Medical Genetics

Sheet: 5

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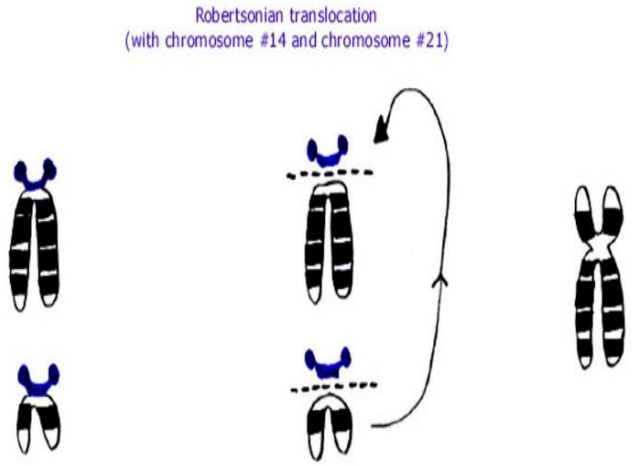
We have previously mentioned that translocations can be divided into two categories:

1) Reciprocal Translocation

2) Robertsonian Translocation



And we said that Robertsonian translocation is a special case for **acrocentric chromosomes**. This is where the long arm (q arm) of one acrocentric chromosome fuses with the q arm of another acrocentric chromosome to end up with one chromosome carrying two q arms joined together by a centromere. What about the P arms? As the cell divides, p arms are lost and will not be found in daughter cells as the q arms retain the centromeres, and if there is no centromere then this chromosome will be lost during meiosis or mitosis.

We also talked about Reciprocal translocation which involves the exchange of genetic material between nonhomologous chromosomes.

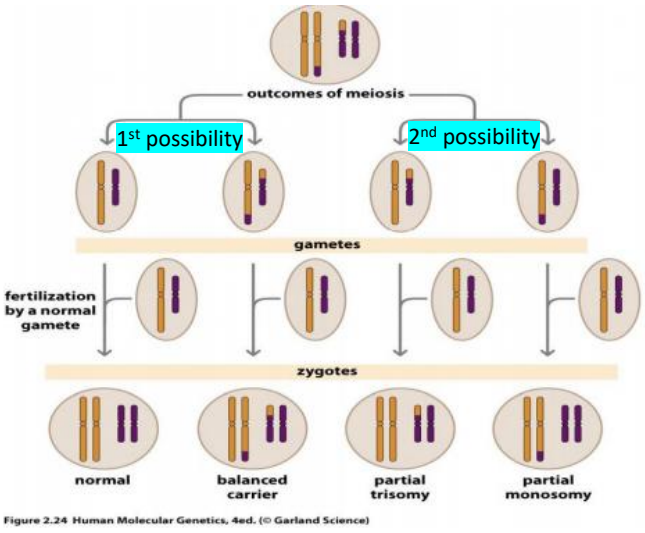
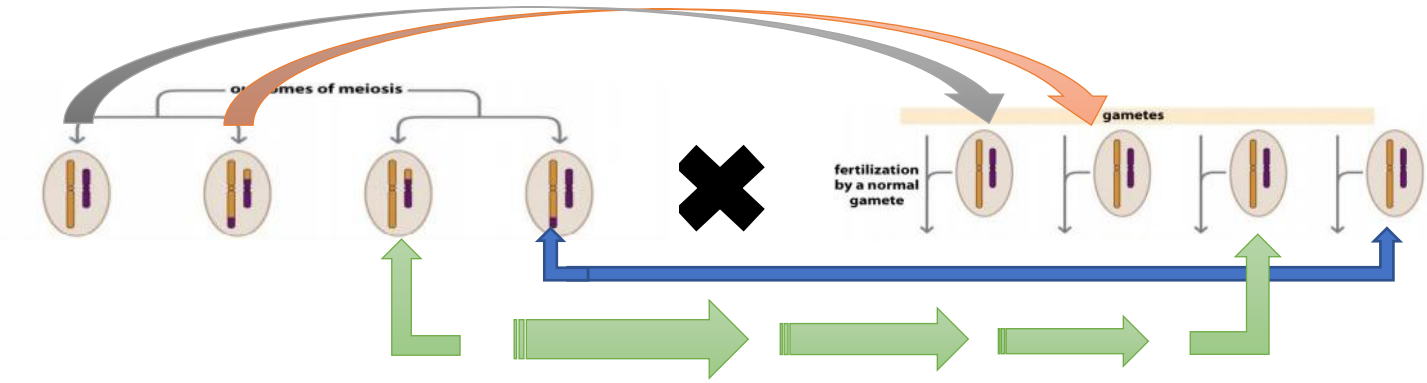


Figure 2.24 Human Molecular Genetics, 4ed. (© Garland Science)

The diagram beside shows two brown homologous chromosomes and two purple homologous chromosomes. As we can see, reciprocal translocation occurs between them as part of the brown colored chromosome fuses with the purple chromosome and vice versa. This individual is a **balanced carrier** meaning that although there was some rearrangement of the genetic material, there was no net gain or loss of the genetic material. In other words, if the overall amount of DNA does not change, then the chromosomal changes are described as “balanced” form.

The problem arises when this individual makes gametes (eggs or sperms). During meiosis, the 23 pairs of homologous chromosomes will separate so that each gamete will carry one version of each homologous chromosome. According to that, the **first possibility** involves a gamete carrying one **totally brown** colored chromosome along with another **totally purple** colored chromosome, leaving the **translocated purple** and the **translocated brown** chromosomes for the other gamete. **Another possibility** is that one gamete will randomly take one **totally brown** colored chromosome and one **translocated *purple*** chromosome, leaving behind the **totally purple** colored chromosome and the **translocated brown** chromosome for the other gamete.

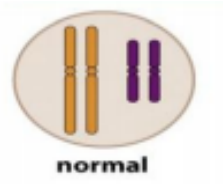
Now, when fertilization occurs with a normal gamete from the partner (normal gamete→ one total brown, and one total purple chromosome) and Since we have 4 different outcomes of meiosis (Remember! there were 4 possible gametes with different genetic material after meiosis) there will also be 4 possible zygotes post fertilization. I hope the figure below makes everything clear.



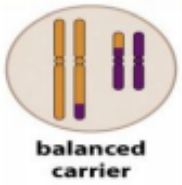
What are the 4 possible zygotes that we might have post fertilization?

As we can see in the figure above

1. The **1st zygote** that we might possibly have will carry two normal brown homologous chromosomes and two normal purple homologous chromosomes.



2. The **2nd zygote** that we might possibly have will carry a **translocated** brown chromosome with its **normal** homologue (totally brown colored) and a translocated purple with its homologue (totally purple colored)



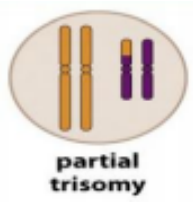
The zygote above is a balanced carrier because the chromosomes are ONLY rearranged without gaining or losing any genetic material => the brown and purple are complete, even though part of them is on the other chromosome but they're still complete.

Before moving on into the last 2 possible outcomes, I would like to make sure that we all remember what the terms "Monosomy" & "Trisomy" mean.

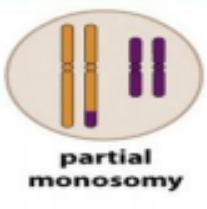
Monosomy is a form of aneuploidy (abnormal number of chromosomes in a cell) with the presence of only one chromosome from a pair. The monosomy is said to be **full** when a whole chromosome has been lost, or **partial** when the loss concerns a portion of a chromosome.

Trisomy is a form of aneuploidy with the presence of three copies of a chromosome rather than the normal two. The trisomy is said to be **full/primary** when a whole chromosome has been copied(added), or **partial** when we have an extra copy of a part of a chromosome.

3. The **3rd zygote** that we might possibly have will carry two normal **brown** homologous chromosomes. Notice here that part of the purple chromosome is missing and is being replaced by an extra copy of part of the brown chromosome. So, regarding the brown chromosome, we have an extra copy of a part of it and since the extra copy is not a whole/complete brown chromosome but rather part of the brown chromosome, then we call it **partial** trisomy for the **brown chromosome.** We can also call it partial monosomy for the **purple chromosome,** as a portion of the purple chromosome is lost.



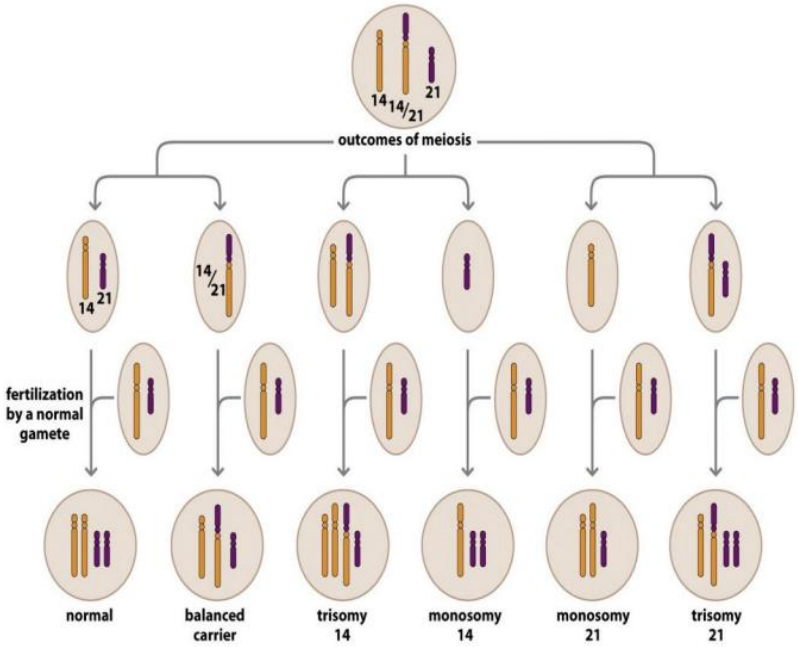
4. The **4th zygote** that we might possibly have will carry two normal **purple** homologous chromosomes. Notice that in this case the opposite happens as part of the brown chromosome is missing and is being replaced by an extra copy of part of the purple chromosome. So, regarding the brown chromosome, we have lost a part of it and since the loss does not involve a whole/complete brown chromosome but rather part of the brown chromosome, then we call it **partial** monosomy for the **brown chromosome.** We can also call it partial trisomy for the **purple chromosome,** as we have an extra copy of a part of the purple chromosome.



Note: in cases 3 and 4, there was net gain and loss of the genetic material.

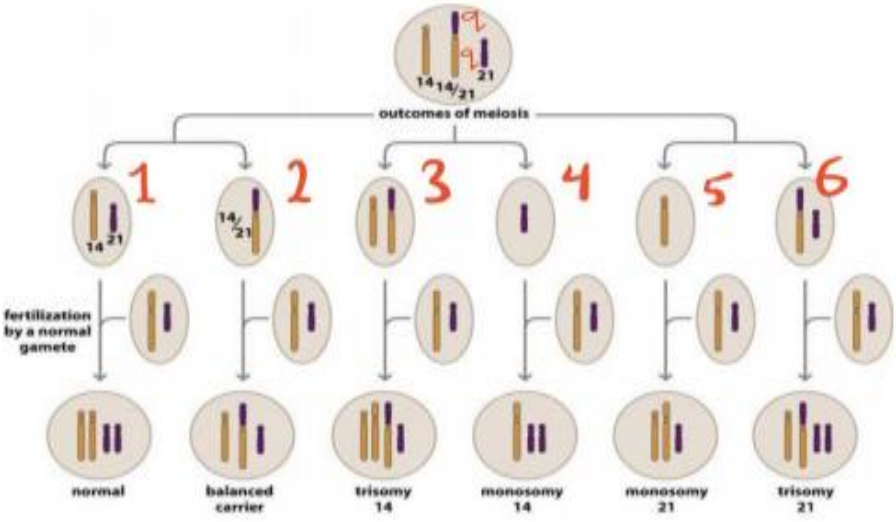
Now, we will talk about **Robertsonian translocation** (you can go back to the definition mentioned in the first paragraph)

The figure beside shows the possible outcomes of meiosis in a carrier of a balanced Robertsonian translocation.



This individual has 2 acrocentric chromosomes (**14** and **21**) and a dicentric chromosome (translocated chromosome) containing the q arms of chromosomes 14 & 21 (their p arms are lost). Genetically speaking, this individual is not missing anything (He/She is normal). But why don't we care about the p arms of acrocentric chromosomes that were lost? Simply because all the p arms of all acrocentric chromosomes carry the same genetic material which is ribosomal DNA and some heterochromatin noncoding DNA (Satellite DNA).

Notice the (**6**) possible combinations of gametes a balanced carrier of Robertsonian translocation can produce. The outcome is based on these combinations.



1. Fertilization of gamete #***1*** by another normal gamete gives a normal zygote.
2. Fertilization of gamete #***2*** by another normal gamete gives a balanced carrier (phenotypically normal) (identical to the parent cell)
3. Fertilization of gamete #***3*** by another normal gamete gives a full trisomy 14. (**lethal**)
4. Fertilization of gamete #***4*** by another normal gamete gives a full monosomy 14. (**lethal**)
5. Fertilization of gamete #***5*** by another normal gamete gives a full monosomy 21. (**lethal**)
6. Fertilization of gamete #***6*** by another normal gamete gives a full trisomy 21. (**viable**)

Notes:

1- The most common types of autosomal trisomy that survive to birth in humans are:

- **Trisomy 21** (**Down syndrome**)
- **Trisomy 18** (**Edwards syndrome**)
- **Trisomy 13** (**Patau syndrome**)

2- The only viable monosomy is Turner Syndrome.

So, we can conclude that a carrier of a balanced Robertsonian translocation can produce gametes that after fertilization can 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.

Polyploidy/euploidy: (A) ***Triploidy***, not to be confused with trisomy, is three sets of chromosomes (3n), a total of 69 chromosomes (23*3).

Causes of **triploidies**:

- **66**% of triploidies are due to two sperms by mistake fertilizing one egg.
- **10**% of triploidies are due to one egg by mistake carrying two sets of chromosomes (2n) with one set of chromosomes being contributed by the sperm.
- **25**% of triploidies is due to a sperm by mistake carrying two sets of chromosomes fertilizing an egg carrying a haploid (1n).

(B) ***Tetraploidy*** involves normal fertilization and fusion of gametes to give a normal zygote (2n). Subsequently, however, Tetraploidy arises by **endomitosis** when DNA replicates (instead of 2n we have 2n+2n) without subsequent cell division (cytoplasm, in this case, does not divide), so we end up with ***one*** cell carrying ***4n***. BOTH cases are not viable.

What are the consequences or clinical outcomes of having three (3n) or four sets (4n) of chromosomes?

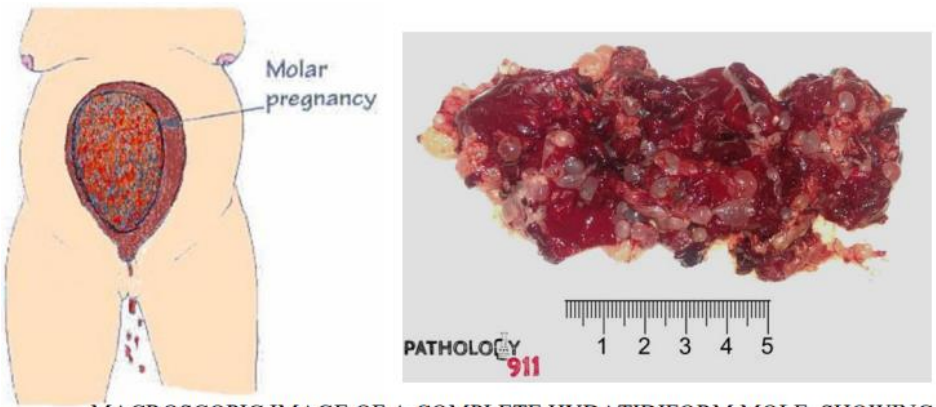
- If the **Triploidy** is caused by the maternal **egg**, then we call it a **maternal Triploidy** (also digyny). In this case, the egg contains the extra set of chromosomes.
- If the **Triploidy** is due to paternal **sperm**, then we call it a **paternal Triploidy** (also diandry or dispermy). Here the sperm contains the extra set of chromosomes.

Synopsis (mentioned in slides)

- 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.

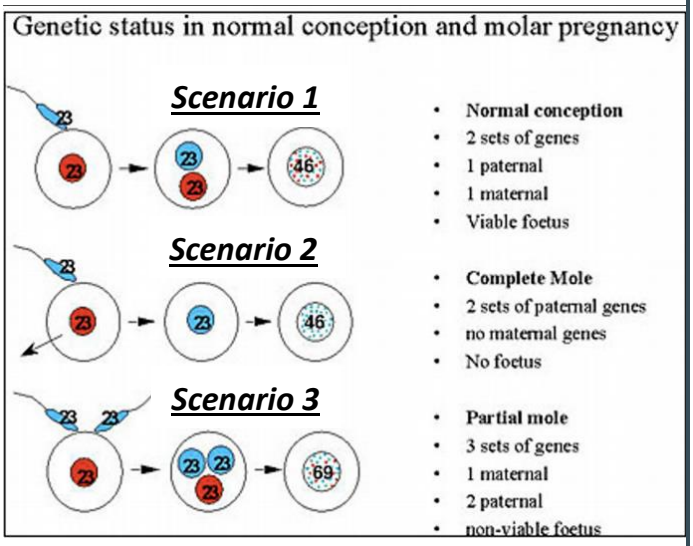
Molar pregnancy

The embryo in this pregnancy lacks **all embryonic tissues** and has an abnormal **benign** growth (it is not cancerous). The uterus is full of this abnormal tissue. The diagram below shows the tissue removed by the surgeon. As you can see, it has a characteristic grape-like appearance called "**Bunches of grapes**" appearance, this is a **complete molar pregnancy** with no embryonic tissue at all.



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

Genetic status in normal conception and molar pregnancy



Scenario 1: we have 23 chromosomes from each parent that would fertilize each other => we get the zygote. In this scenario, the fetus is viable.

Scenario 2: the sperm gets into the egg and by mistake throws out the maternal DNA in the egg leaving the egg with the paternal chromosomes only. Cell in oocyte (immature egg) carries only paternal DNA and the maternal DNA is absent. The cell, which has 23 chromosomes, in this case undergoes a process known as **chromosomal rescue.**

Chromosomal rescue: A mechanism that takes place when there are 23 chromosomes instead of 46 chromosomes. To cope with this situation, the cell replicates its DNA to end up with 46 chromosomes (all of which are paternal), with no maternal genes. This is considered a complete molar pregnancy, since we only have paternal genes. In this scenario, there is **no fetus**.

Scenario 3: two sperms fertilize one egg; the zygote will contain three sets of chromosomes (3n). In this case there is a maternal contribution (one set of chromosomes from egg), so there **will be** a **fetus**, however it is **not viable** and will die during the pregnancy.

Note: Scenario 2 and 3 are abnormal and shouldn't normally happen.

Partial vs complete mole

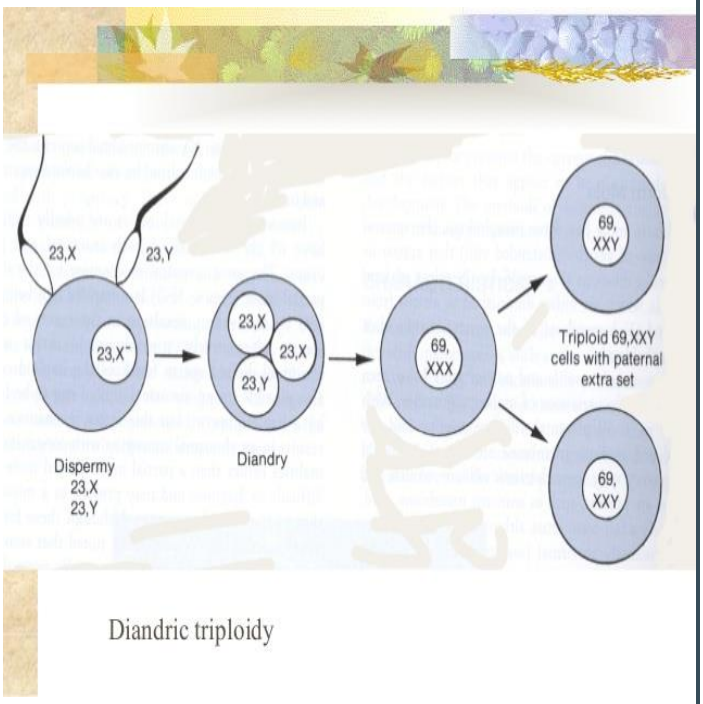
Complete mole:

- **The oocyte only carries the paternal DNA, while the maternal DNA is missing. So, we say it has somehow lost its DNA.**
- Option A: The oocyte is fertilized by one sperm and the paternal DNA reduplicates itself (*homozygous*)
- Option B: The oocyte is fertilized by two separate sperms. (*heterozygous*)
- **Karyotype: Diploid – 46 chromosomes (46XY or 46XX – the 46YYs are not viable)**
- All paternal, no maternal DNA →"Androgenetic"

Partial Mole:

- The oocyte has an intact set of maternal DNA.
- Option A: The oocyte is fertilized by one sperm and the paternal DNA reduplicates itself.
- Option B: The oocyte is fertilized by two separate sperms.
- Karyotype: triploid - 69 chromosomes (69 XXY- an extra set of paternal DNA)

Physiopathology (slides)



Diandric triploidy

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.

- 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 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.

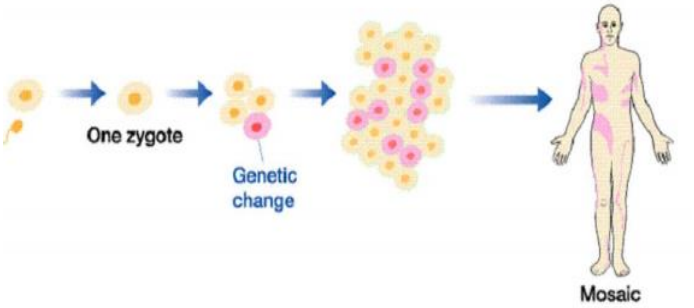
Digynic: Macrocephaly Severe intrauterine growth retardation

The professor did not go over this page, yet it is mentioned in our slides.

Mosaicism

Two or more distinct cell lines from single zygote differing because of a mutation or non-disjunction.

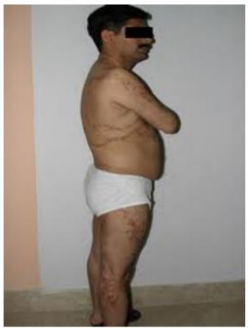
in the figure besides, a sperm fertilizes an egg to form a normal zygote (2n) with no mutations and no chromosomal abnormalities. Now the zygote will undergo massive rounds of mitosis. And as It does so, abnormal genetic changes might occur. These could be due to

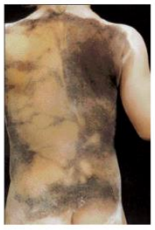


- Mistakes made by DNA polymerase during the S phase causing a sequence mutation.
- a non-disjunction taking place during anaphase.

Recall that mitosis is a type of cell division in which one cell (the mother) divides to produce two new cells (the daughters) that are genetically identical to itself. By that, we can predict what happens in the presence of a mutated (or abnormal) parental cell. Simply all its daughter cells will be mutated (will have the same abnormality) too! So, when this mutated (or abnormal) cell divides, it will result in the formation of a new population of cells in the embryo and consequently in an individual that will be different from the rest of the population. In other words, this individual carrys 2 different populations of cells (the normal cells and the mutant ones). This is called mosaic, which means an individual carrying two different population of cells (or more than one population of cells) that came from the same zygote.

This individual expresses mosaicism as the mutation took place in a population of cells but not in the other.





Chimera

Let us suppose that by chance a female has 2 eggs in her uterus. The 2 eggs are then fertilized by 2 different sperms to form 2 zygotes. Each of them will develop into an embryo to eventually end with 2 fetuses that will develop into non identical twins, this is what usually happens. But sometimes at an early stage, the embryonic cells will stick/fuse together, making one population of embryonic cells. Consequently, the individual will carry two different population of cells that originated from two different zygotes. Another possible cause includes the exchange of cells between these 2 different populations of embryonic cells. So, if we assume that the red highlighted cell joins the 2nd population, then this individual would carry cells that are identical to his non-identical twin. So in chimera we have an individual formed from 2 zygotes.