Genetics
& Cell biology

◉Sheet ○Slides

Number

9

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Note: everything in the slides is included.

Genomic imprinting (imprinting = silencing)

During the formation of the eggs and sperms, the egg or the sperm independently will decide that out of the 22,000 protein-coding genes, it will imprint a couple of hundreds of genes. This is done by ***methylation*** of those genes. So the sperm will choose around 200 genes and methylate them rendering them ***silent (not expressed).*** And the egg will choose a different group of genes and will methylate them, therefore silencing them. This is called as imprinting.

Note: all males have the same 200 silenced genes, and all females have the same 200 silenced genes,, but the silenced genes of males differ from those of females.

We have homologous chromosomes in the nucleus; one from each parent, the imprinted genes on each one are known (not a random process in the gamete). So:

- For a few mammalian traits, the phenotype depends on which parent passed along the alleles for those traits
- Such variation in phenotype is due to **genomic imprinting.**
- Genomic imprinting involves the silencing of certain genes that are "stamped" with an imprint during gamete production

***An example of imprinting:

The Igf2 gene is related to the growth of the mouse. For the paternal chromosome, the allele for Igf2 gene is expressed, while the maternal allele is imprinted (so the gene is expressed only from the paternal allele and this is the **normal** situation). If there is a mutation in the paternal allele, would you expect to have a clinical outcome? The answer is yes, because it is the only one being expressed, while a mutation in the maternal allele is of no clinical importance; because the gene is already hypermethylated and not being expressed.

Notes:

- It appears that imprinting is the result of the methylation (addition of $-CH_3$) of ***cytosine*** nucleotides
- Genomic imprinting is thought to affect only a small fraction of mammalian genes
- Most imprinted genes are critical for embryonic development.
- **Definition of imprinting**: the differential expression of a gene depending on the sex of the parent from which it is inherited (i.e., the parental origin of the gene).

- **Implications**:
- Implies that there is a critical or sensitive period during development (i.e. during or before gametogenesis) during which the genetic information is marked or imprinted in order to permit differential expression based on parental origin.
- The imprint must persist stably through DNA replication and cell division in the body cells.
- The imprint must be capable of affecting gene expression (i.e. turning genes on or off).
- Imprinting is not a permanent alteration since it must be erased in the germ cell line of every individual so that new imprinting may be introduced.

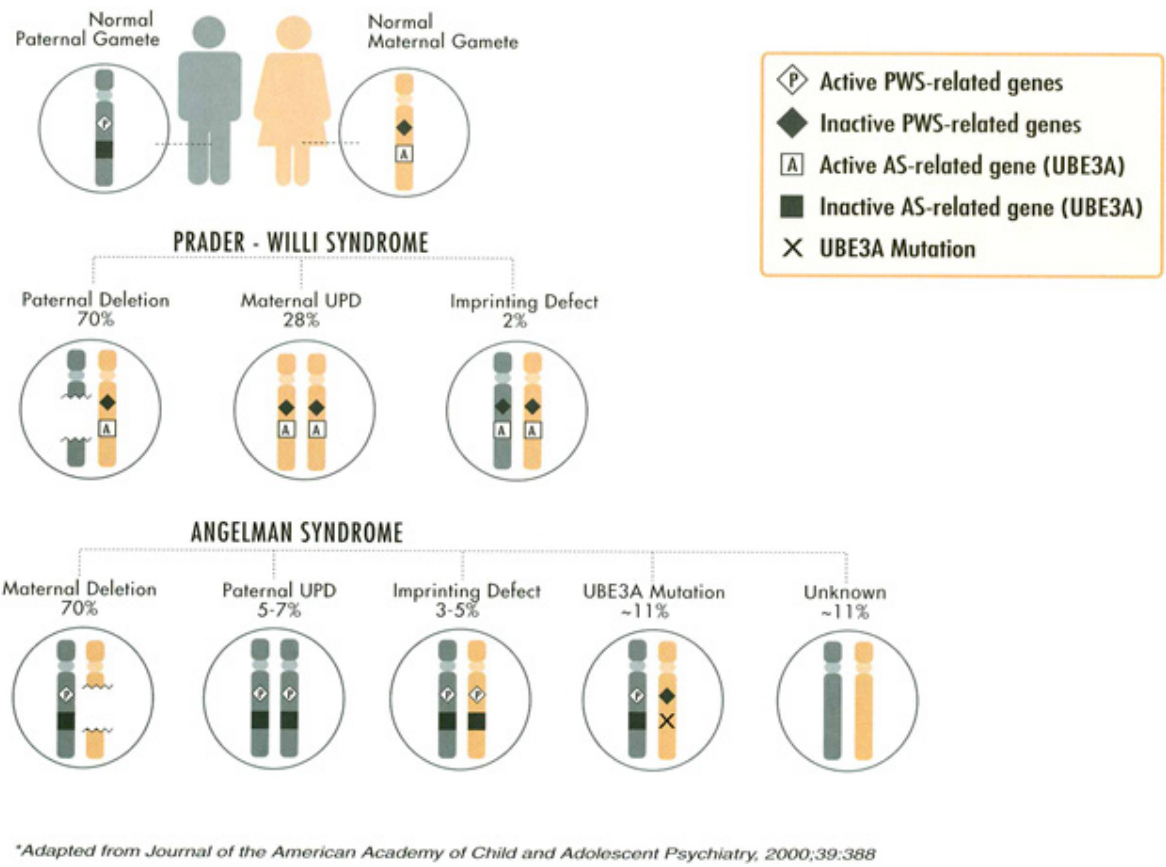
Clinical importance:

There are two diseases: Prader-Willi Syndrome and Angelman syndrome that are related to imprinting in humans. Both diseases are caused by deletion of the same region on the chromosome (deletion of chromosome15,q arm, regions 11-13) but the clinical manifestations are ***different*** between the two diseases (two distinct diseases):

➔ Prader-Willi syndrome: obesity, voracious appetite, and mental retardation
➔ Angelman: gait ataxia, smiling faces and happy demeanor, and mental retardation

So if this region (15q 11-13) is deleted-same size of deletion-, sometimes it results in Prader-Willi Syndrome, and sometimes in ANGELMAN Syndrome, but why? You should know that this region contains two sets of genes: Prader-Willi genes and Angelman genes.

The below picture is very important (it shows everything). It shows the father and the mother under normal conditions; on 15q 11-13, the genes for Prader-Willi are expressed in the paternal chromosome, while imprinted in the maternal chromosome. Next to those genes (in the same region) exist the genes for Angelman, which are expressed in the maternal chromosome and silent in the paternal chromosome. If this region (15q 11-13) is deleted from the **father** (the ***paternal*** chromosome that will go in the sperm does not contain this region so both sets of genes are deleted-lost-), this means that for those two genes (PRADER-WILLI and Angelman), you have the following:



*Adapted from Journal of the American Academy of Child and Adolescent Psychiatry, 2000;39:388

For Prader-Willi: PATERNAL→deleted , MATERNAL→ silenced (imprinted)

For Angelman: PATERNAL→deleted , MATERNAL→ expressed

The result is **no** expression at all of Prader-Willi gene (paternally-deleted and maternally-silenced), and this causes ***Prader-Willi Syndrome.***

If this region is deleted ***maternally***, the result will be:

Prader-Willi genes: PATERNAL→expressed , MATERNAL→ deleted

Angelman genes: PATERNAL→imprinted , MATERNAL→deleted

So the result is no expression of the Angelman genes (paternally-silenced and maternally-deleted), resulting in ***Angelman Syndrome***.

So deleting the paternal chromosome→PRADER-WILLI SYNDROME and deleting the maternal chromosome→Angelman Syndrome.

-This explains around 70% of cases of PRADER-WILLI SYNDROME and 70% of Angelman cases. So what about the other cases?

Sometimes happens, that both copies of chromosome15 in the zygote are from the same parent (by mistake (non-disjunction), mentioned further ahead). In the case that both 15 chromosomes are **maternal** (while missing the paternal chromosome), this means that both

alleles for Prader-Willi genes are imprinted while expressing Angelman genes. **This causes PRADER-WILLI SYNDROME**, and we say it is caused by maternal UPD (uniparental disomy- Uniparental = one parent, disomy= two chromosomes-). This case accounts for 28% of Prader-Willi Syndrome cases.

The opposite can also occur (**Paternal UPD**; having two paternal copies of chromosome 15). This means expression of Prader-Willi genes and imprinting Angelman genes paternally while missing Angelman genes (that should be normally present in the maternal copy). **This causes Angelman Syndrome** and accounts for about 5-7% of cases of Angelman Syndrome.

Sometimes the paternal and maternal chromosomes are present, but the sperm made a mistake (by imprinting Prader-Willi genes and expressing the Angelman genes, and this is called as imprinting defect). Now both copies of Prader-Willi genes (paternal and maternal) are imprinted→ Prader-Willi Syndrome (2% of cases).

If the imprinting defect is maternal (maternal chromosome15 has imprinted Angelman and expressed Prader-Willi genes), then this will cause Angelman Syndrome (11% of cases).

Note: other cases of AS, the cause is unknown.
A single gene mutation in the UBE3A gene causes imprint defect.

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Some patients experience retinal damage, which causes *retinitis pigmentosa* (progressive deterioration in the retina. At first, patients experience night blindness, then they start losing peripheral vision and they just have central vision -it's like looking in a tube or a tunnel. With time, more deterioration leads to full vision loss). It can be caused by mitochondrial DNA mutations.

Mitochondrial DNA is inherited maternally, because the cytoplasm comes from the egg.

There are many genes that are on the nuclear chromosomes, but also the mitochondria carry their own DNA (because as we think, in evolution they were as separate prokaryotes). So mitochondria have their own DNA, which is circular. In addition, they have their own ribosomes, which are prokaryotic not eukaryotic ribosomes. Many genes on mitochondrial DNA are expressing proteins that are related to the electron transport chain and oxidative phosphorylation and ATP production. So a mutation in these genes→ shortage of ATP. Tissues with high need for ATP (i.e. *neural tissue and muscle tissue*) will have the worst outcome (the first to be affected).

Another disease caused by mutated mitochondrial DNA is ***leber congenital amaurosis,*** which leads to optic nerve atrophy due to missing surplus of ATP (shortage of ATP). These patients, if we sequence their nuclear DNA, we will find nothing wrong (problem is in Mitochondria).

Mitochondrial myopathy→ muscle weakness due to a mutation in the mitochondrial genes.

The extranuclear DNA might have a clinical consequence especially in muscles and nerves

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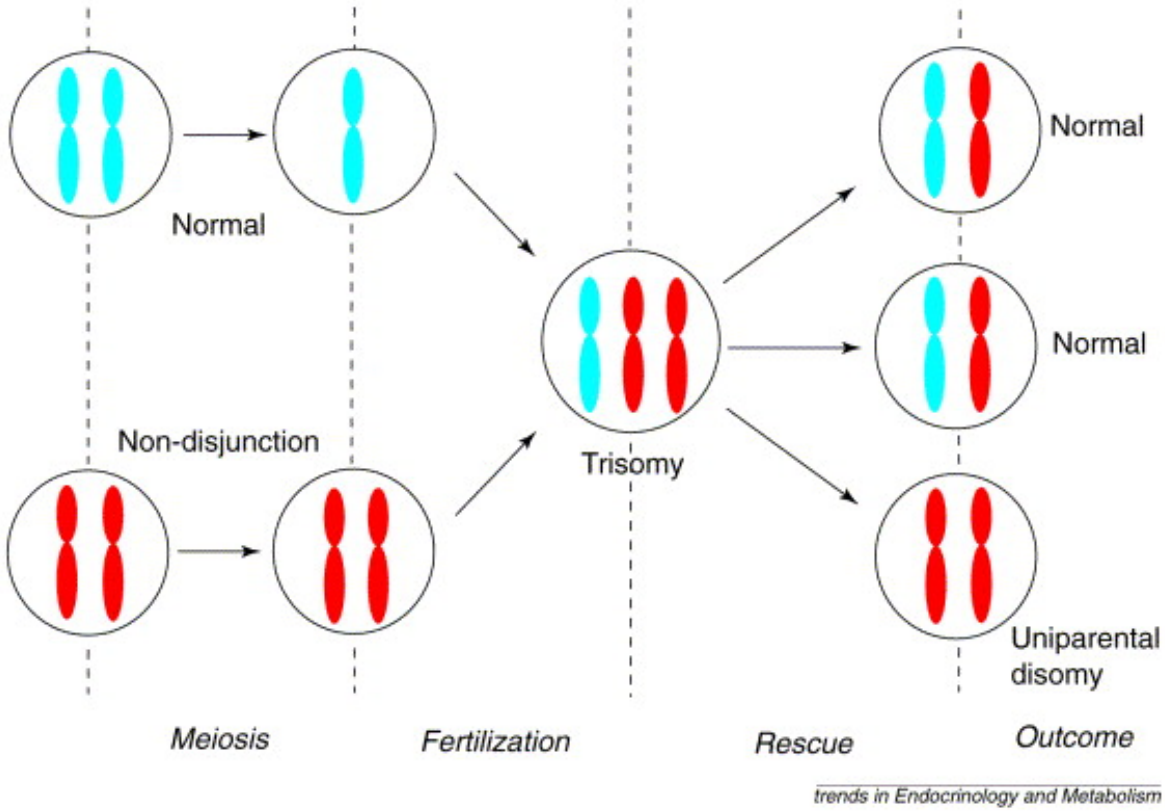

We have a diploid cell (primordial germ cell, 2n) that produces gametes (1n) by meiosis. Sometimes something wrong would happen, like non-disjunction resulting in trisomy (extra chromosome). The cell (zygote) knows something is wrong (this does not always happen) and tries to rescue the situation. It doesn't always succeed but sometimes it does. In order to rescue a trisomy, one of the solutions is to remove the extra chromosome (to yield 2 chromosomes instead of 2). Now look to the picture above, if the rescue involves deleting the green chromosome, we'll end up with two chromosomes from the same parent, and this is known as uniparental disomy. The problem with UPD is the imprinting issue (remember: its one of the causes of Prader-wilii and Angelamn syndromes) . But if the rescue involves deleting one of the red chromosomes, it will yield a better situation.

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Let us take this scenario:

A normal sperm fertilizes a normal egg to yield a zygote, which will undergo massive rounds of mitotic divisions. During mitosis, one of two abnormal scenarios might happen:
1- A mutation occurs during the S phase (DNA replication).

2- Non-disjunction (2 daughter cells carrying trisomy and monosomy).
So the mutation/lesion could be on the genetic level or on the chromosomal level. The cell that harbours this lesion –assuming that this lesion is not fatal to it- will continue undergoing mitosis, resulting in a population of cells all having this abnormal lesion. The individual (the organism that will finally develop) is carrying two populations of cells: one mutated and one normal (resulted from normal cells undergoing mitosis) even though this individual came from one zygote. This is known as ***mosaic*** individual.

*** A Down Syndrome patient that does not have all the symptoms of Down Syndrome (or not as severe) could be caused by being mosaic→ not all of his/her cells carry trisomy 21, due to non-disjunction occurring at a later stage rather than being at the time of gamete formation. So logically, the clinical features of 100% cells with trisomy 21 will be more severe than 50% of the cells having trisomy 21, and so on.

*** DNA sequencing for these individuals: assume an individual with Huntington's disease (AD) and we took blood samples from both parents and sequence for the mutation and there is no mutation! This is probably caused by a *de novo* mutation (acquired not inherited) ***OR*** the mutation developed in the cell that is going to develop into the sex organs (in one of the parents). It is like having the population of cells in the father's testes having the mutation while all of his body constitutes another population of cells which are normal, thus a blood sample reveals nothing wrong (because it was taken from the normal population).

Mosaic→ two populations of cells coming from one zygote.

Chimera→two populations of cells coming from two zygotes.

There are reports of individuals that come from two zygotes building one body resulting in a chimera. It is like one zygote makes the upper limb and another one makes the lower limb in the same individual. The consequence is the same –two populations of cells.

NOTES: 1- When fertilization of 2 eggs occur (having 2 zygotes), what typically happens is the development of non-identical twin, but a chimera scenario may also occur if these two zygotes condense together.
2- No fusion occurs between the 2 zygotes, so the individual is **2n**.
3- These individuals may develop Auto-immune diseases due to different antigens in each population (but unlikely due to the fact that the parents are the same).
4- If neither one of the 2 zygotes have any abnormality (e.g. mutation), ***no clinical features will manifest.***

The End