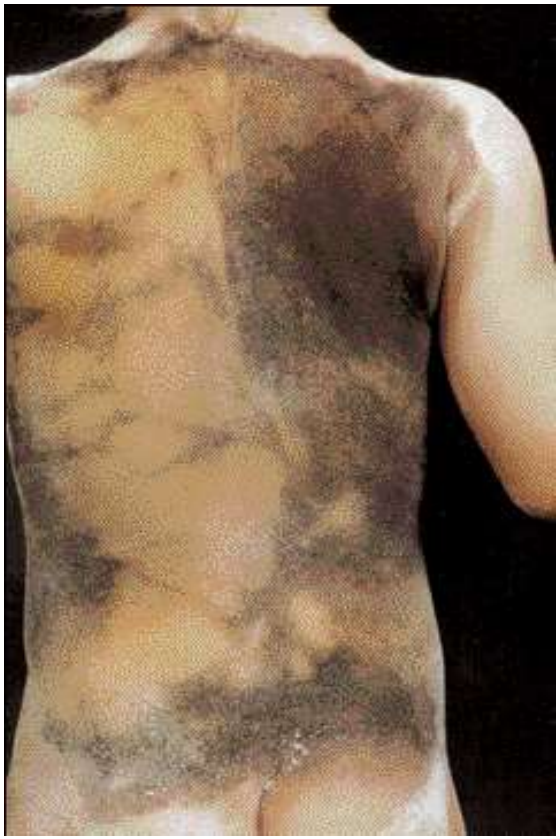

different sequence

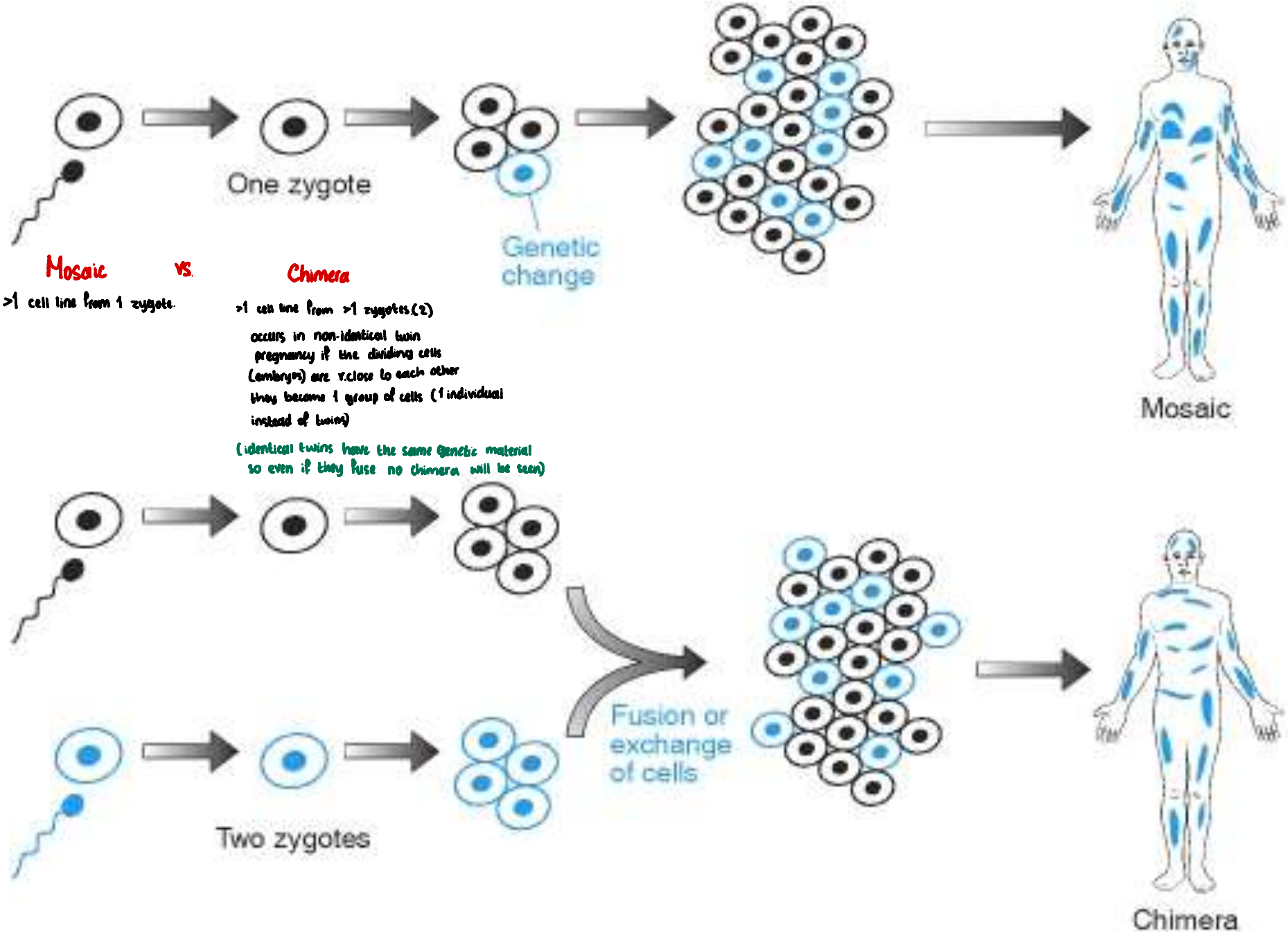
Somatic Mosaicism Gives Different Cell Lines

- *Mosaicism*: occurrence of two or more cell lines in same person



McCune Albright Syndrome





Mosaic vs. **Chimera**

>1 cell line from 1 zygote.

>1 cell line from >1 zygotes (2)

occurs in non-identical twin pregnancy if the dividing cells (embryos) are v.close to each other they become 1 group of cells (1 individual instead of twins)

(identical twins have the same genetic material so even if they fuse no chimera will be seen)