Incidence of Chromosomal Abnormalities in Newborns

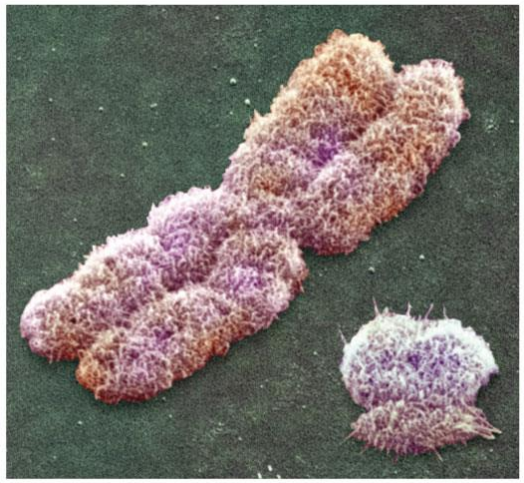
Type of Abnormality	Prevalence at Birth
Sex Chromosome Aneuploidy	
Males (43,612 newborns)	
47,XXY	1/1000
47,XYY	1/1000
Females (24,547 newborns)	
45,X	1/5000
47,XXX	1/1000
Autosomal Aneuploidy (68,159 newborns)	
Trisomy 21	1/800
Trisomy 18	1/6000
Trisomy 13	1/10,000
Structural Abnormalities (68,159 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

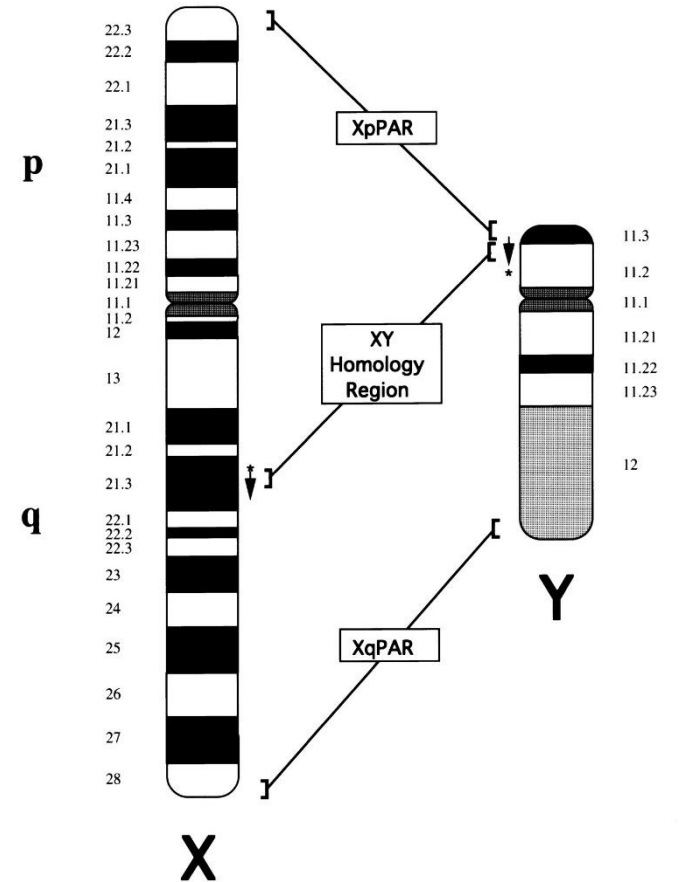
Data from Hsu LYF (1998) Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A (ed.), *Genetic Disorders and the Fetus*, 4th edition, Johns Hopkins University Press, Baltimore, pp. 179-248.

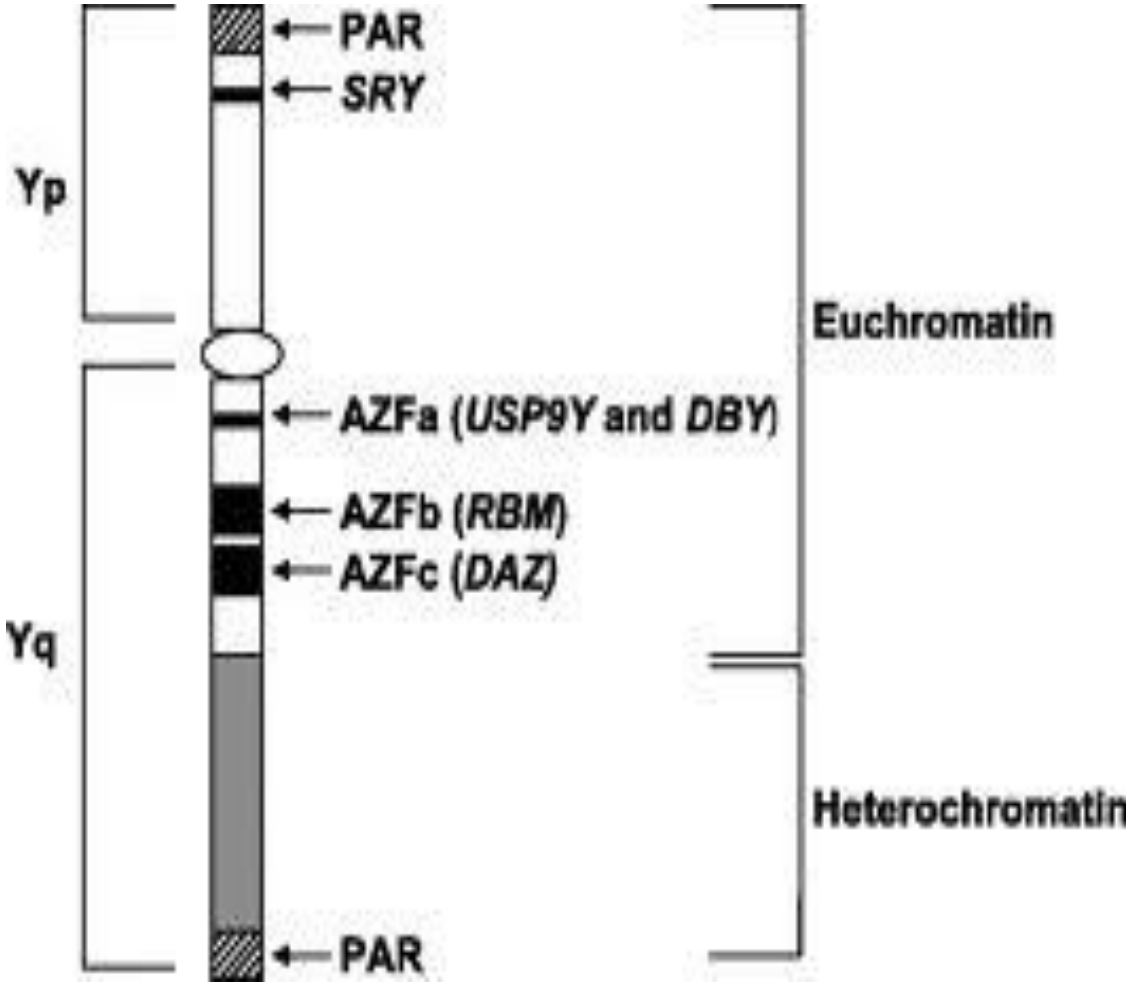
The Chromosomal Basis of Sex

- 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







SRY (Sex-determining region Y)

- X and Y chromosomes are obviously different. In fact, the genes on these two chromosomes are different, except at the ends of the chromosomes.

- The homologous regions between the X and Y chromosomes are located **at the ends**, known as the pseudoautosomal regions ***(PARs)***.

- PAR refers to the pseudoautosomal region at the end of the p arm, and there is another pseudoautosomal region at the end of the q arm. These are the two regions where **similarity exists between the X and Y chromosomes.**

➢ **Y chromosome:**

- The ends of the chromosomes have sequence homology with the X chromosome, whereas other regions contain sequences unique to the Y chromosome that are absent from the X chromosome.

✓ For example, the ***SRY*** region is located on a distal area of the p arm. SRY stands for **sex-determining region of the Y chromosome**, and this region induces development toward the male phenotype.

- The default embryonic and fetal development is female unless the SRY gene is present. When SRY is present, development shifts from the female pathway to the male pathway.

- A **46,XY** individual may be **biologically female** if a mutation or deletion affects the SRY gene. When the SRY gene is missing, development follows the default pathway toward female differentiation despite the presence of an XY chromosomal complement.

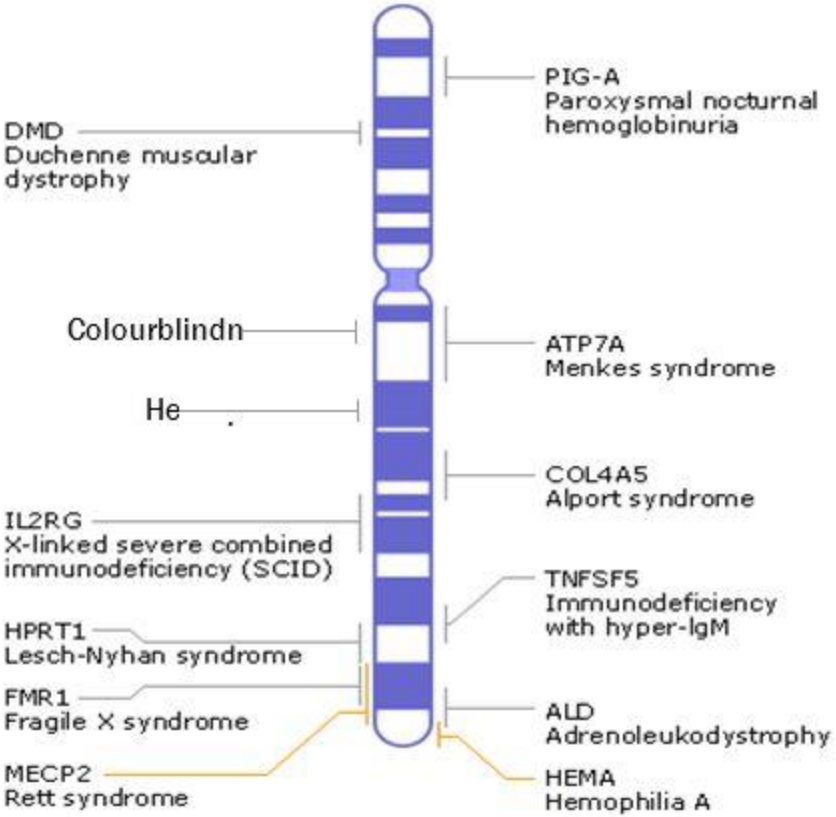
- The SRY is responsible for initiating male development. In its absence, embryonic development proceeds as female.

- Other important regions on the Y chromosome are the ***AZF*** (**Azoospermia Factor) regions**. If these regions are deleted or missing, the individual remains **biologically male** and develops normal male reproductive organs and sexual characteristics. However, **fertility is affected**, as sperm production becomes minimal or absent, a condition known as **azoospermia**.

- Notably, the distal part of the q arm of the Y chromosome consists mainly of **heterochromatin**. This region does **NOT** contain clinically relevant genes. Therefore, deletion of this region generally has **no clinical consequences**. The size of this heterochromatic region is variable among males.

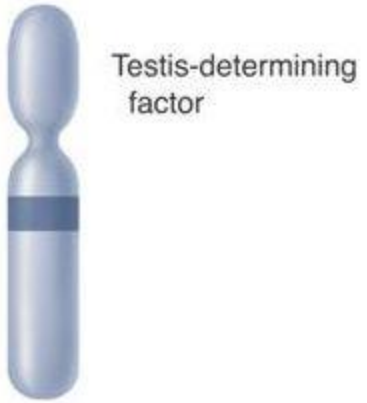
Sex Chromosomes

X chromosome



900-1600 genes

Y chromosome



70-200 genes

- **X chromosome:**

  - The X chromosome carries many genes.

  - For example, on the p arm, there is a well-known gene called DMD. Mutation of this gene causes **Duchenne muscular dystrophy**.

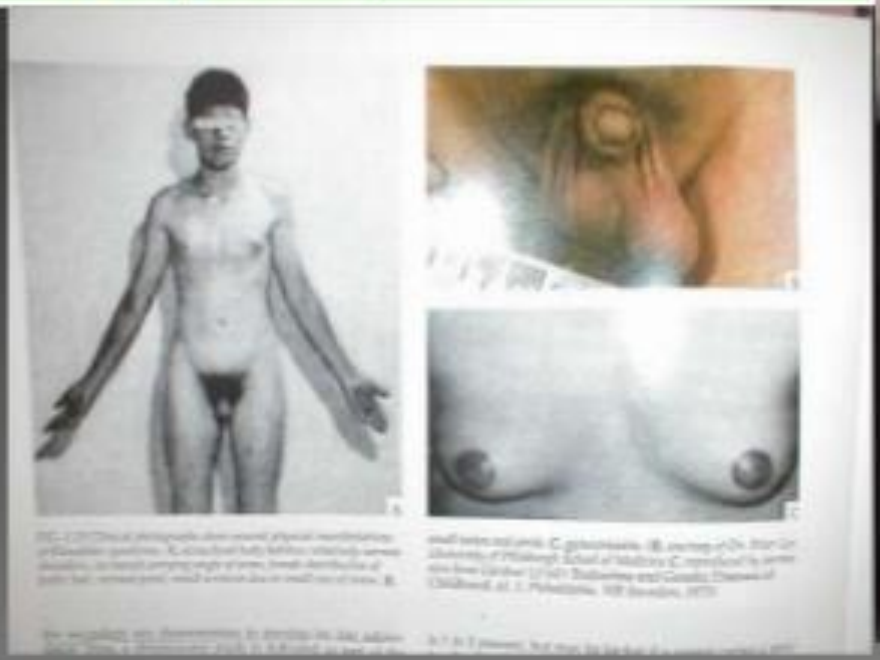
  - Another example is **hemophilia A**, which is also caused by a gene located on the X chromosome.

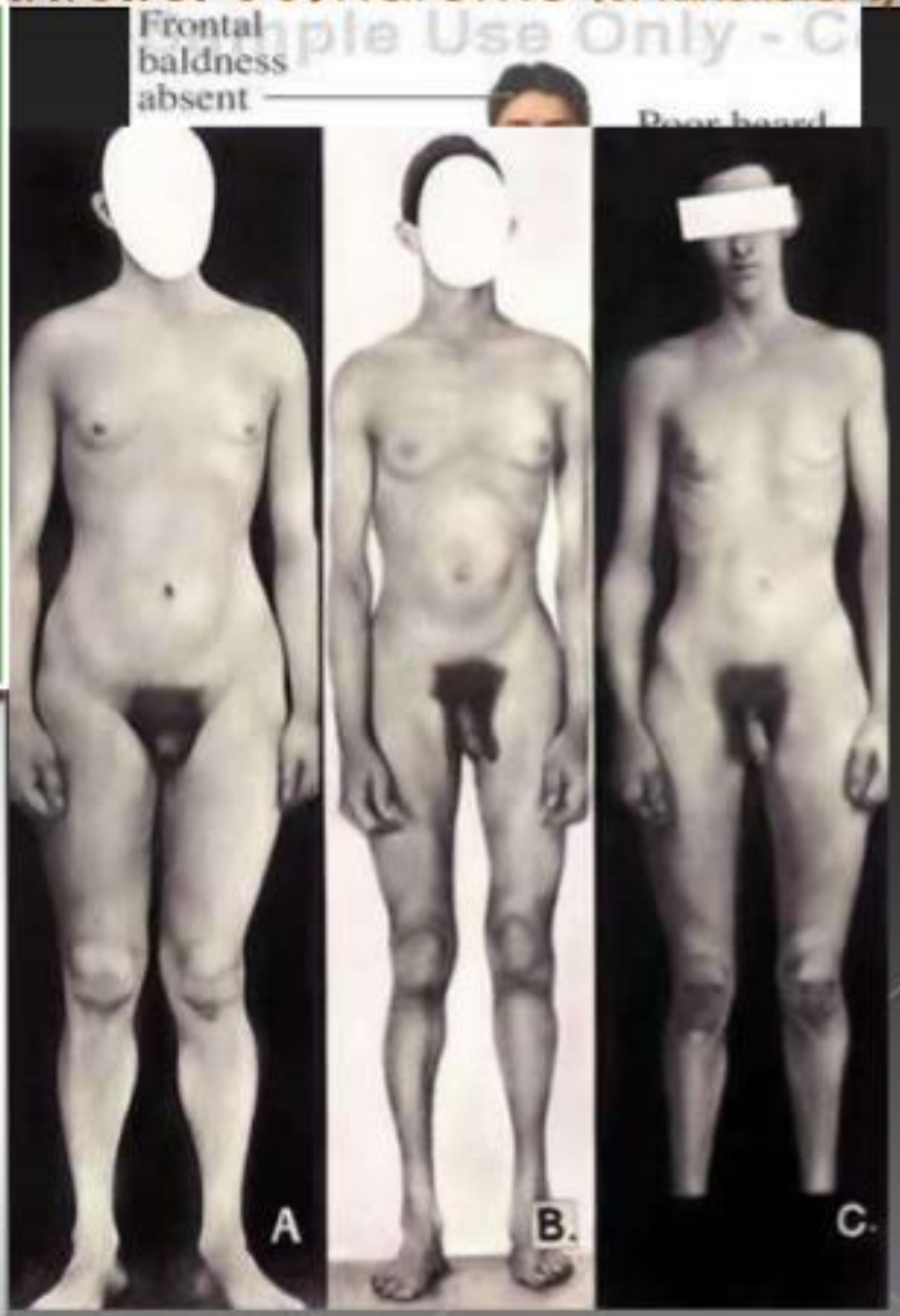
  - **Lesch–Nyhan syndrome** is another disorder associated with genes on the X chromosome.

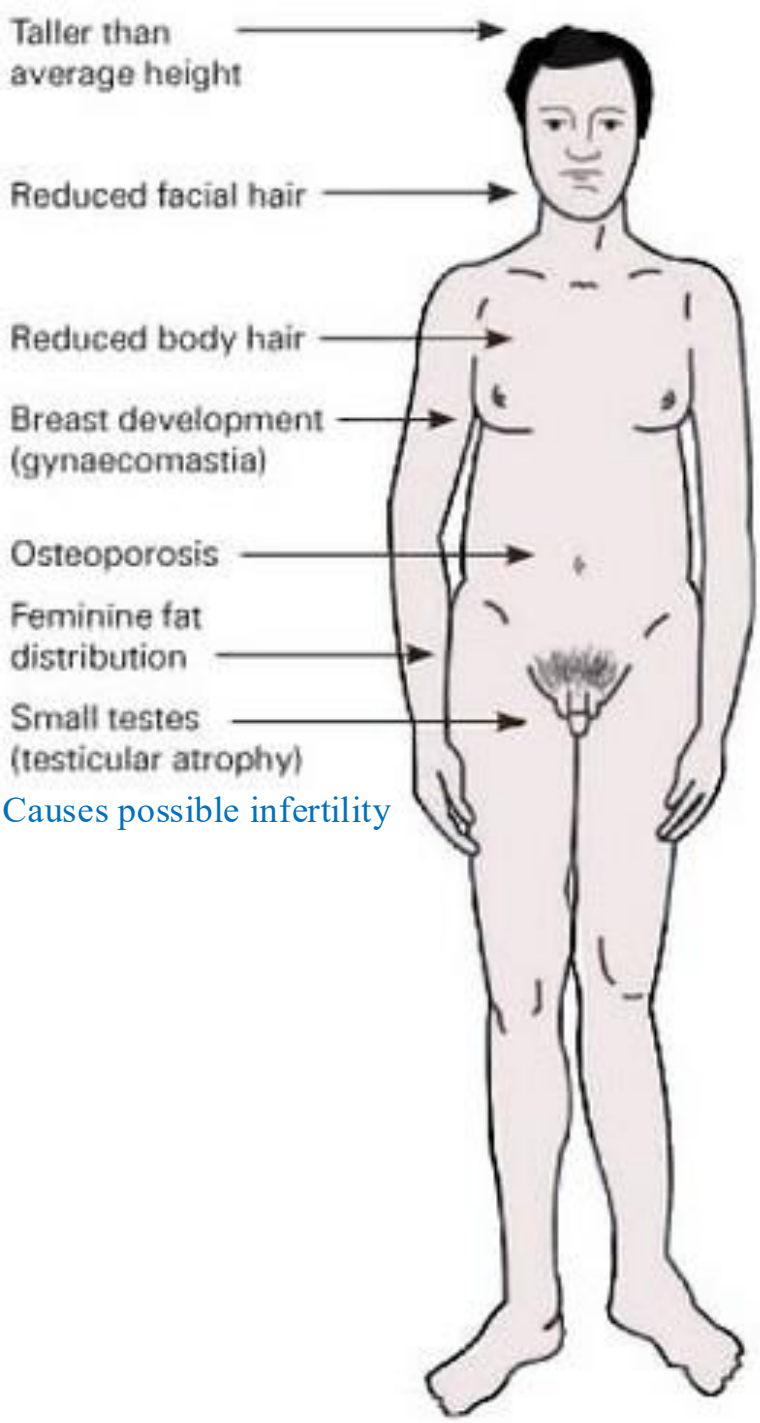
  - Additionally, the most common hereditary cause of intellectual disability is **Fragile X syndrome**, which results from mutation of the FMR1 gene located on the X chromosome.

Kleinfelter's syndrome (or Klinefleter's)

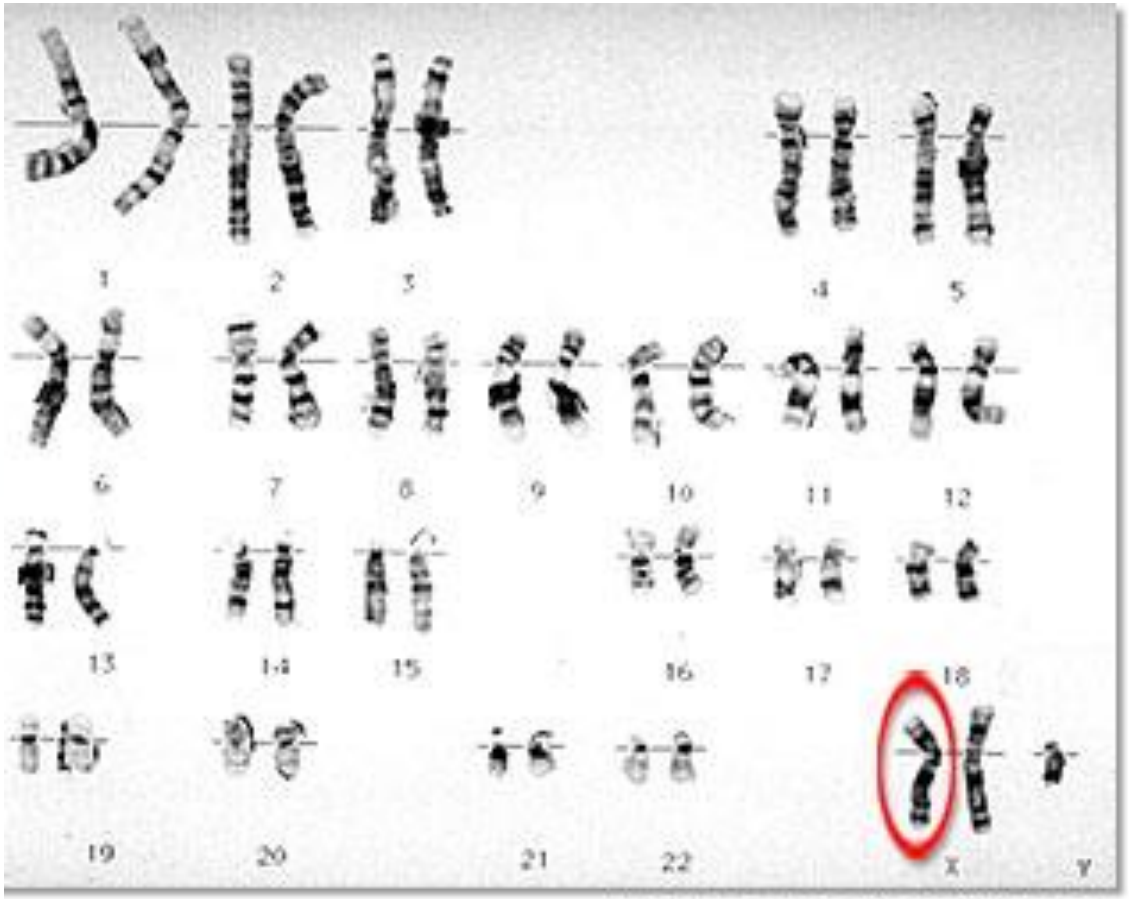
- Males with some development of breast tissue normally seen in females.
- Little body hair is present, and such person are typically tall, have small testes.
- Infertility results from absent sperm.
- Evidence of mental retardation may or may not be present.



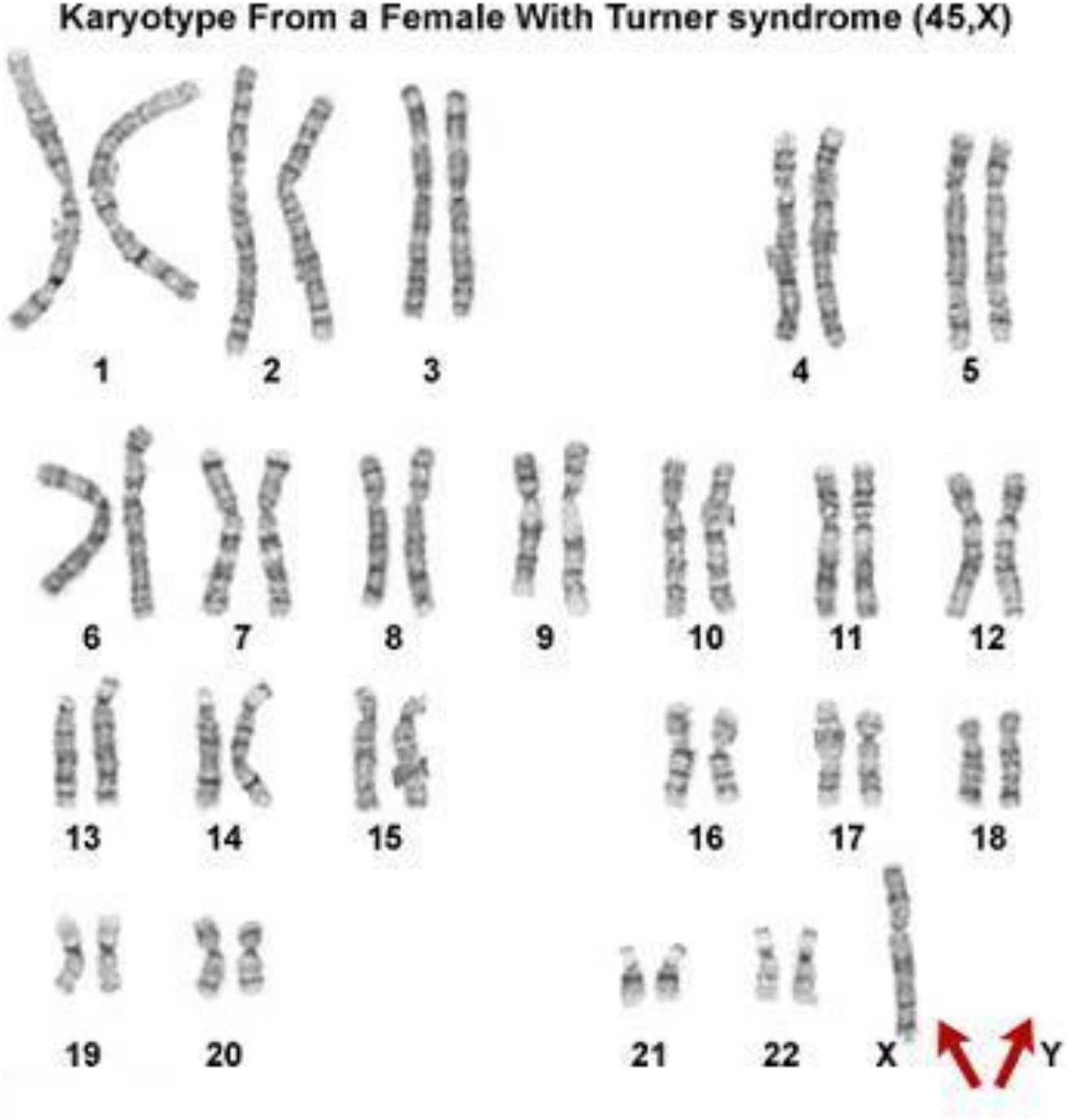


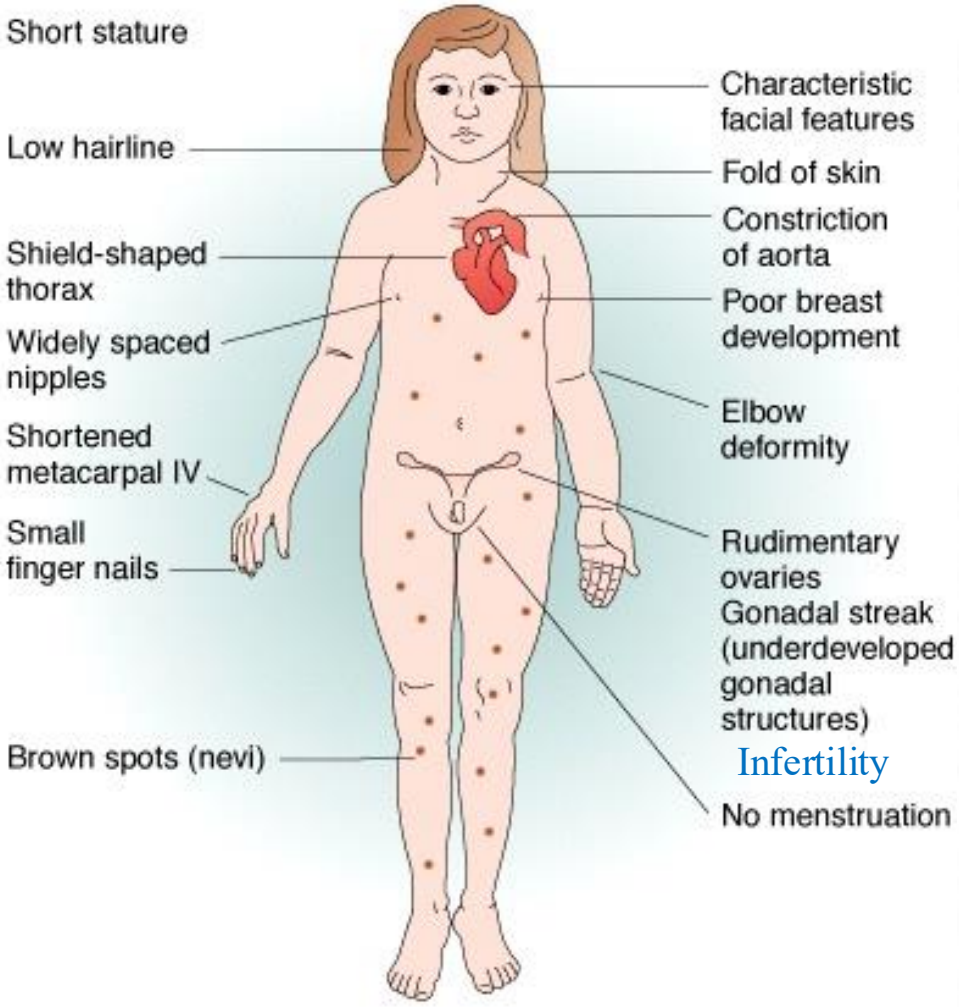


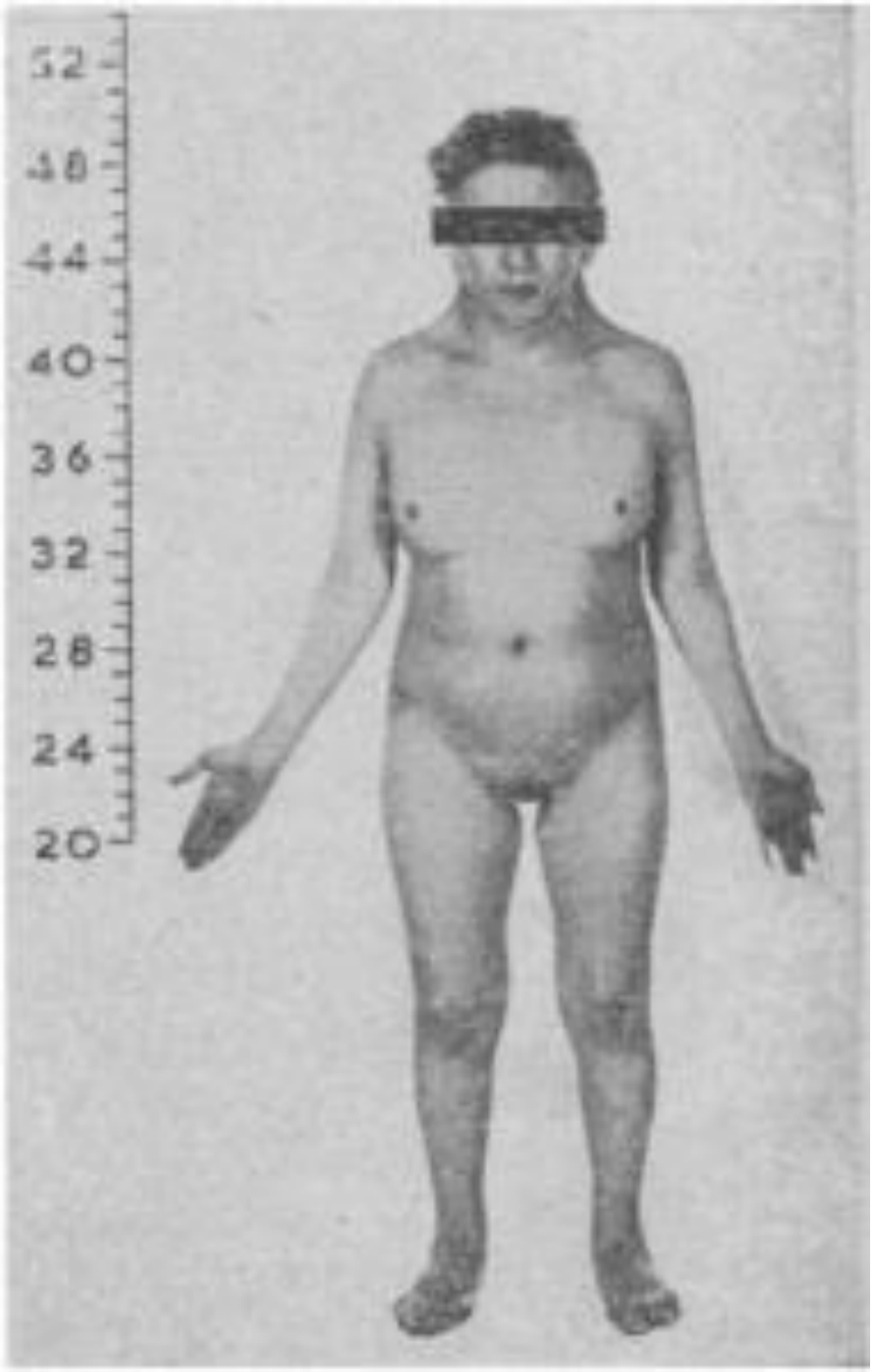
Causes possible infertility

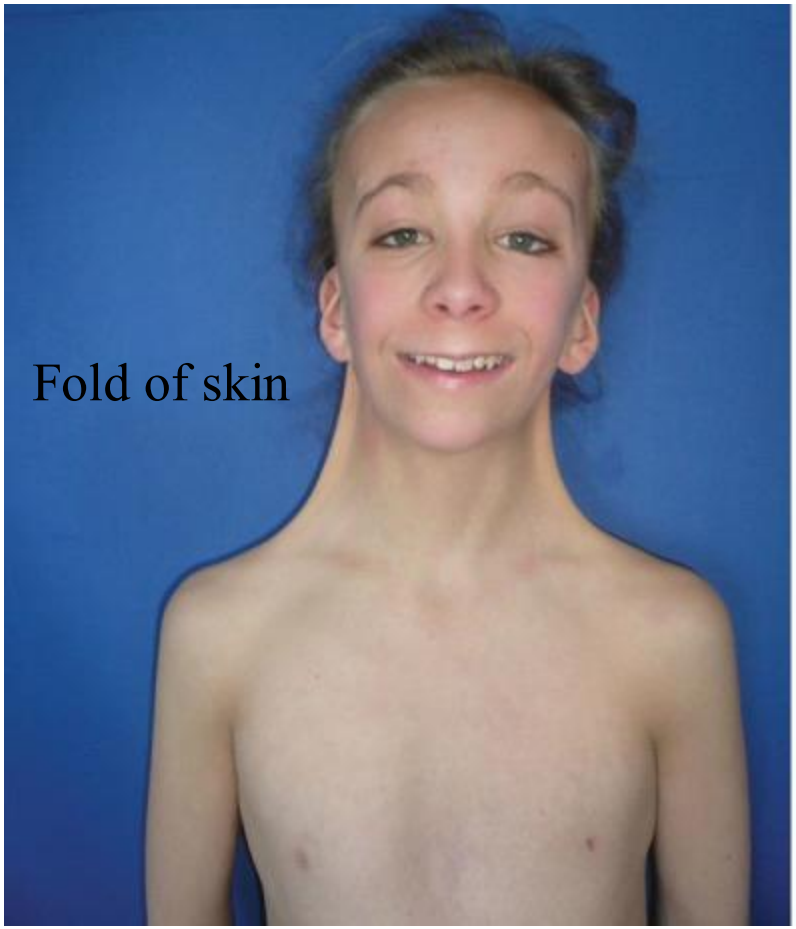


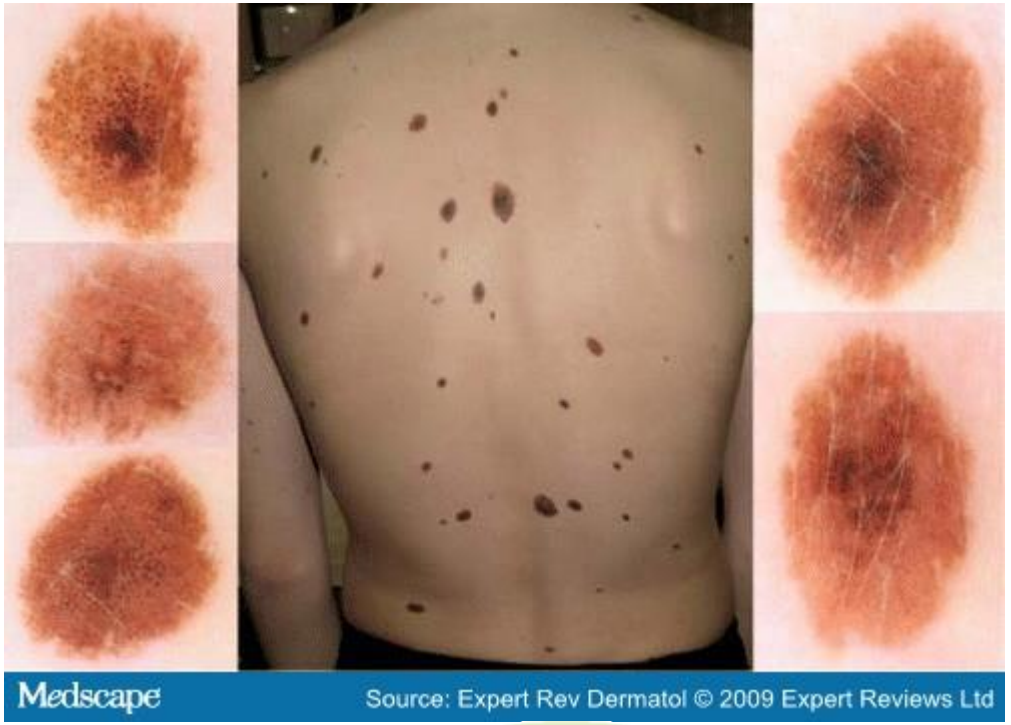
47, XXY

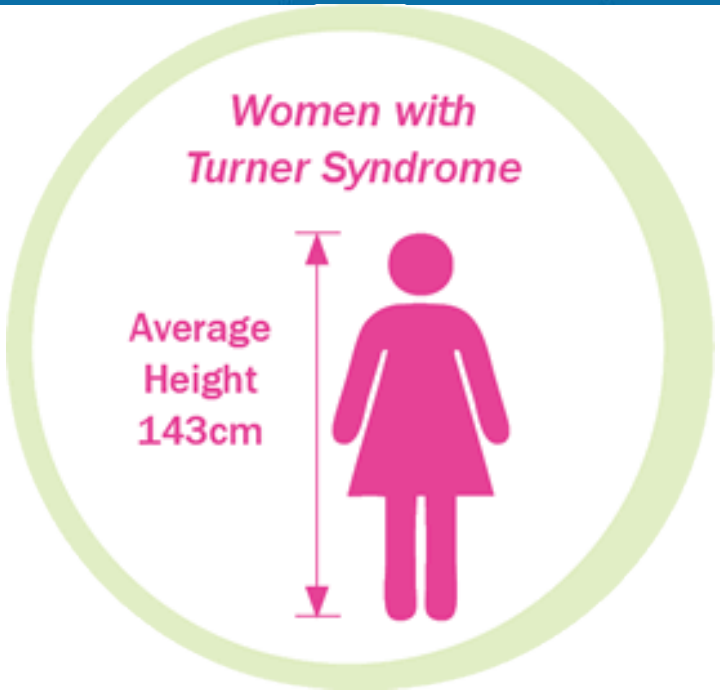

Karyotype From a Female With Turner syndrome (45,X)
Female
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y


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)
Infertility
No menstruation


52
48
44
40
36
32
28
24
20

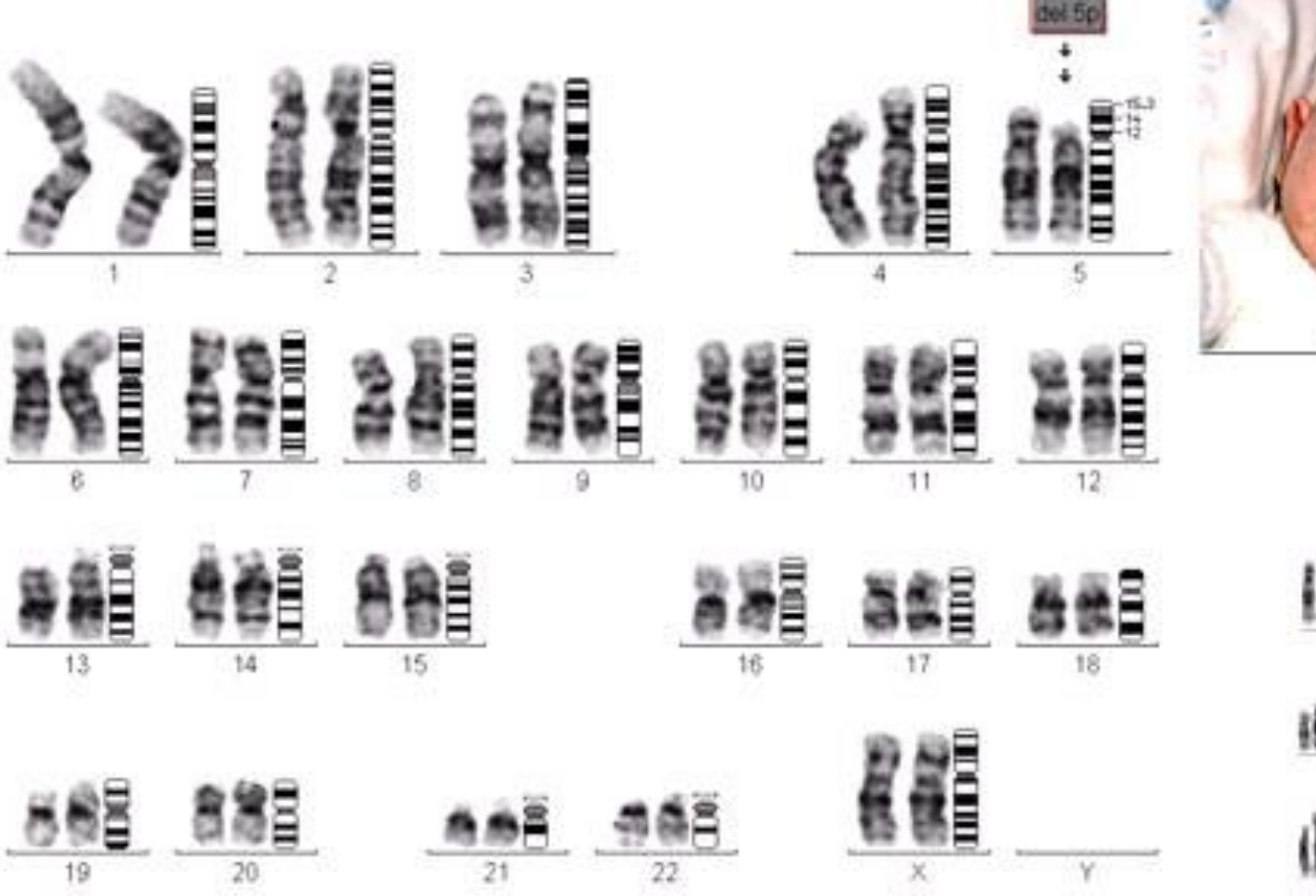

Fold of skin

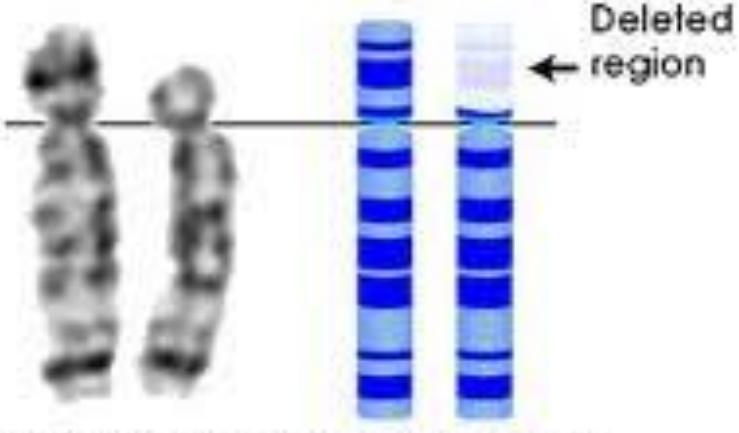

Medscape
Source: Expert Rev Dermatol © 2009 Expert Reviews Ltd


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

Looking at Ch.5, there is a **deletion** involving part of the p arm of one of the two chromosome 5 homologues.

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

Opposite to Down syndrome patients who are benign and friendly

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

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

✓ Chronic myelogenous leukemia could develop from either the **stem cell** or from the **myeloid stem cell**.

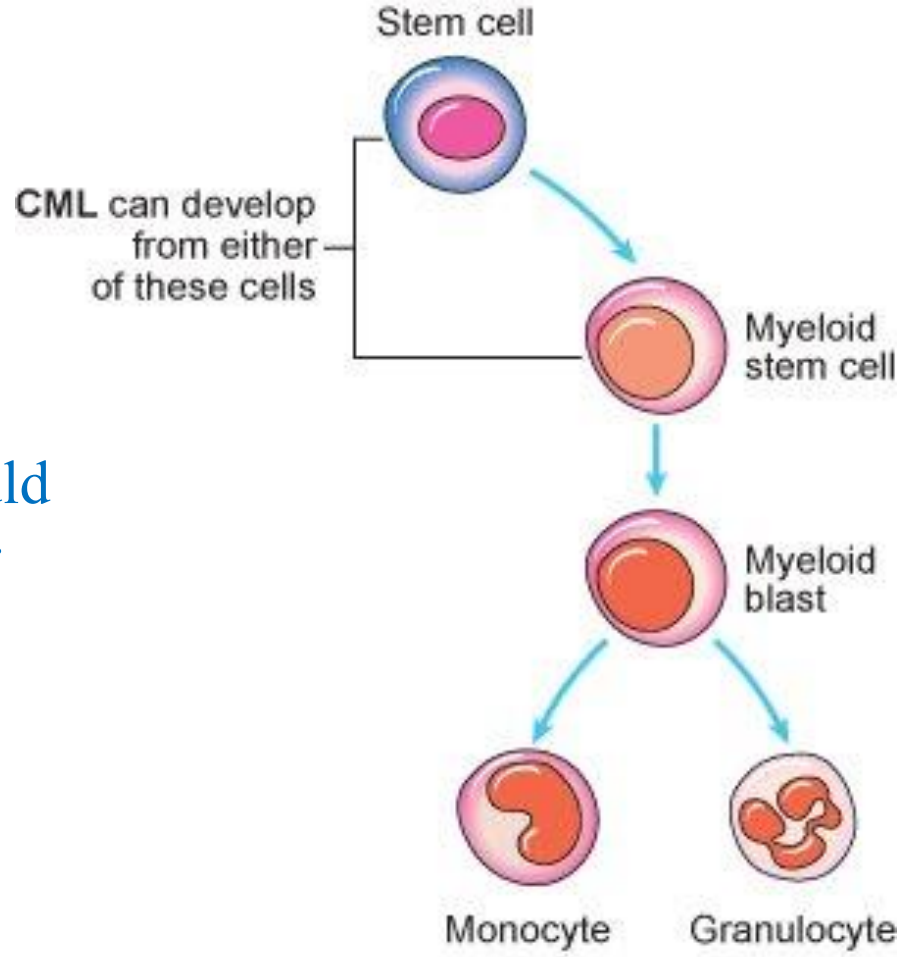
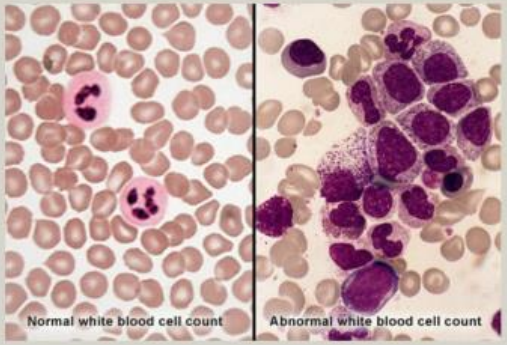


Diagram showing which cells CML can start in
© CancerHelp UK

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.

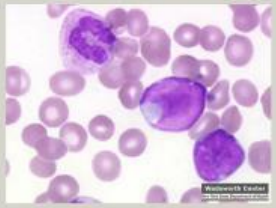


4 types of leukemia

Acute lymphoblastic leukemia

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

ALL



Acute myelogenous leukemia

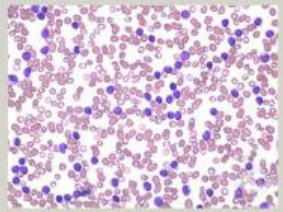
Found in myeloid cells
Grows quickly
Common in adults and children
18,000 cases a year

AML

Chronic lymphoblastic leukemia

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

CLL



Chronic myelogenous leukemia

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

CML

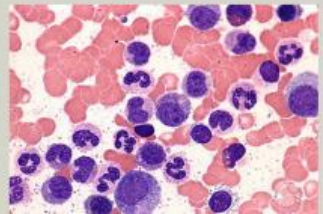
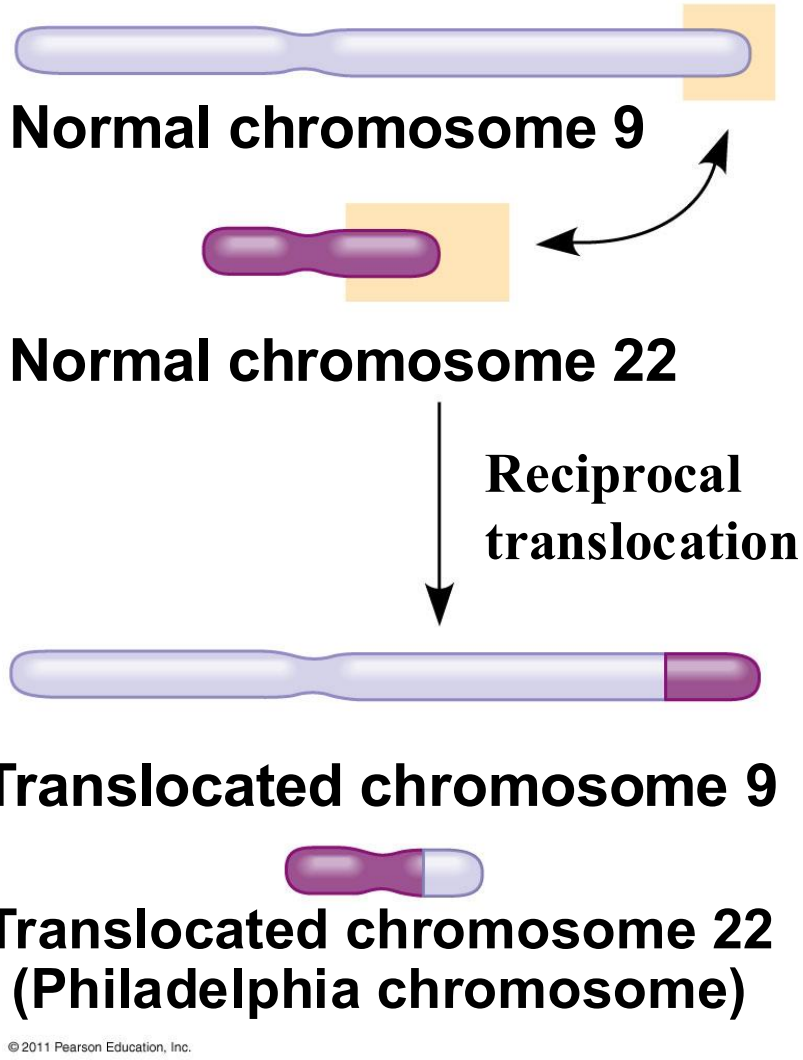
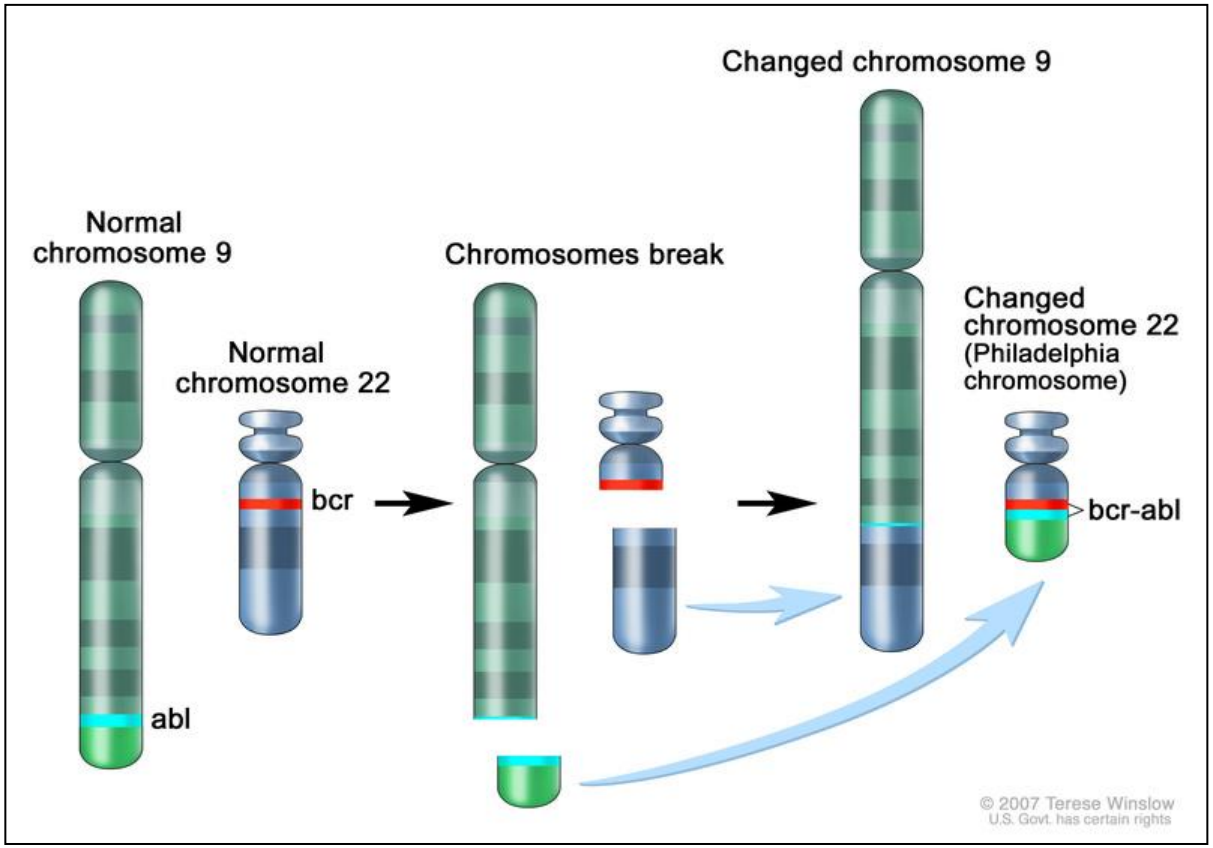


Figure 15.16

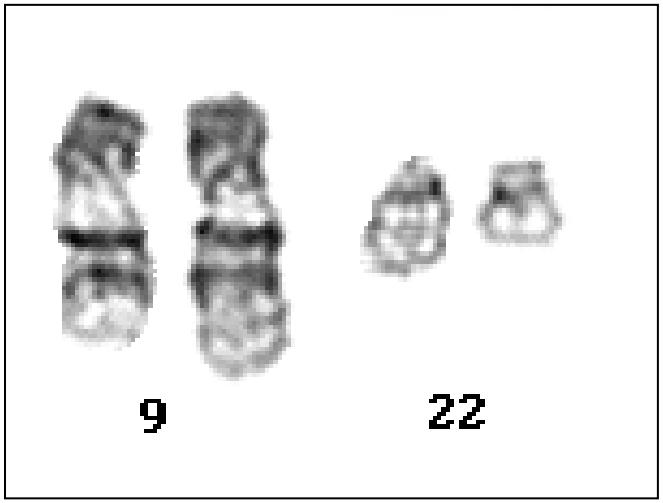


- A translocation can occur between chromosomes 9 and 22, involving an exchange of genetic material between them.
- This results in a translocated chromosome 22 carrying part of chromosome 9, as well as a translocated chromosome 9.
- The translocated chromosome 22 is known as the **Philadelphia chromosome**, which is *the main cause of chronic myelogenous leukemia (CML).*

✓ When a hematopathologist suspects CML in the differential diagnosis, karyotyping is requested to test for the presence of the Philadelphia chromosome. If they don't, establishing the diagnosis of CML becomes challenging.



See the next slide



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)

- The **ABL** gene is located on chromosome **9,** while the **BCR** gene is located on chromosome **22**.
- A translocation occurs when a cut happens in chromosome 9 and another break occurs in chromosome 22, specifically at the ABL and BCR regions. This results in the ABL gene, together with adjacent DNA from chromosome 9, moving to chromosome 22.
- The breakpoint on chromosome 22 **occurs within the BCR gene**. Protein-coding genes normally contain a **promoter region** and a **protein coding region**. The promoter is the site where transcription factors and RNA polymerase bind to initiate transcription and produce mRNA from the coding exons.
- After the translocation, the coding region (exons) of the ABL gene becomes **controlled by the BCR promoter** instead of its original ABL promoter. The **BCR promoter is stronger**, leading to *increased transcription of ABL and therefore increased production of ABL protein.*
- ABL encodes a tyrosine kinase protein, which promotes cell cycle progression and cell division. Although the ABL protein itself is **structurally normal and not mutated**, its **quantity becomes abnormally increased**. The excessive kinase activity drives increased cell proliferation, predisposing cells to malignant transformation.
- Importantly, there is **NO overall gain or loss of genetic material**; the total DNA content remains the same. The disease results from rearrangement of genetic material, which leads to chronic myelogenous leukemia (CML).

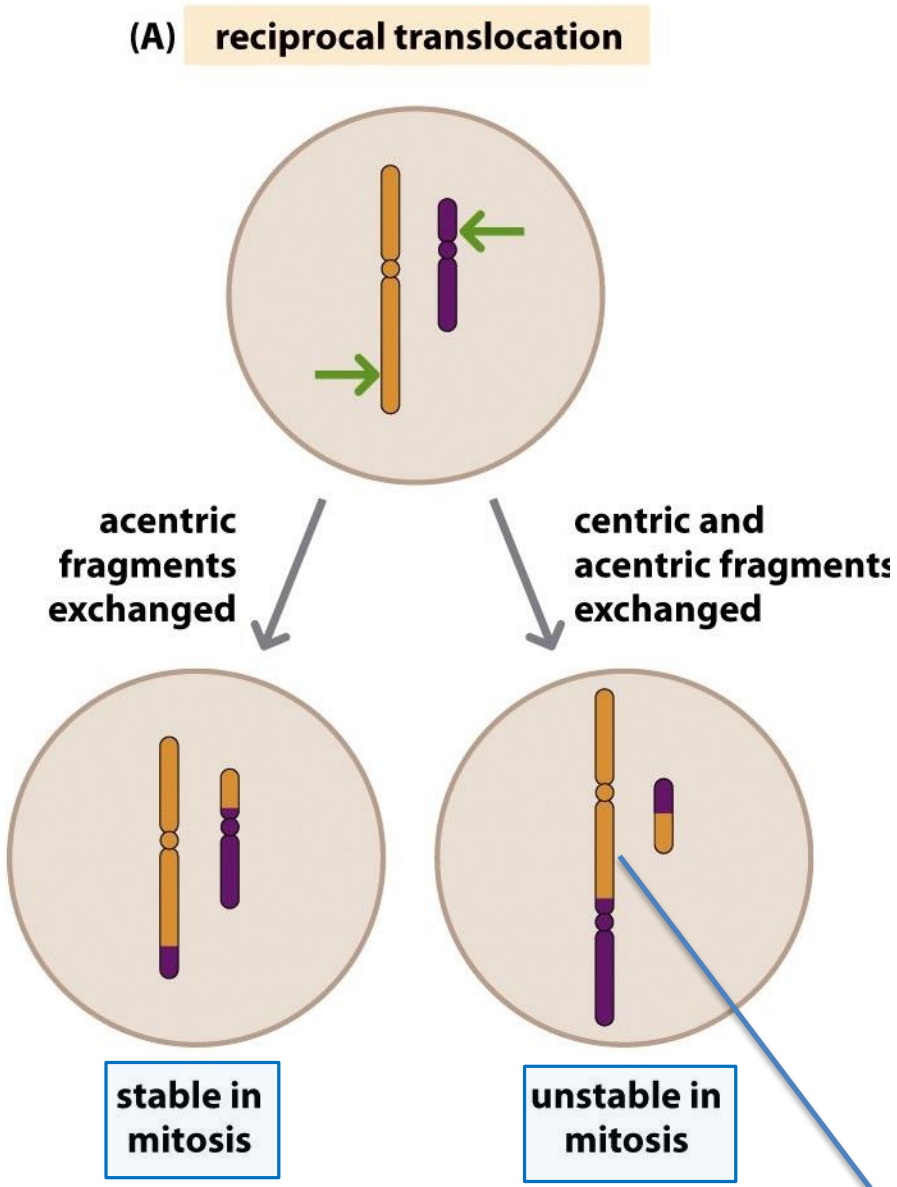


Figure 2.23 Human Molecular Genetics, 4ed. (© Garland Science)

(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.

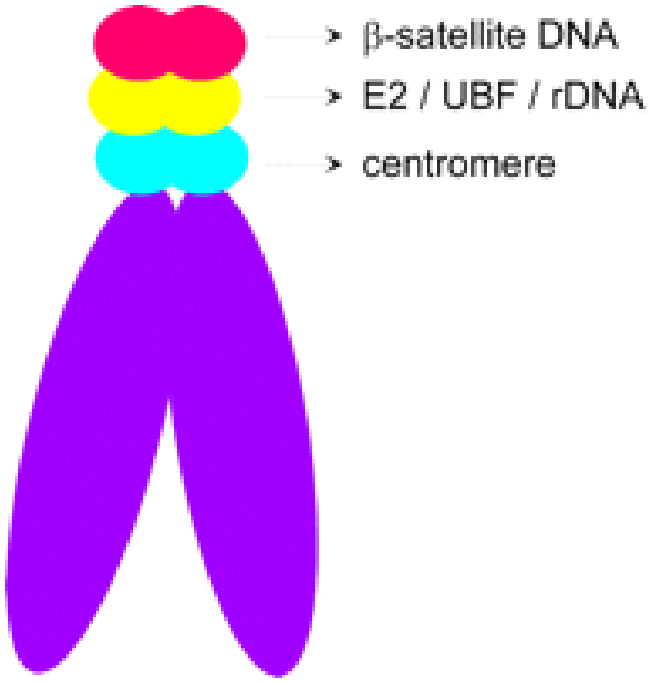
If an acentric fragment from one chromosome is exchanged for an acentric fragment from another, the products are stable in mitosis, however exchange of an acentric fragment for a centric fragment results in acentric and dicentric chromosomes that are unstable in mitosis.

The two centromeres are farther apart from each other.

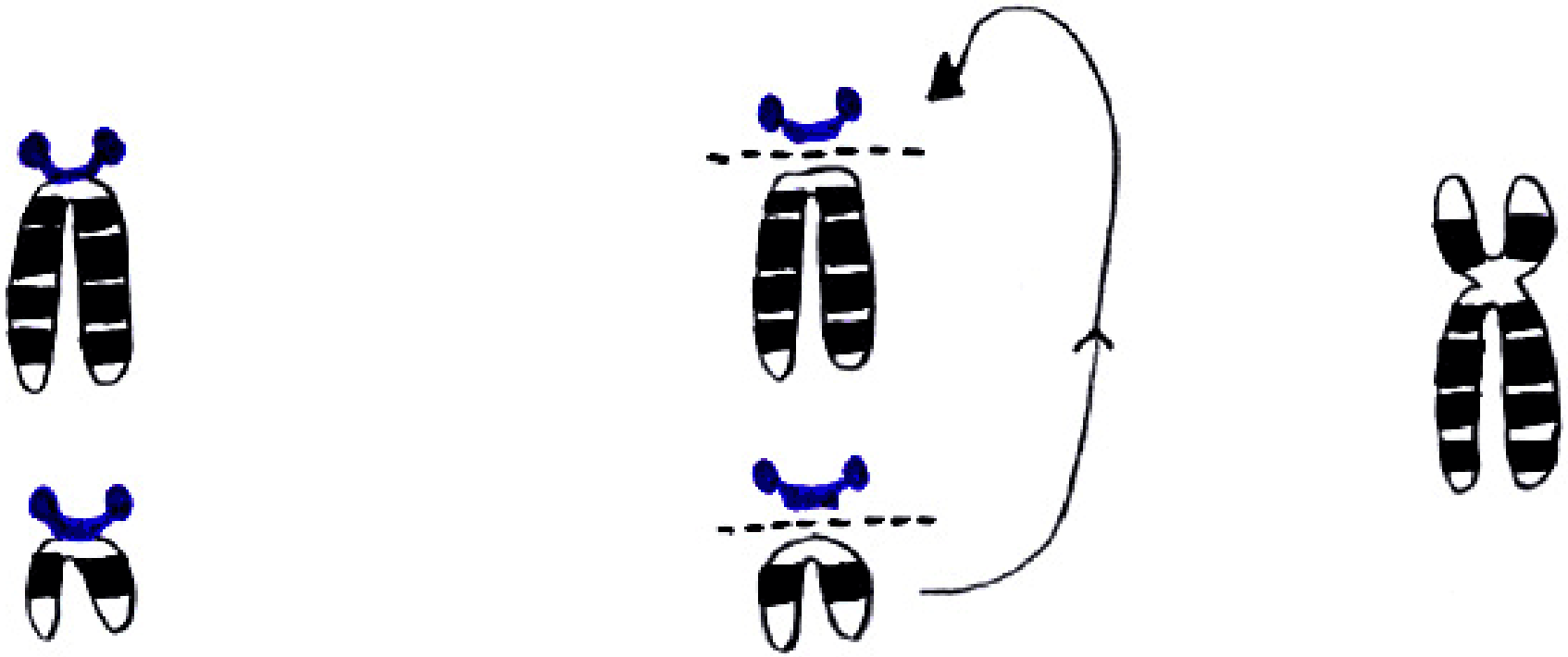
- **A robertsonian translocation** is a specialized type of translocation between two of the five types of **acrocentric** chromosome in human (13,14,15,21,and 22) the short arm is very small and very similar in DNA content ,each contains **1-2Mb** of tandemly repeated rRNA genes sandwiched between two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

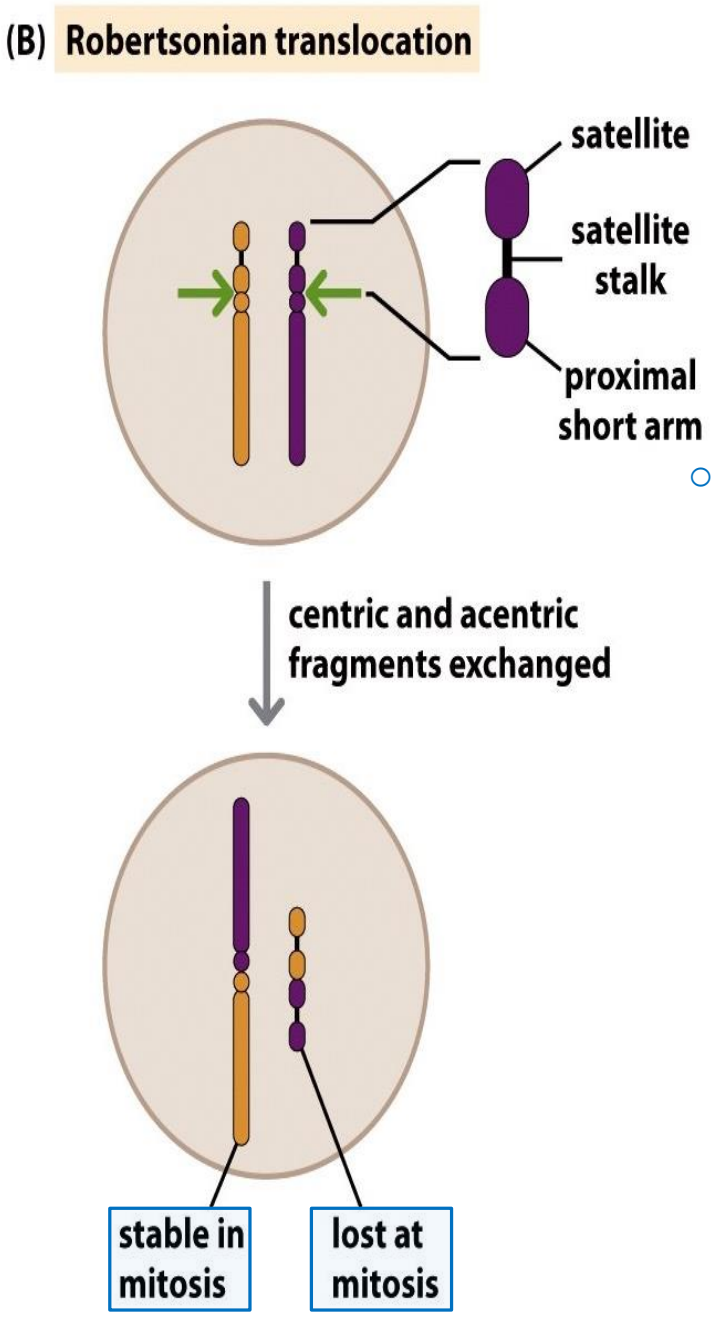
- After loss of the p arms, the q arm of one acrocentric chromosome fuses with the q arm of another acrocentric chromosome.

- A classic example involves chromosomes 14 and 21. Two acrocentric chromosomes, chromosome 14 and chromosome 21, undergo fusion to form a single **translocated chromosome that contains the long arms (q arms) of both chromosomes**.



Robertsonian translocation
(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 two centromeres are located very close to each other and function as a single centromere for the spindle fibers. Therefore, the anaphase during cell division proceeds normally.

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

Reciprocal translocation

Those are the different possible gametes, the four different possible gametes that an individual with a balanced reciprocal translocation would produce.

Those gametes may fertilize a normal gamete from an individual who does not carry the translocation.

During fertilization, there is a 50% chance of producing a clinically normal zygote and a 50% chance of producing a clinically abnormal zygote.

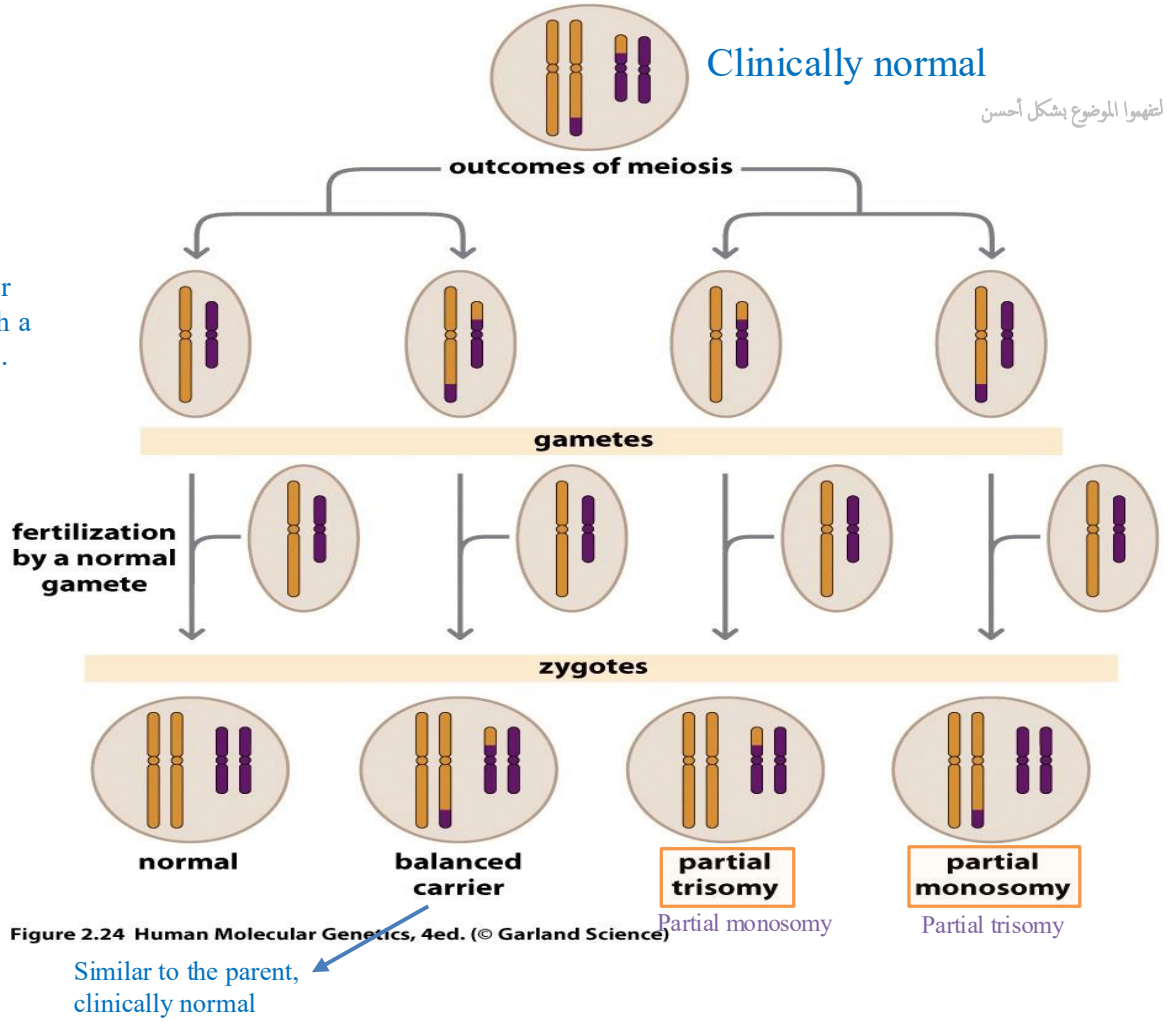


Figure 2.24 Human Molecular Genetics, 4ed. (© Garland Science)

احضروا شرح الدكتور لتفهموا الموضوع بشكل أحسن

- Sometimes, chromosomal translocations are not necessarily disease-causing, especially when the breakpoints occur in gene-poor regions or outside the genes themselves, leaving the genes intact.

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

A clinically healthy individual carrying a Robertsonian translocation involving chromosomes 14 and 21 is expected to have *45 chromosomes*. In this case, the q arm of chromosome 14 is fused with the q arm of chromosome 21, forming a single translocated chromosome. There is no significant loss of genetic material. Although the p arms are lost, they are not clinically important.

Watch this video

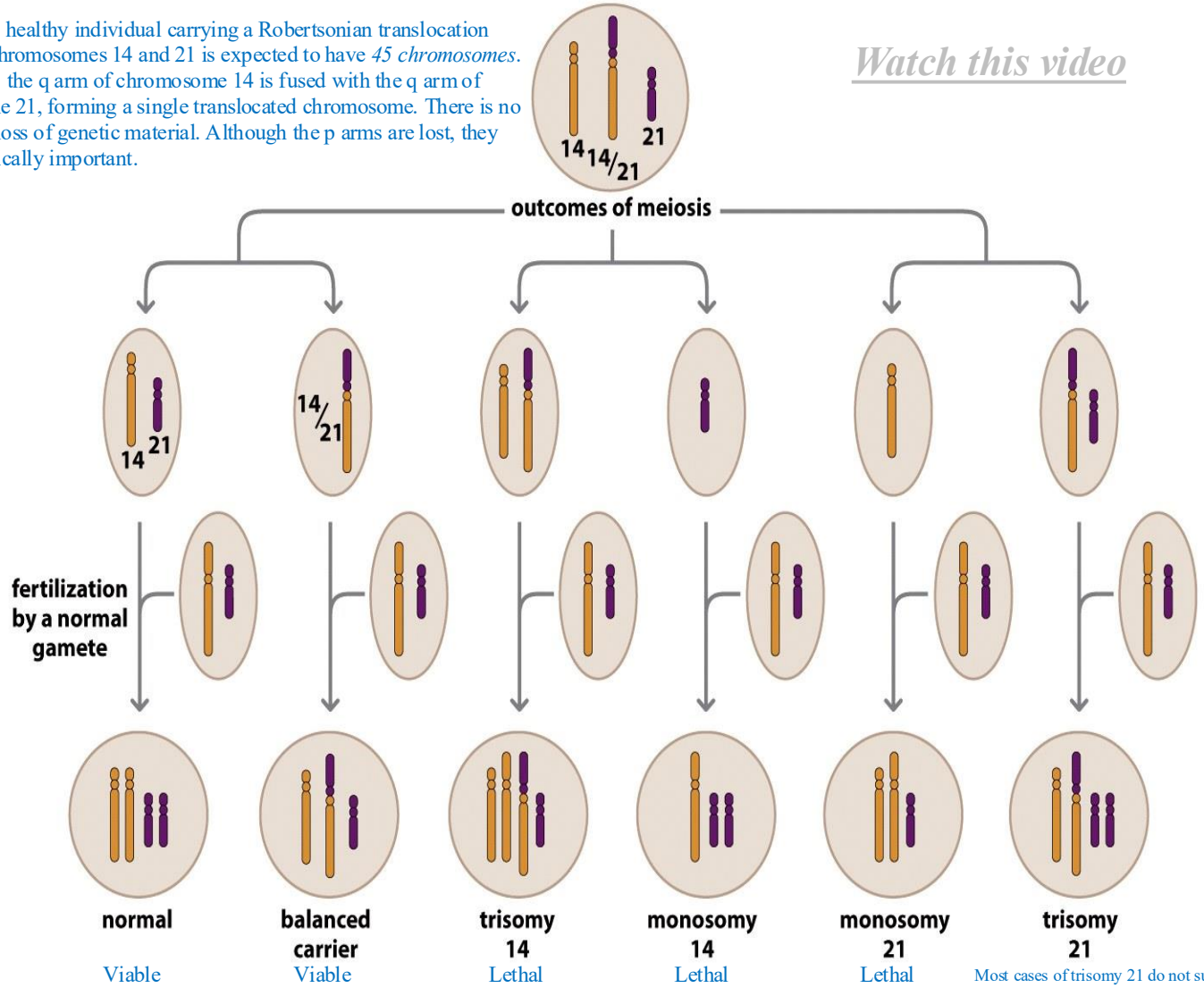


Figure 2.25 Human Molecular Genetics, 4ed. (© Garland Science)

Chromosome 14 is larger and contains more genetic material than chromosome 21. Therefore, trisomy 14 is not compatible with life and does not survive to birth, whereas trisomy 21 can survive to birth.

Most cases of trisomy 21 do not survive to birth and are lost during embryonic development. However, a small fraction survive to birth, resulting in **Down syndrome**.

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.

Origins of triploidy and tetraploidy.

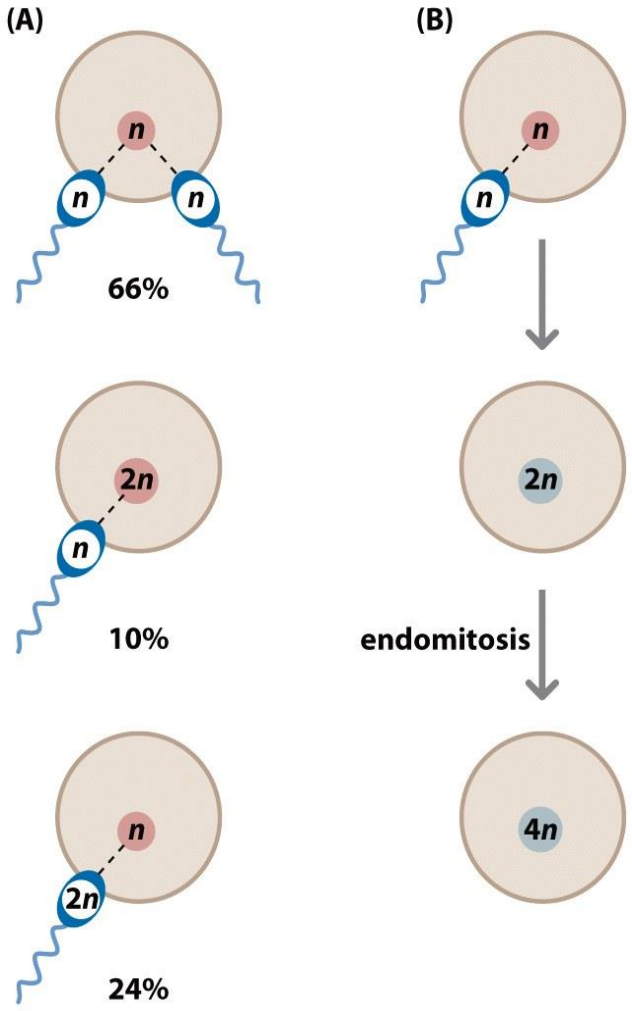


Figure 2.21 Human Molecular Genetics, 4ed. (© Garland Science)

(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.

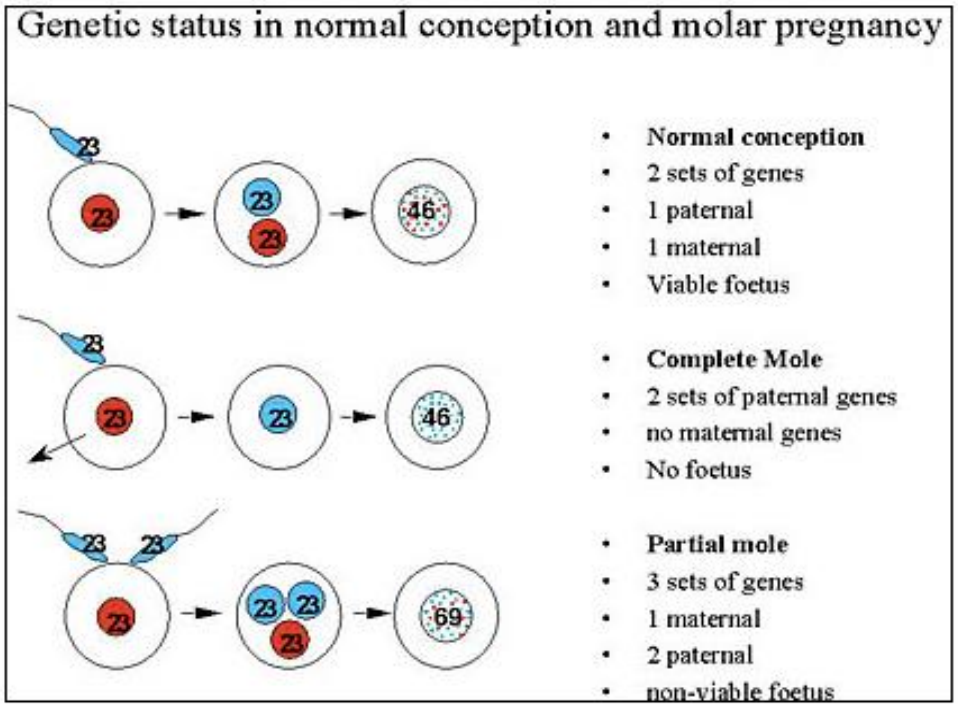
- Sometimes (66%), two sperm cells fertilize a single egg by mistake, resulting in three sets of chromosomes.
- 10% of cases occur when an egg abnormally contains two sets of chromosomes and is fertilized by a sperm carrying one set of chromosomes.
- About 24% of cases occur when a sperm containing two sets of chromosomes fertilizes an egg carrying one set of chromosomes.

✓ This produces a total of 69 chromosomes (23 × 3), a condition known as **triploidy**.

(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.

- Tetraploidy occurs when a normal sperm fertilizes a normal egg, each contributing one set of chromosomes, forming a zygote with 46 chromosomes.
- After fertilization, the zygote undergoes multiple rounds of mitotic division during development. Normally, mitosis separates sister chromatids into two daughter cells through proper cytokinesis.
- However, an abnormal process known as endomitosis may occur. In endomitosis, sister chromatids are duplicated but are not separated into two daughter cells. Cytokinesis occurs abnormally, or fails, resulting in all chromosomes remaining within a single cell.

✓ This leads to duplication of the entire chromosomal content within the same cell, producing a 4n chromosomal complement (tetraploidy).



- A sperm fertilizes an egg, but by mistake, the maternal nucleus of the egg is lost from the zygote. As a result, the fertilized egg contains only the paternal chromosomal complement.
- In order to survive, the zygote replicates its chromosomes, resulting in a total of 46 chromosomes. However, all 46 chromosomes are of paternal origin.
- This condition leads to a complete molar pregnancy (***complete mole***), which occurs when maternal DNA is completely absent.
- ✓ In this case, there is no fetal development. Instead, there is trophoblastic growth consistent with pregnancy, but without formation of a fetus.

- In another scenario, dispermy occurs when two sperm fertilize a normal egg. This results in three sets of chromosomes (3n), with one maternal set and two paternal sets.
- Although this condition is not viable, the presence of maternal genetic material allows fetal development to occur. However, the fetus is nonviable and is typically severely malformed.
- ✓ This condition is known as a ***partial mole.***

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

Born dead

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.

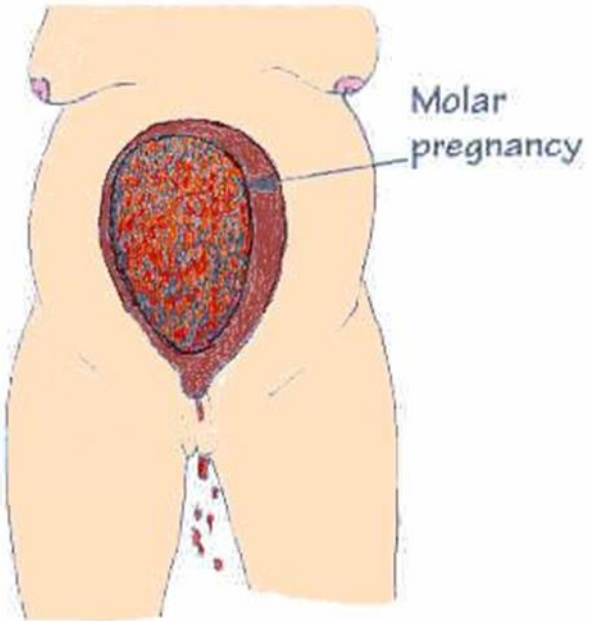
Types

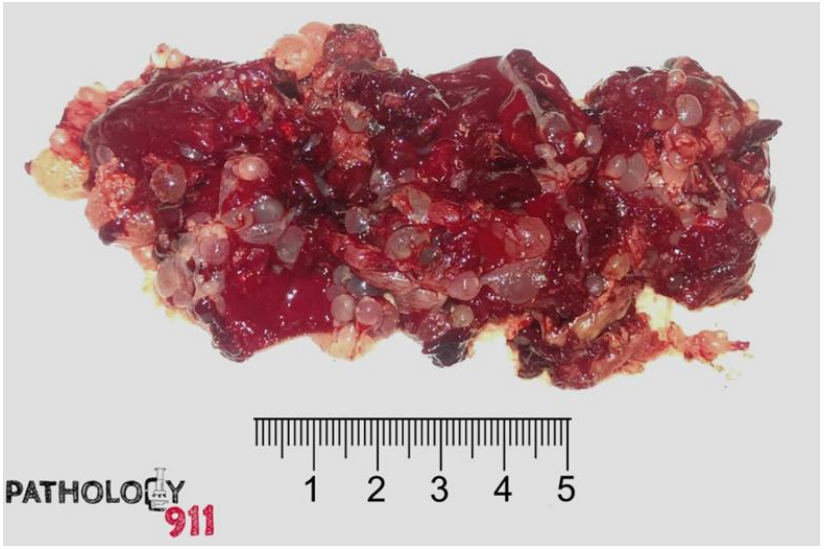
- maternal triploidy (triploidy by **digyny**)
- paternal triploidy (**diandry** or dispermy)

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)

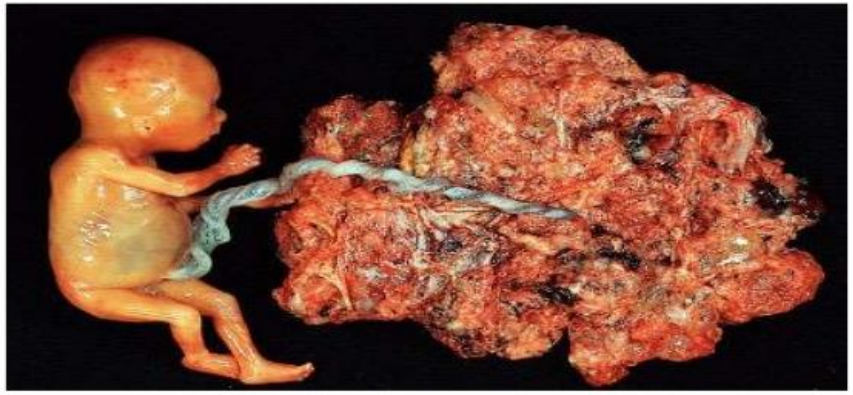
COMPLETE MOLE

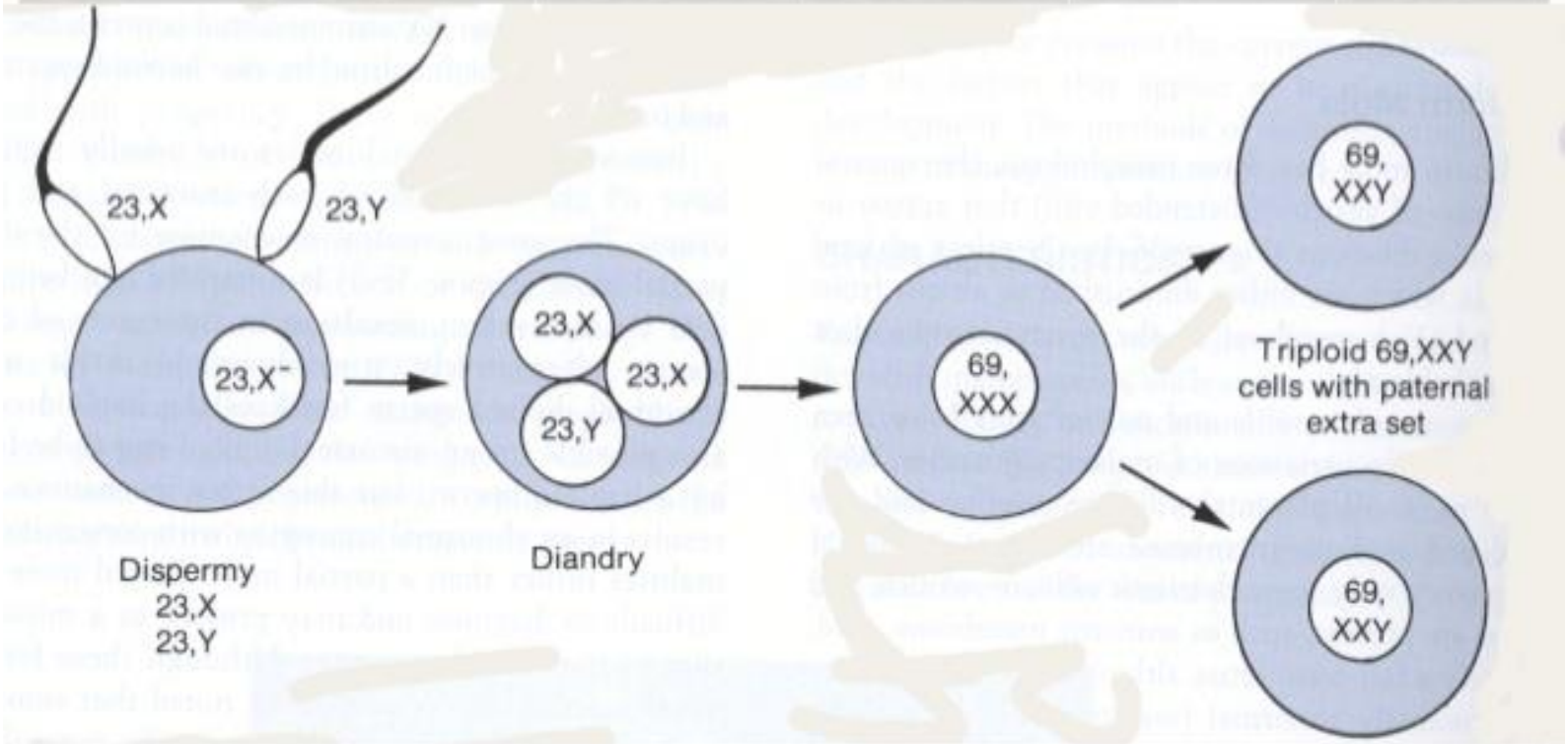
- The oocyte has somehow lost its DNA – it is 'empty' of DNA
- Option A: Fertilised by one sperm – reduplicates its own DNA = *homozygous*
- Option B: Fertilised by two sperm = *heterozygous*
- Karyotype: Diploid – 46 chromosomes (46XX or 46XY – the 46YYs are not viable)

Because the second chromosome is an exact couple of the first chromosome

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

Partial mole



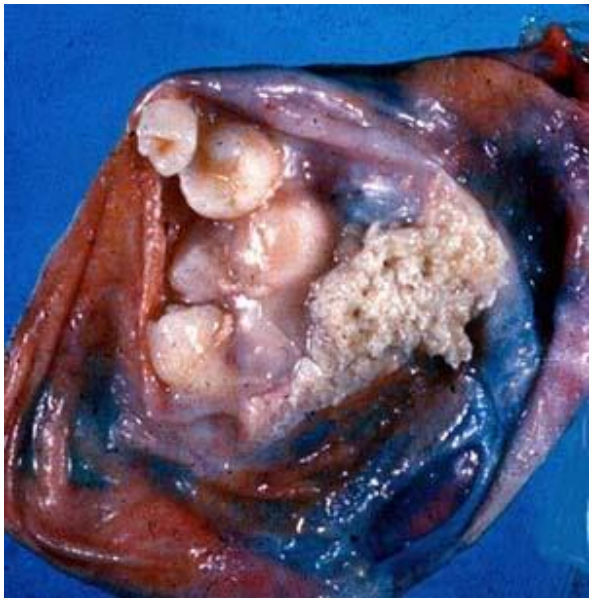


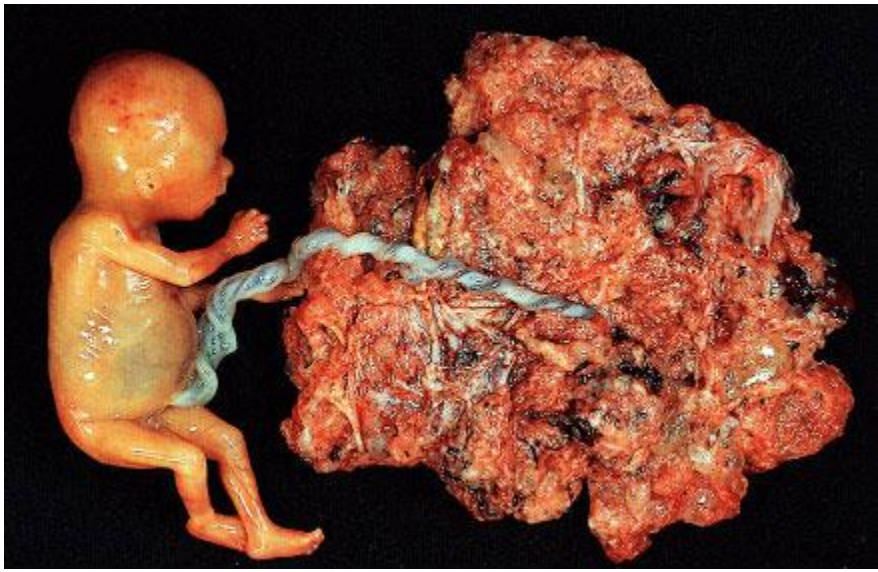
Diandric triploidy

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

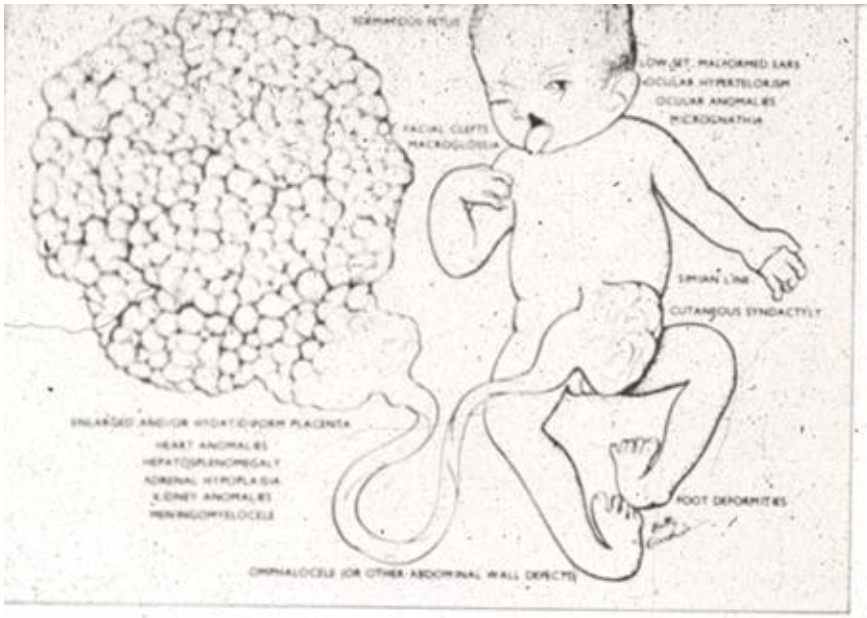
- **Paternal uniparental diploidy** produces hydatidiform moles, abnormal conspectuses that develop to show widespread hyperplasia (overgrowth) of the trophoblast but no fetal parts, they may transform into choriocarcinoma.

- **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.





Triploidy



24.1

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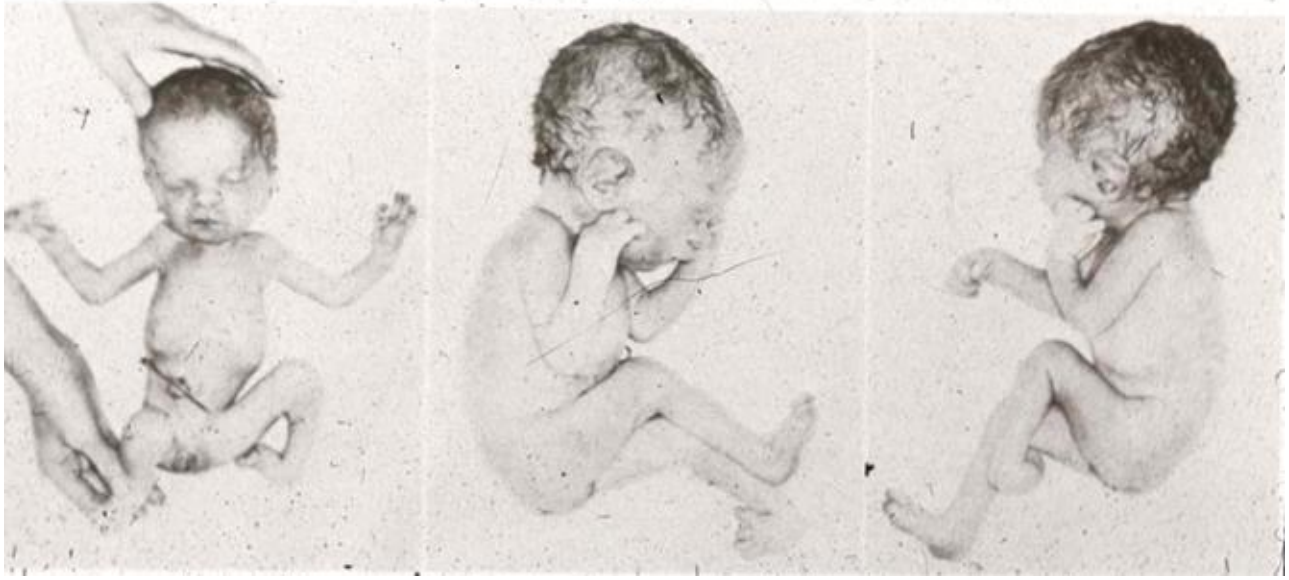


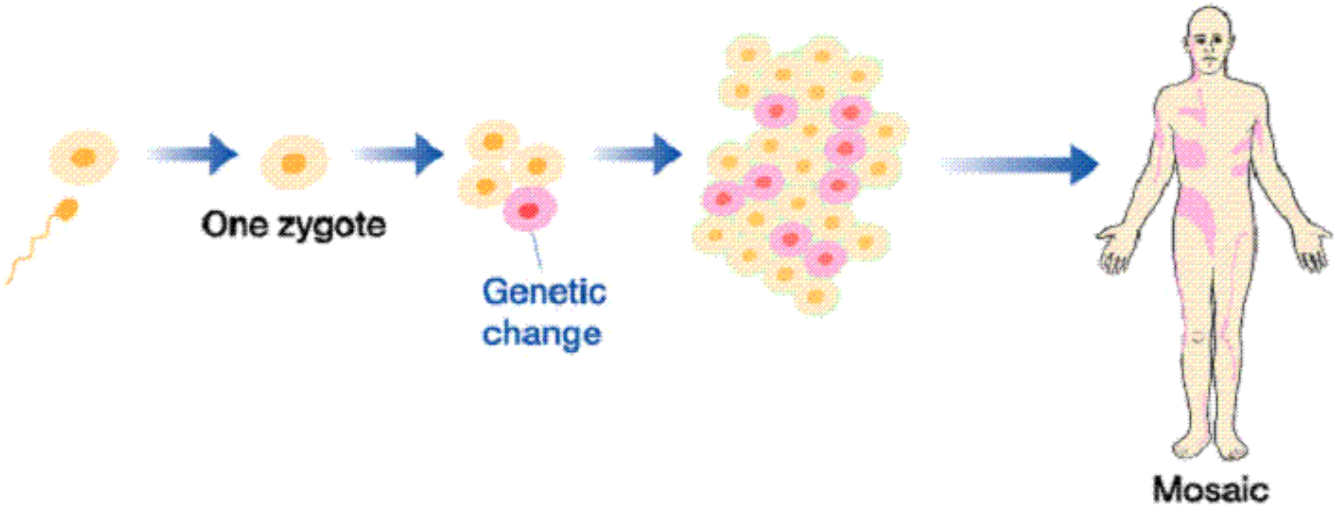
Findings:
CHD
Kidney anomalies
Low-set, malformed ears
Hypertelorism
Foot deformities
Abdominal wall defects

<u>Diandric</u>
Enlarged placenta
Cyst-like placenta
Well-formed fetus with or without microcephaly

<u>Digynic</u>
Macrocephaly
Severe intrauterine growth retardation

Mosaicism

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



- A normal sperm fertilizes a normal egg, resulting in a normal zygote. This zygote undergoes multiple rounds of mitotic divisions.
- During mitosis, a genetic insult may occur, either at the **chromosomal level** or at the **gene level**. For example, nondisjunction of chromosome 21 may occur, producing two daughter cells: one with a missing chromosome 21 and one with an extra chromosome 21.
- The daughter cell with missing chromosome 21 is not viable and dies, while the daughter cell with extra chromosome 21 may survive.
- Since mitosis produces genetically identical daughter cells, any genetic change occurring in a cell will be passed on to all its descendant cells. This results in two populations of cells originating from the same zygote: **one normal cell line and one abnormal cell line.**

✓ This leads to the formation of a ***mosaic individual***, which is not uncommon in genetic disorders at either the gene or chromosomal level.

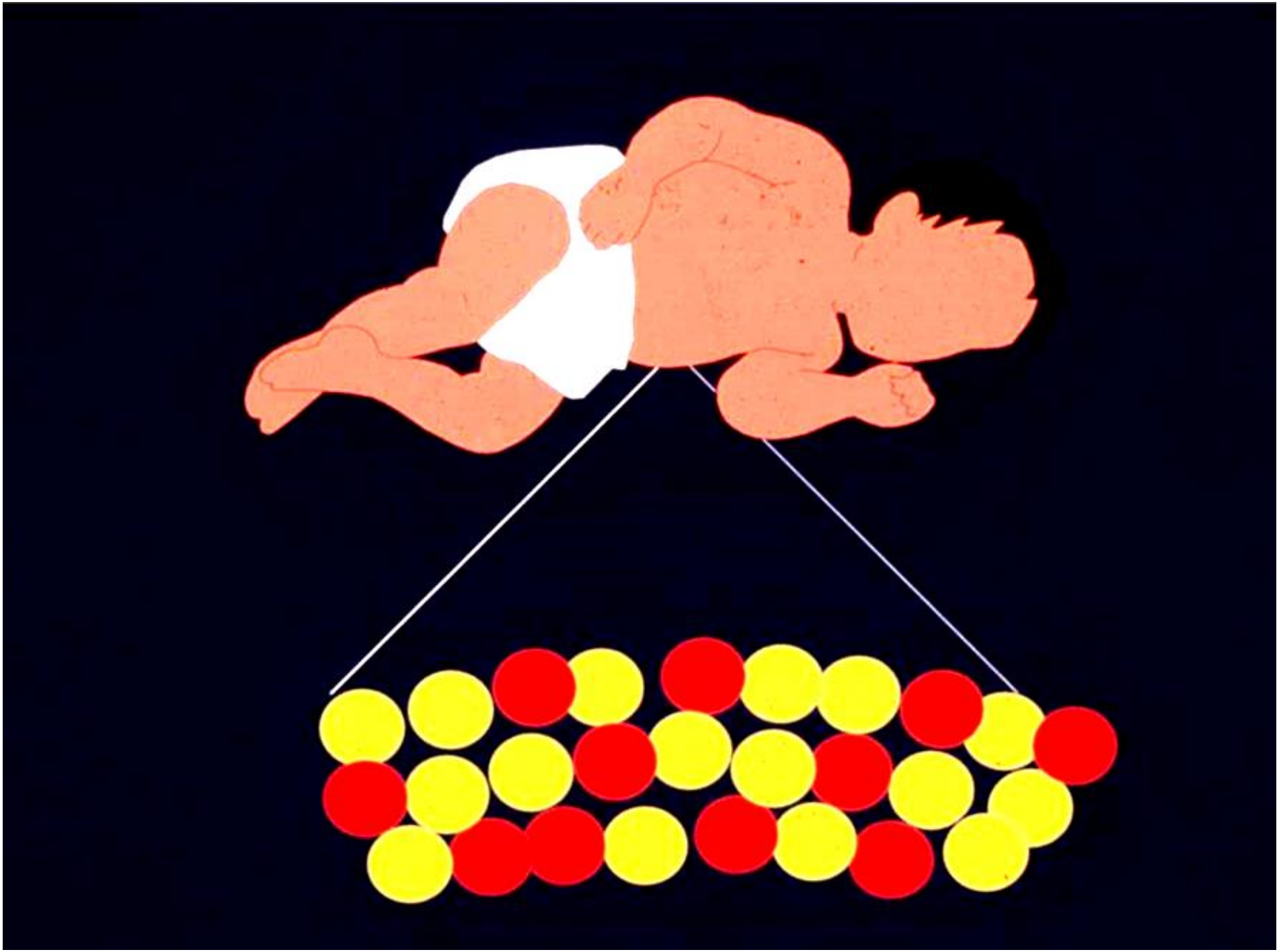
- An individual with trisomy 21 (Down syndrome) may develop the condition either because the sperm carried an extra chromosome 21 or because nondisjunction occurred during mitosis.

- ✓ Germline (full) Down syndrome is more clinically deleterious than mosaic Down syndrome because **all cells carry trisomy 21**, whereas mosaic **individuals have both normal and abnormal cell populations.**

- In a mosaic individual, the clinical severity depends on when the mosaic cell appears during development.

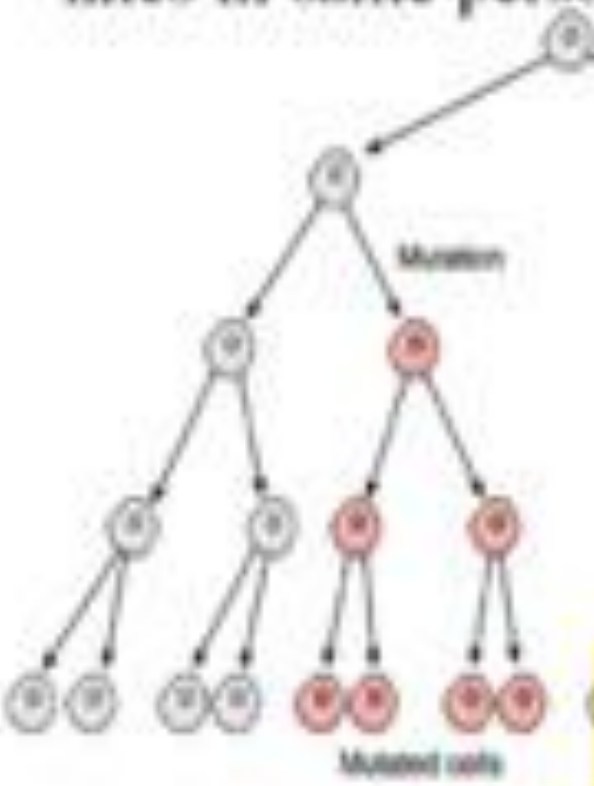
- If the mosaic event occurs in the first trimester, it will be more deleterious than if it occurs in the third trimester, because **early embryonic cells undergo extensive mitotic divisions.**

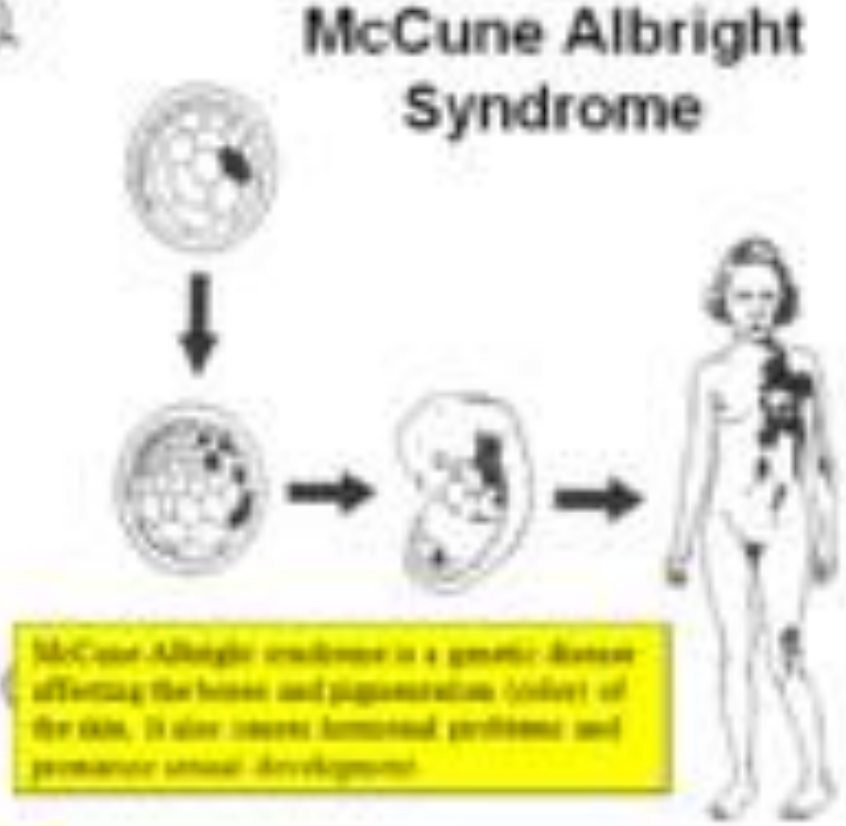
- ✓ The earlier the genetic anomaly appears, the greater the number of daughter cells that will carry the abnormality. Consequently, earlier occurrence results in a larger proportion of affected cells.

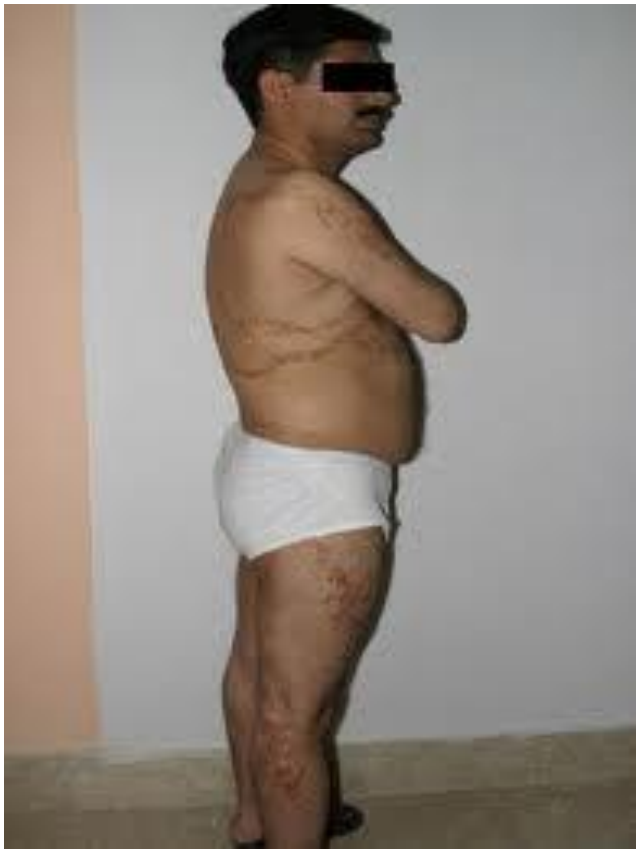


Somatic Mosaicism Gives Different Cell Lines

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

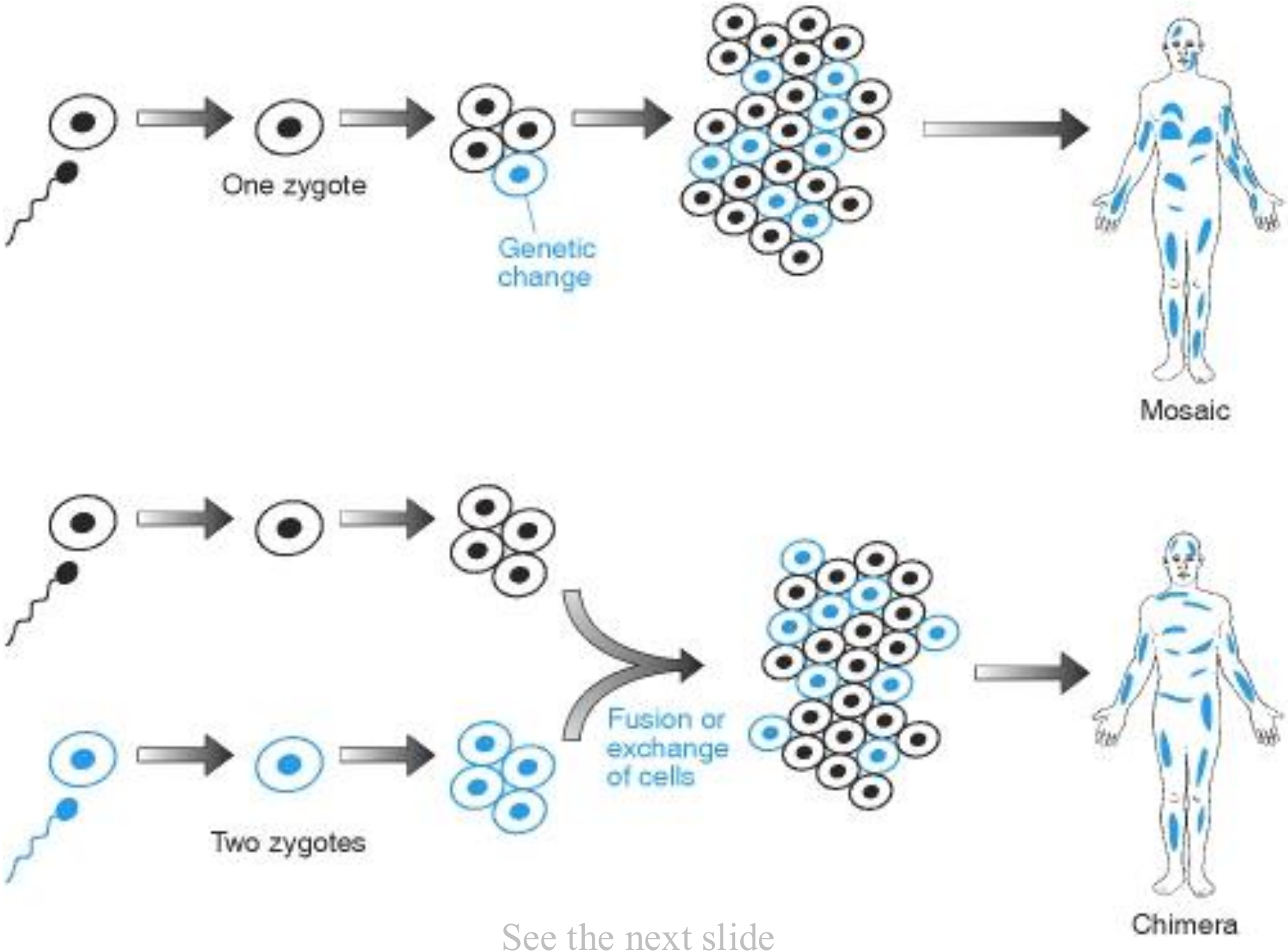






- A classic example is certain skin diseases in which only specific regions of the skin are affected rather than the entire skin.

- This represents mosaicism, where the affected tissue originates from daughter cells that are descendants of a single mosaic cell carrying the genetic change.



See the next slide

- A ***mosaic*** individual has more than one cell line derived from a single fertilized zygote.

- However, sometimes more than one cell line may arise from more than one zygote, typically two zygotes. This can occur in non-identical twin pregnancies.

- If two eggs are released and fertilized, they normally develop into twins. However, if the developing embryos are physically very close to each other during early development and implantation in the uterus, their dividing cells may merge and form a single group of cells.

- Instead of forming twins, a **single individual** develops from the combined cell populations. This individual is known as a ***chimera***.