بسم الله الرحمن الرحيم

Cytogenesis Study Sheet

Comprehensive notes built from the uploaded lecture slides

Covers chromosomal abnormalities, sex chromosome disorders, structural rearrangements, triploidy, uniparental diploidy, mosaicism, and chimerism.

What is inside	How to use it
• Incidence figures for common chromosomal abnormalities • X/Y chromosome basics and SRY • Clinical patterns of Klinefelter and Turner syndromes • Deletion, translocation, Robertsonian, triploidy, and mosaicism patterns	• Read the summary first • Use the figures to connect the concepts • Check the appendix to confirm no slide topic was missed

اللهم أعنا على ذكرك و شكرك و حسن عبادتك

1. Chromosomal abnormalities at birth

Key idea: chromosomal abnormalities are common enough to matter in newborn screening and counseling. The lecture's opening table gives the classic prevalence estimates below.

Category	Examples	Approx. prevalence at birth
Sex chromosome aneuploidy	47,XXY; 47,XYY; 45,X; 47,XXX	1/1000, 1/1000, 1/5000, 1/1000
Autosomal aneuploidy	Trisomy 21, 18, 13	1/800, 1/6000, 1/10,000
Structural abnormalities	Robertsonian, reciprocal, other balanced; unbalanced rearrangements	1/1000, 1/885, 1/17,000
All chromosome abnormalities	Autosomal disorders + unbalanced rearrangements; balanced rearrangements	1/230; 1/500
Total	All chromosome abnormalities combined	1/154

Takeaway: aneuploidies and structural rearrangements are a real part of clinical genetics.

Incidence of Chromosomal Abnormalities in Newborns

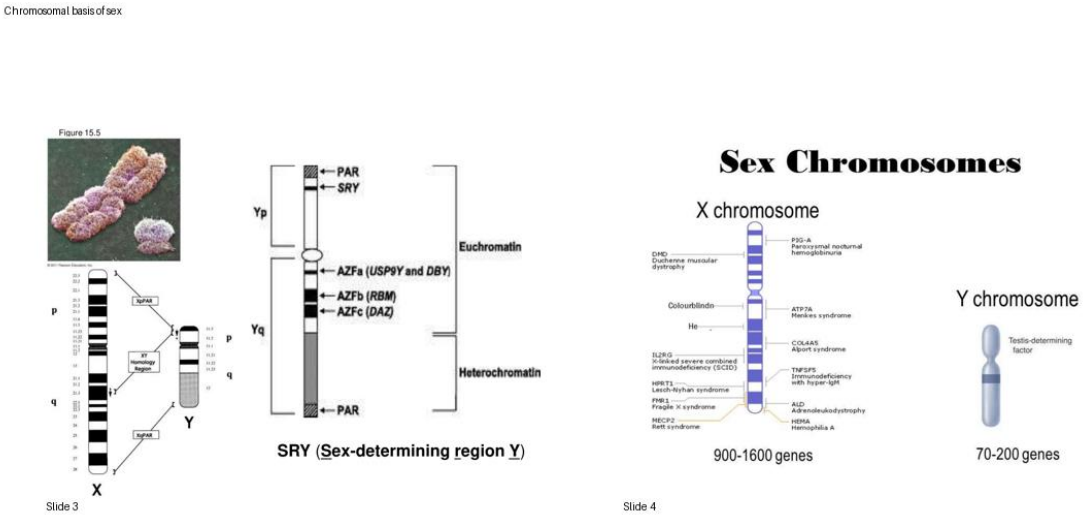
Type of Abnormality	Prevalence at Birth
Sex Chromosome Aneuploidy	
Males (43,612 newborns)	
47,XXY	**1/1000**
47,XYY	**1/1000**
Females (24,547 newborns)	
45,X	**1/5000**
47,XXX	**1/1000**
Autosomal Aneuploidy (68,159 newborns)	
Trisomy 21	**1/800**
Trisomy 18	**1/6000**
Trisomy 13	**1/10,000**
Structural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

Lecture opening slide: incidence of chromosomal abnormalities in newborns.

2. Chromosomal basis of sex

- Humans have one larger X chromosome and one smaller Y chromosome.
- Only the ends of the Y chromosome are homologous with the corresponding regions of the X chromosome.
- The SRY gene on the Y chromosome encodes a protein that directs male anatomical development.
- The X chromosome contains roughly 900-1600 genes, while the Y chromosome contains about 70-200 genes.

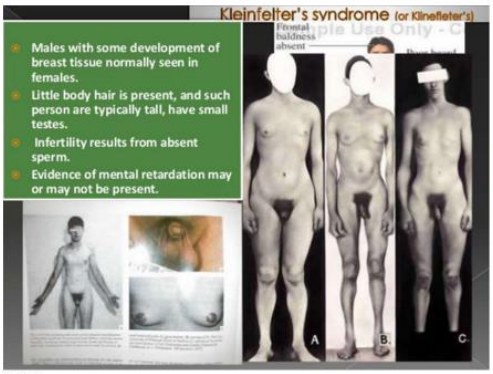


Slides 3-4: SRY, pseudoautosomal regions, and chromosome gene content.

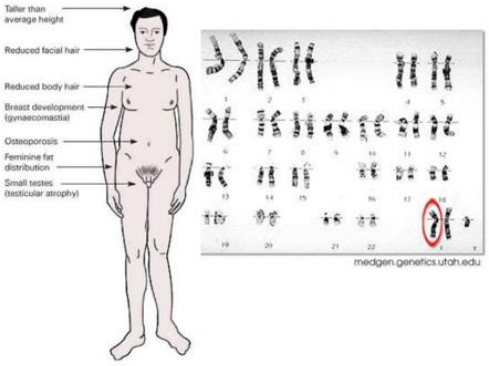
Exam cue: the Y chromosome is small, but SRY has an outsized developmental impact.

3. Sex chromosome aneuploidies

- Klinefelter syndrome (47,XXY): male phenotype with gynecomastia, sparse body hair, tall stature, small testes, infertility, and variable learning or intellectual impairment.
- Turner syndrome (45,X): female phenotype with short stature, webbed neck or low hairline, shield chest, widely spaced nipples, streak ovaries, primary amenorrhea, and infertility.
- The lecture also lists 47,XYY and 47,XXX among sex chromosome aneuploidies with birth prevalence around 1/1000.



Slide 5



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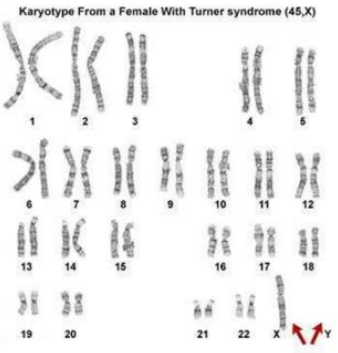

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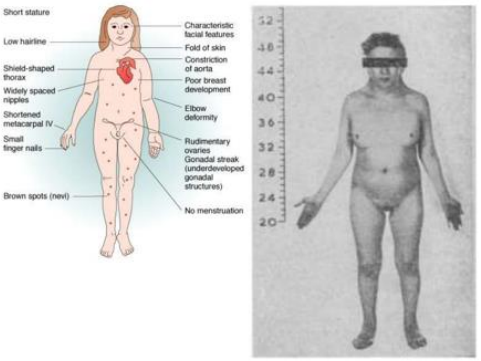

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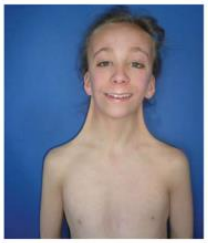
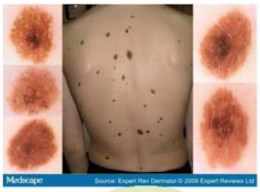




Slide 9

Slides 5-9: Klinefelter syndrome and Turner syndrome appearances, karyotypes, and characteristic findings.

4. Structural chromosome disorders

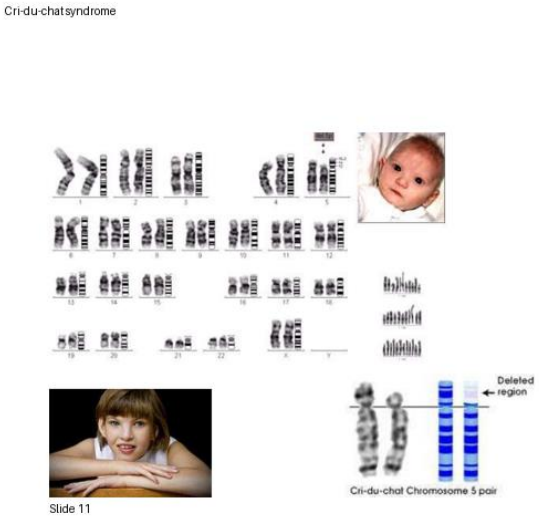
Cri-du-chat syndrome

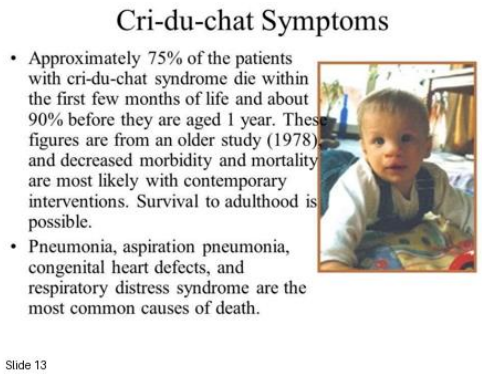
• Caused by a specific deletion on chromosome 5 (classically 5p deletion).

• Classic clues: catlike cry, mental retardation/developmental delay, microcephaly, round face, small chin, widely spaced eyes, epicanthal folds, and a small nose bridge.

• Other problems can include heart defects, skeletal and muscular problems, hearing and sight problems, poor muscle tone, hyperactivity, and aggression.

• The lecture notes high early mortality in older series, with pneumonia, aspiration pneumonia, congenital heart defects, and respiratory distress among major causes of death.





Slides 11-13: deletion of chromosome 5 and the classic cri-du-chat phenotype.

CML, Philadelphia chromosome, and translocation logic

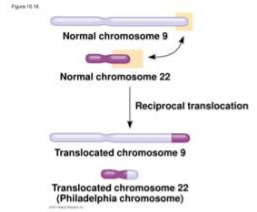
• Certain cancers, including chronic myelogenous leukemia (CML), are caused by chromosome translocations.

• The classic lesion is the reciprocal translocation between chromosomes 9 and 22, producing the Philadelphia chromosome.

• The translocation creates the BCR-ABL fusion gene on the derivative 22 chromosome; the encoded tyrosine kinase is constitutively active, so the cell keeps dividing.

• Balanced reciprocal translocations can be mitotically stable when acentric fragments are exchanged for acentric fragments; centric-for-acentic exchange can create unstable dicentric and acentric products.

Translocations and outcomes



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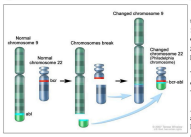
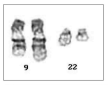


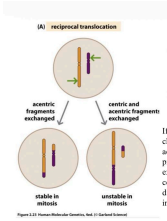


result of the translocation is the oncogenic BCR-ABL gene fusion, located on the shorter derivative 22 chromosome. This gene encodes the Bcr-abl fusion protein

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)

Slide 17

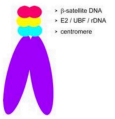


(A) Reciprocal translocation. The derivative chromosomes are stable in mitosis when one acentric fragment is exchanged for another; when a centric fragment is exchanged for an acentric fragment, unstable acentric and dicentric chromosomes are produced.

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.

Slide 18

- **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



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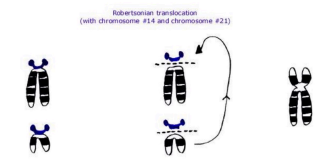

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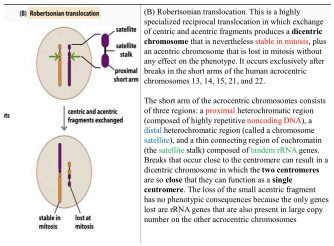


(B) Robertsonian translocation. This is a highly specialized reciprocal translocation in which exchange of centric and acentric fragments produces a **dicentric chromosome** that is nevertheless stable in mitosis, plus an acentric chromosome that is lost in mitosis without any effect on the phenotype. 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

Slide 21

- 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

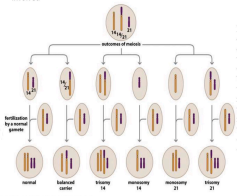


Figure 2.25 Possible outcomes of meiosis in a carrier of a Robertsonian translocation. Carriers are asymptomatic but often produce unbalanced gametes that can result in a monosomic or trisomic zygote. The two monosomic zygotes and the trisomy 14 zygote in this example would not be expected to develop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

Slide 22

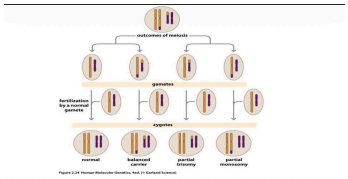


Figure 2.24 Possible outcomes of meiosis in a carrier of a balanced reciprocal translocation. Other modes of segregation are also possible, for example 3:1 segregation.

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

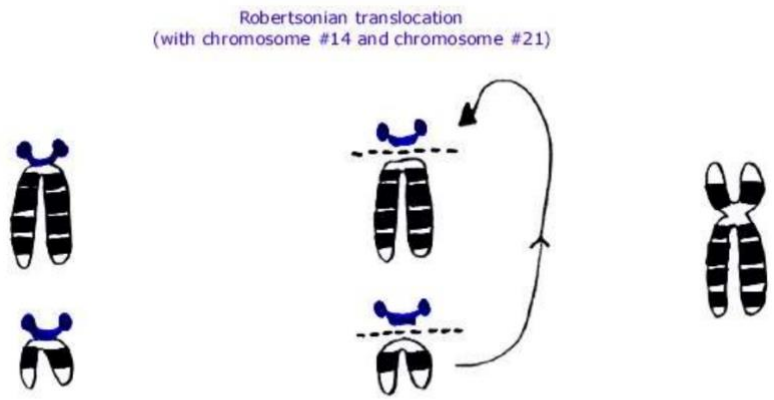
The risk of a carrier having a child with each of the possible outcomes depends on its frequency in the gametes and also on the likelihood of a conceptus with that abnormality developing to term.

Slide 23

Slides 16-23: Philadelphia chromosome, BCR-ABL, reciprocal translocations, and Robertsonian translocations.

5. Robertsonian translocation

- A Robertsonian translocation is a specialized exchange involving the short arms of acrocentric chromosomes 13, 14, 15, 21, and 22.
- The short arms contain repetitive rRNA genes and heterochromatin; losing the small acentric fragment usually has no phenotypic effect because those genes are redundant elsewhere.
- A carrier is often asymptomatic, but meiosis can produce normal, balanced-carrier, trisomic, or monosomic conceptions.
- The lecture highlights that the risk of an affected child depends on both the gamete frequency and whether the conceptus survives to term.



Slide 20: example of Robertsonian translocation with chromosomes 14 and 21.

6. Triploidy, tetraploidy, and uniparental diploidy

- Triploidy is the presence of an extra haploid set of chromosomes, giving 69 total chromosomes in humans.
- Main origins of triploidy: dispermy (66%), diploid ovum (10%), and diploid sperm (24%).
- Triploid karyotypes can be 69,XXX; 69,XXY; or 69,XYY.
- Triploidy is linked to spontaneous abortion, premature birth, and perinatal death; the lecture also notes the classic partial mole association with extra paternal material.
- Parent-of-origin matters: diandric triploidy tends to have a large placenta and relatively better-grown fetus; digynic triploidy tends to have severe growth restriction and a small placenta.
- Common findings include CHD, kidney anomalies, low-set malformed ears, hypertelorism, foot deformities, abdominal wall defects, macrocephaly or microcephaly depending on subtype, and syndactyly of the third and fourth fingers.
- Hydatidiform mole is a hallmark of pure triploidy and is classically described as a vesicular "bunches of grapes" chorionic villus appearance.
- Paternal uniparental diploidy produces hydatidiform moles with trophoblast overgrowth and no fetal parts; maternal uniparental diploidy can produce ovarian teratomas.
- Tetraploidy can arise after normal fertilization by endomitosis, when DNA replicates without cell division.

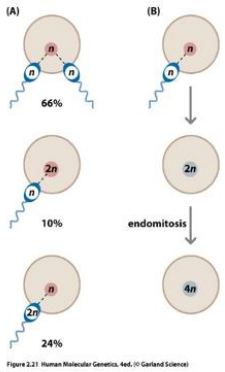


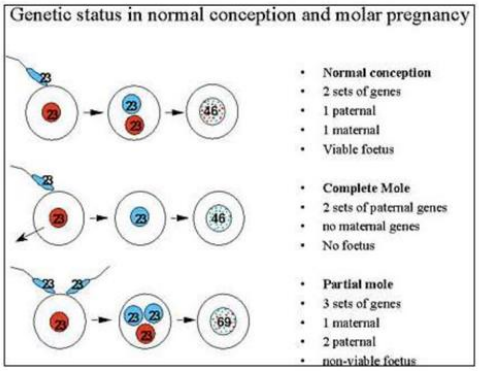
Figure 2.21 Human Molecular Genetics, 4ed. (© Garland Science)

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.

Slide 24



Slide 25

PARTIAL MOLE

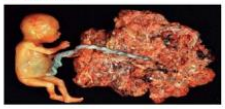
- The oocyte has an intact set of maternal DNA
- Option A: Fertilised by one sperm – reduplicates its own DNA
- Option B: Fertilised by two sperm
- Karyotype: Triploid – 69 chromosomes (69 XXY – an extra set of paternal DNA)

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)

Partial mole



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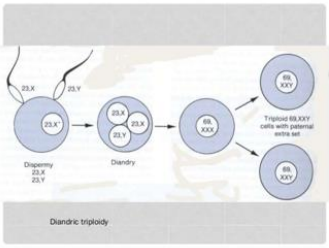
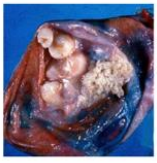
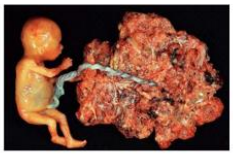


Slide 30

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.





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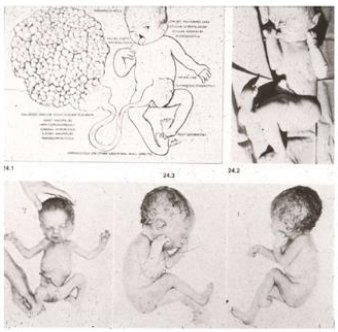


Triploidy

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

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

Digynic
Macrocephaly
Severe intrauterine growth retardation

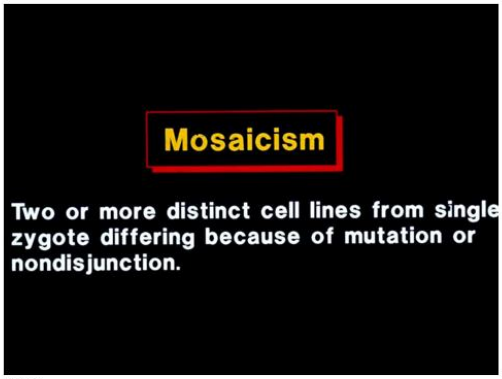
Slide 32

Slides 24-32: triploidy origins, molar pregnancy, parent-of-origin effects, and clinical findings.

7. Mosaicism and chimerism

- Mosaicism means two or more distinct cell lines in one person arising from a single zygote, usually because of a post-zygotic mutation or nondisjunction.
- Somatic mosaicism can create body-wide patches or mixed cell populations, depending on when the event happened in development.
- Chimerism comes from two genetically distinct cell lines derived from different zygotes or embryos.
- The lecture's diagrams compare mosaic development from one zygote with chimeric development from fusion of two zygotes.

Mosaicism and chimerism



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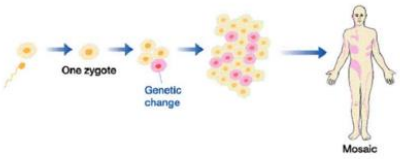

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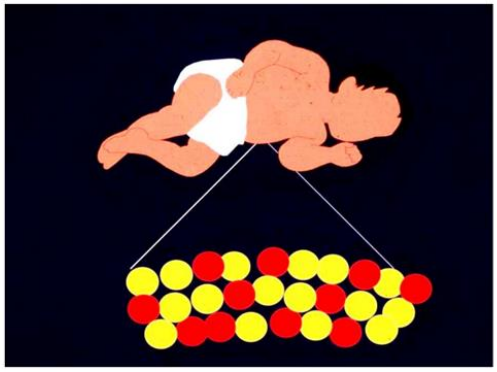

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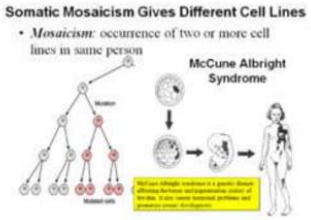

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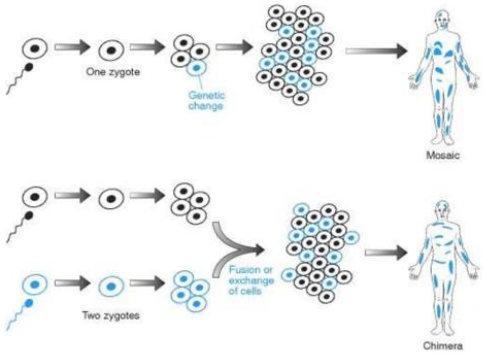

Slide 38

Slides 33-38: mosaicism, somatic mosaic patterns, and chimerism.

Thanks for using this sheet.
If you found it helpful please share it

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