Genetics & molecular biology

◉ Sheet ○ Slide

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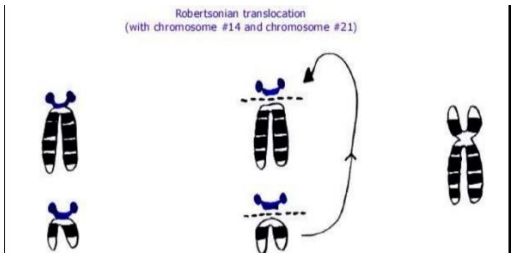
Translocations can be divided into two categories:

1)**Reciprocal Translocation**

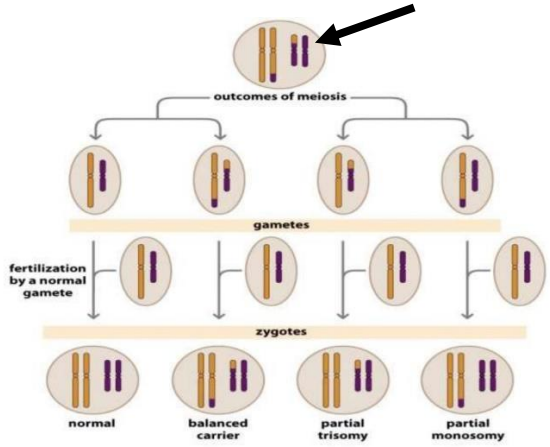
2)**Robertsonian Translocation**

Robertsonian translocation is specific to acrocentric chromosomes, where the q arm of one acrocentric chromosome will fuse with the q arm of the other acrocentric chromosome so we will end up with a chromosome carrying two q arms each from one acrocentric chromosome, between the two q arms is the centromere. As the cell divides the p arms are lost and will not be found in the daughter cells since they don't carry a centromere.



Reciprocal translocation is the exchange of genetic material between nonhomologous chromosomes.

The following diagram shows <u>two homologous chromosomes brown and two homologous chromosomes purple, and reciprocal translocation occurs between them where some of the purple is found on the brown chromosome and some of the brown is found on purple.</u>



This individual is a **balanced carrier** meaning that although there was rearrangement of the genetic material there was no net gain or loss of the genetic material.

The problem arises when this individual makes gametes. During meosis the 23 pairs of homologous chromosomes will separate so that each gamete will carry one version of each homologous chromosome.

One possibility is that a gamete will contain one total brown and one total purple chromosome, which leaves the translocated purple and the translocated brown chromosome for the other gamete.

Another possibility is that one gamete will randomly take one total brown chromosome and one translocated purple chromosome, which leaves the normal (total) purple chromosome and the translocated brown chromosome for the other gamete.

When **fertilization** occurs with a **normal** gamete from the partner (normal gamete→one total brown, and one total purple chromosome):

- Since there were 4 possible gametes with different genetic material after meiosis, there will also be 4 possible zygotes post fertilization.

1) Normal →two normal brown homologous and two normal purple homologous chromosomes

2) Balance carrier→translocated brown chromosome with its homologue (total brown) and translocated purple with its homologue (total purple).

Note: remember that its balanced because the chromosomes are rearranged without gaining or losing genetic material = the brown and purple are complete, even though part of them is on the other chromosome but they're still complete.

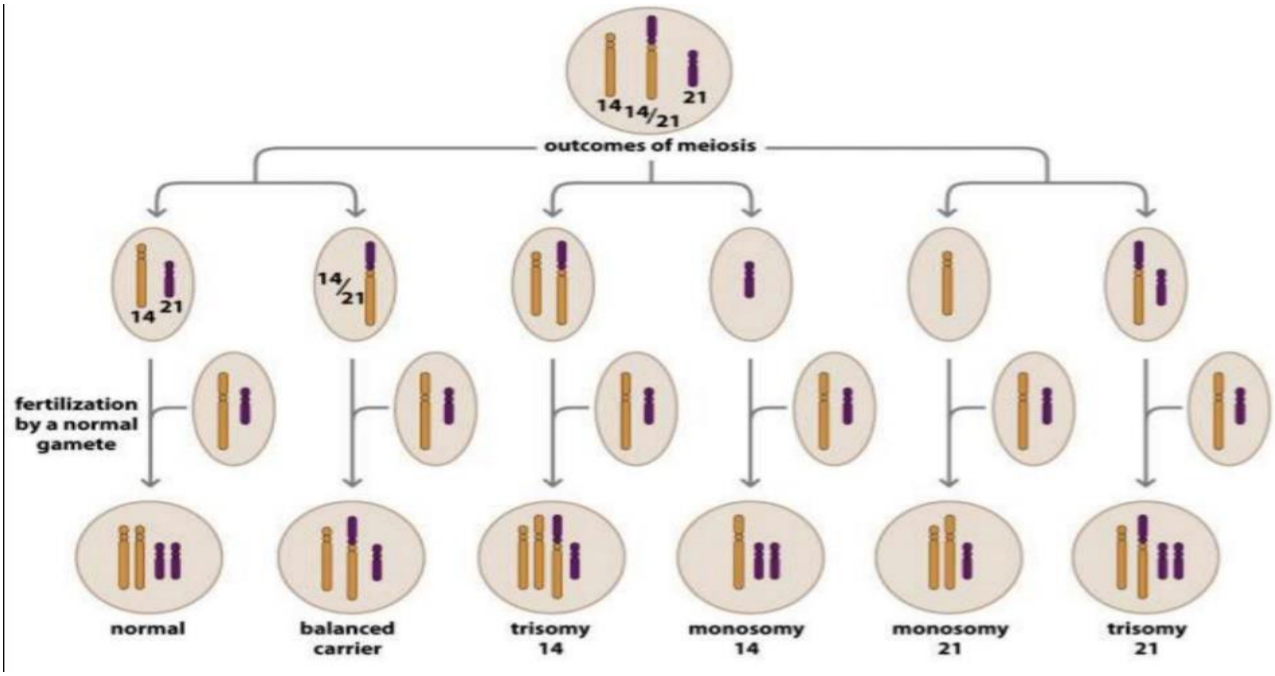
3) Partial trisomy (extra gen. mtrl. on brown)→ normal brown + normal brown, this called "disomy". AND normal purple + purple with "partial monosomy" which means that part of its p arm is missing AND an EXTRA peace of the brown on the translocated purple chromosome, this results in **partial trisomy for the brown**.

4) Partial monosomy (missing gen. mtrl. from brown)→the opposite of partial trisomy: here we have **partial monosomy for the brown** chromosome since the brown chromosome has missing genetic material.

Note: in 3 and 4, there are extra and missing genetic material at the same time = partial monosomy for one and partial trisomy for the other.

Robertsonian translocation

The following diagram shows a balanced carrier of robertsonian translocation that produces gametes and after fertilization will produce; either an entirely normal child, phenotypically normal balanced carrier, full trisomy or monosomy for one of the chromosomes involved. *(robertsonian transl: 2 acrocentric fused together at the q arms)*



The individual has the **chromosome 14, chromosome 14/21** which contains the homologue of 14 and the q arm of chromosome 21, and **chromosome 21.** This individual doesn't have any missing genetic material.

Note: we don't care about the p arms of acrocentric chromosomes since all p arms of all acrocentric chromosomes carry the same genetic material which is some ribosomal DNA and heterochromatin noncoding DNA (Satellite DNA).

Recall: The p arms are lost during mitosis and meiosis since they lack the centromere which is attached to q arms.

In gametogenesis by meiosis we will get one chromosome without its homologue in each egg or sperm.

In the figure, we can see the possible gametes produced that will then fertilize with another gamete to go back to diploid set of chromosomes !!!!*(study the figure thoroughly)*

After fertilization we would get one of the following:

1) Normal →2 normal homologous chromosomes for purple and brown

2) Balance carrier→1 brown chromosome+1 purple chromosome+1 chromosome carrying the **q arms** of the purple and brown chromosomes. The genetic material is rearranged, nevertheless this individual is normal, has 45 chromosomes.

3) Trisomy 14→ 2 brown chromosomes + an extra **q arm** of the brown chromosome *(2+extra q arm →trisomy)* +1 purple chromosome + an extra q arm for the purple chromosome. This is a trisomy for the brown chromosome.

4) Monosomy 14→in this case the gamete only contained the purple chromosome and didn't contain the homologue brown chromosome (chromosome 14), so after fertilization the zygote will have 2 purple homologous chromosome 21, and only one chromosome 14.

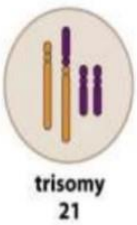
Monosomy 14 and Trisomy 14 are not viable.

5) Monosomy 21→in this case the gamete had the chromosome 21 missing so the zygote produced had 2 chromosomes 14 and one chromosome 21, thus this is monosomy 21.

Monosomy 21 is not viable.

6) Trisomy 21→the zygote contains 2 homologous purple chromosomes and a brown chromosome with its homologue, there is also an extra q arm for the purple chromosome, this is trisomy for the purple chromosome 21.

Trisomy 21 is viable.



Note: The brown chromosomes are homologous since they have the same q arm

Note: The only viable aneuploidies are Trisomy 13, 18, and 21. The only viable monosomy is turner syndrome (monosomy X). The only viable monosomy is turner syndrome.

Down syndrome: trisomy 21 Edwards syndrome: trisomy 18 Patau syndrome: trisomy13

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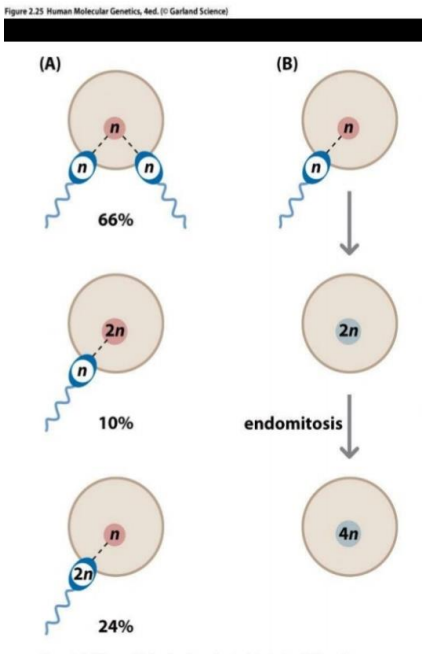
Polyploidy/aneuploidy:

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



Causes of triplodies:

- 66% of triploidies are due to two sperms by mistake fertilizing one egg
- 10% of triploidies is 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).

Tetraploidy zygote contains four sets of chromosomes(4n). At first, we have normal fertilization of the two gametes resulting in a zygote with normal set of chromosomes(2n). The zygote then undergoes **"endomitosis"→ absence of cytokenesis:** the nucleus divides similar to a typical mitotic division however unlike normal mitosis cytokinesis (division of cytoplasm) doesn't take place so we end up with two nuclei in the cell each having 2n, in total the cell has 4n four sets of chromosomes**. Tetraploidy is not viable.**

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

If the triploidy is caused by maternal egg we call it a **maternal triploidy** (also digyny), the egg contains the extra set of chromosomes.

If the triploidy is due to paternal sperm we call it a **paternal triploidy** (also diandry or dispermy), sperm contains the extra set of chromosomes.

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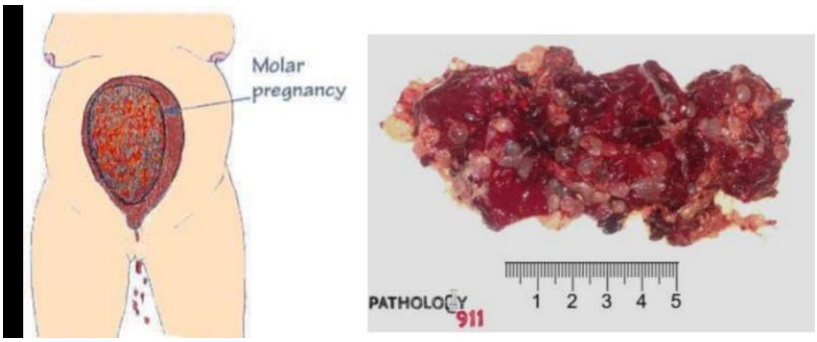
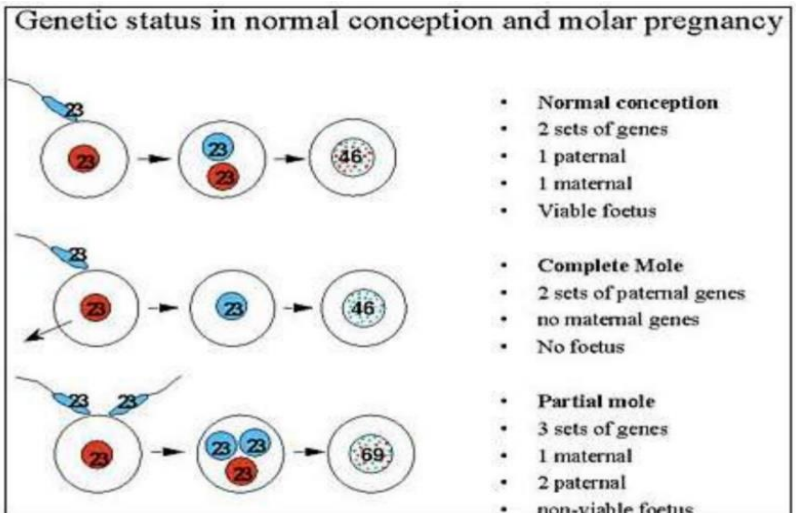
Molar pregnancy

The embryo in this pregnancy lacks all embryonic tissue and has an abnormal growth, however it's not cancerous, it's a benign growth. The uterus is full of this abnormal tissue, when the surgeon excises it this is the tissue removed and as you can see it has a grape-like appearance called Bunches of grapes appearance, this is a **complete** molar pregnancy with no embryonic tissue at all.



Genetic status in normal conception and molar pregnancy



- Normal conception:

23 chromosome from each parent, gamete fertilization results in 46 chromosomes

zygote → viable fetus

!!!!*(study the figure thoroughly)*

What might abnormally happen but shouldn't in this process(fertilization)?

- **Complete mole**: the sperm will throw 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 solution available for the cell is chromosomal rescue.

Chromosomal rescue

A mechanism that happens when there are 23 chromosomes instead of the normal no. 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.**

Since we only have paternal genes and no maternal genes this is a **complete mole** pregnancy and there is **no viable foetus**.

In this scenario, the oocyte DNA (maternal) is lost by an unknown mechanism (empty of DNA), then;

Option A: it's fertilized by one sperm, and the sperm chromosomes replicate with the help of DNA polymerase and here all the DNA is **homozygous** since homologous chromosomes are used as a template.

Option B: it will be fertilized by two sperms and the maternal nucleus is kicked out. The DNA sequence from the father will be **heterozygous.**

So, the zygote is 46 diploid cell all genetic material is paternal, because maternal DNA is removed from oocyte.

→ 46 XX,46XY are viable in complete mole

→ 46YY is not viable in complete mole

All paternal, no maternal DNA →**"Androgenic"**

- **Partial mole:** 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 chromosome from egg) so there will be a foetus however it is not viable, and will die during the pregnancy. In partial mole, the oocyte contains an intact set of maternal DNA, there are two pathways for the occurrence of the partial mole:

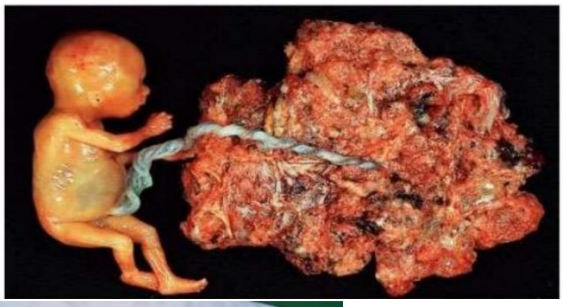
  Option A: oocyte is fertilized by one sperm and the paternal DNA reduplicates itself.

  Option B: The oocyte is fertilized by two separate sperms

  No matter what path was chosen in partial mole we must end up with **69 chromosomes(triploid).**

Below is an example of partial mole, where the maternal DNA is contributed into the zygote.

Partial mole



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)

Good Luck