Medical Genetics

Sheet: 10 – Genomic Imprinting

Writer: Mohammed Bushnaq

Scientific: Mohammed Nihad

Final: Mothana Olimat

Doctor: Bilal Azab

To resume our discussion about Huntington's disease from the last lecture:

Huntington's disease is caused by a repeat expansion occurring in HD gene on chromosome 4 and has a variable age of onset, it can start as early as twenty or as late as sixty. If the patient already had children before the clinical features appear (late age of onset), his children have a 50% chance to develop the disease. And if they develop the disease, we expect that they will develop it earlier in life with more severe clinical features, and this is anticipation.

Remember that repeat expansion in Huntington's occur at coding region level but Fragile x-syndrome at non-coding (regulatory) level.

Genomic Imprinting

During formation of eggs and sperms we have around 22,000 protein encoding genes, around a couple of hundred of them will be methylated (Silenced by addition of –CH3 to cytosine nucleotides) and the genes that sperms methylate differ from the genes that eggs methylate, and these genes are well known.

- Definition: 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).

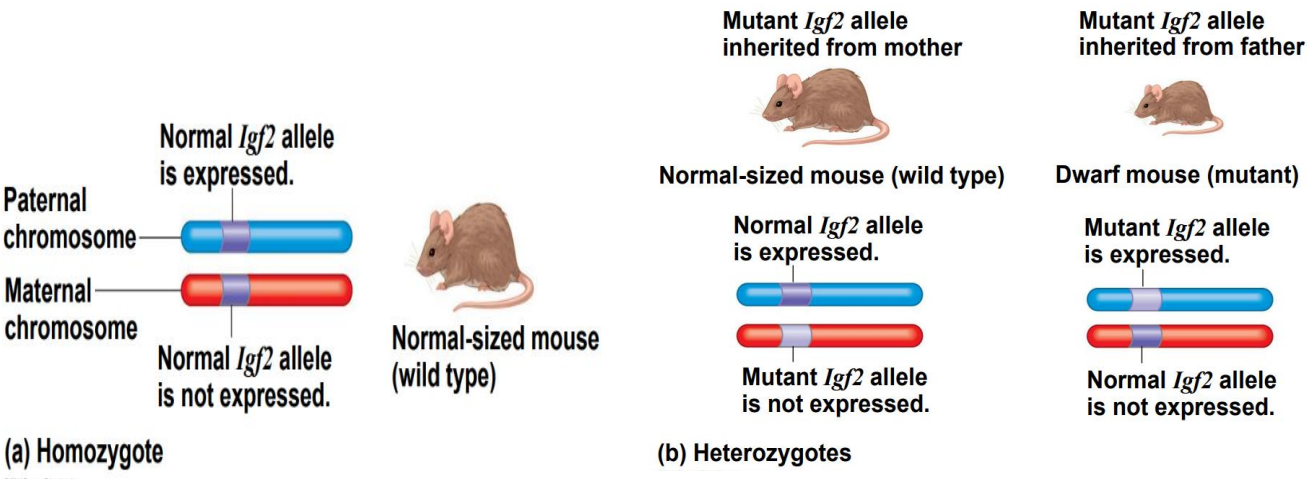
For a few mammalian traits, the phenotype depends on which parent passed along the alleles for those traits, such variation in phenotype is called genomic imprinting

Genomic imprinting involves the silencing of certain genes that are "stamped" with an imprint during gamete production which will eventually affect the phenotype.

Examples:

Igf2 gene is normally silenced in the egg (methylated) but not in the sperm (not methylated), so the only allele that can express this gene will be only the paternal one.

NOTE THAT any mutation in the maternal allele will not affect the clinical picture (simply because it's a silenced gene), but a mutation in the paternal will affect the clinical picture of the mouse.



Implications:

A. 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.
B. The imprint must persist stably through DNA replication and cell division in the body cells.
C. The imprint must be capable of affecting gene expression (i.e. turning genes on or off).
D. 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.

Most imprinted genes are critical for embryonic development.

We are going to discuss two syndromes :

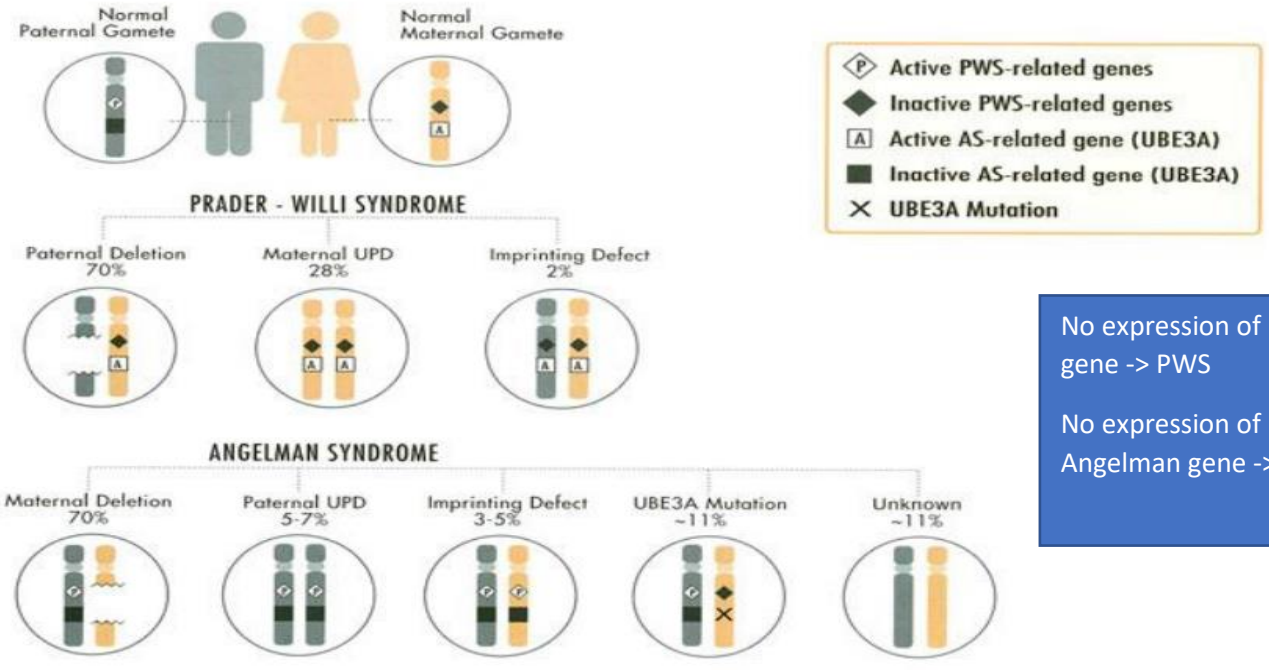
A- Prader-Willi syndrome is characterized by obesity, voracious appetite, and mental

Retardation

B- Angelman syndrome is characterized by gait ataxia, smiling facies and happy demeanor, and mental retardation and we call it happy puppet syndrome.

Both syndromes are due to deletion of 15q11-13, the phenotype will be one of these two syndromes, BUT HOW the same deletion will cause either of these two syndromes???

Normally maternal gametes have imprinted form of Prader-Willi related gene and unimprinted form of Angelman related gene, paternal gametes have the opposite (***P***aternal gametes express the ***P***rader-Willi gene, the ***MA***ternal gametes express the Angel***MA***n)



No expression of PW gene -> PWS

No expression of Angelman gene ->AMS

Simply we have unimprinted (expressed) Prader-Willi related gene from our father, so if it was **deleted**, we will have Prader-Willi syndrome. Conversely, we have unimprinted Angelman related gene from our mother, so if it was **deleted**, we will have Angelman syndrome, and this is what happens in about 70% of the cases.

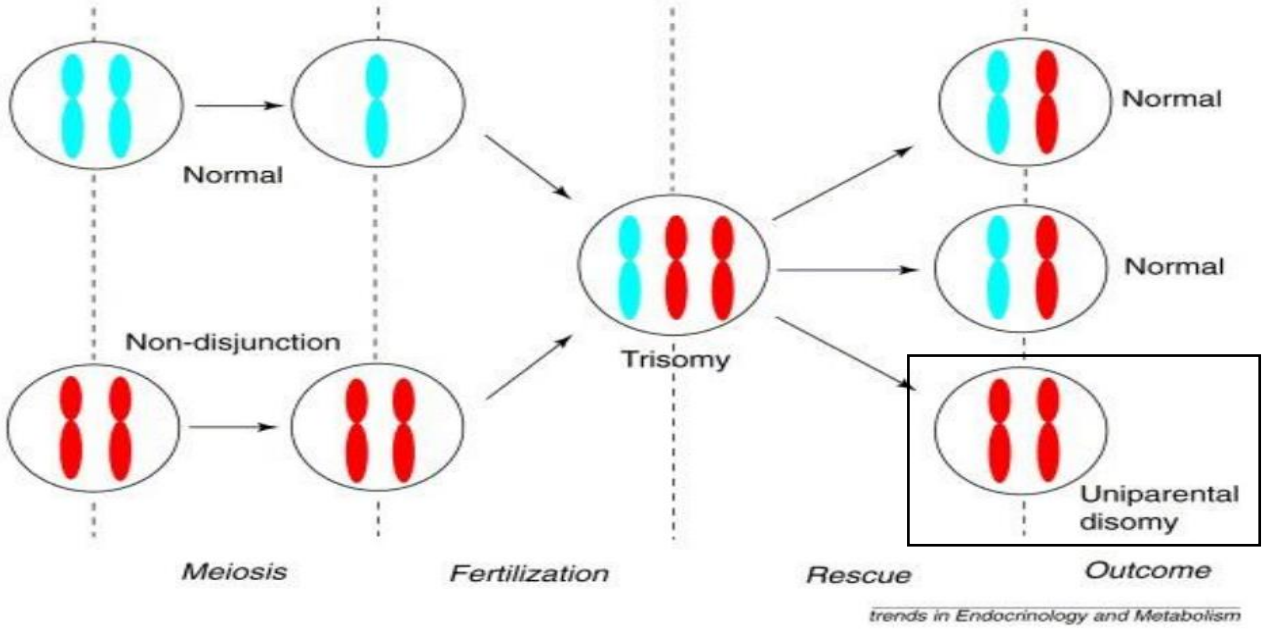
Some cases happen due to **imprinting defects** such as imprinting Prader-Willi related gene and expressing Angelman related gene in the paternal chromosome and this causes Prader-Willi syndrome or imprinting Angelman related gene and expressing Prader-Willi related gene in the maternal chromosome causing Angelman syndrome.

We have something called **uniparental disomy** (**UPD**) which means that we have both chromosomes coming from our father or from our mother. If both come from our mother, then we are missing Prader-Willi related gene so we will develop Prader-Willi syndrome. And if both come from our father, then we don't have Angelman related gene so we will develop Angelman syndrome.

Now how does UPD happen? Remember trisomy that results from a non-disjunction?

Here we have 2 options, either this extra chromosome will remain in the zygote (leading to trisomy) or the zygote will try to ***rescue*** the situation by eliminating the extra chromosome. By mistake it may delete the chromosome that came alone from one parent and keep the 2 chromosomes that came from the other parent and then we will get two copies from the same parent for the same chromosome in that zygote → **UPD**.

- Some cases of PWS (about 30%) have been attributed to maternal uniparental disomy and some cases of AS (about 5%) have been attributed to paternal uniparental disomy. About 10-15% of cases of AS are caused by a single gene mutation in the UBE3A gene. Other causes of PWS and AS include defects in the imprinting center, chromosomal translocation within the PWS/AS critical region, and unknown cause.



Let us think of ourselves as humans, and we are talking about Angelman related gene; normally we get 2 copies for this gene, paternal and maternal, and the maternal copy isn't imprinted (expressed). You may think that when a male forms his gametes half of them will carry the silenced (imprinted) copy from the male's father and the other half

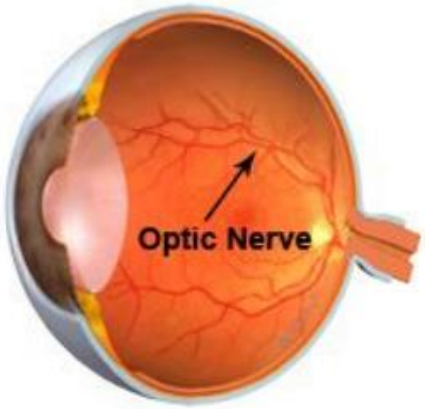
will carry the unimprinted (expressed) copy from the male's mother, but this doesn't happen. What really happens is that during the formation of gametes they remove the imprinting which means now the 2 copies of the gene are not methylated (as if they're both expressed) and then there will be reprograming. So we first thought that we have 2 patterns for the gene in the gametes either imprinted Angelman gene from the father or non-imprinted from the mother BUT actually we have 1 pattern of this gene in the gametes: which is that all aren't imprinted in the female gametes and imprinted in the male gametes. In other words, after the reprogramming (removal of imprintation) gametes from a female will all remain unimprinted -for Angelman related gene- and the gametes from a male will all get imprinted again.

Inheritance of Organelle Genes

Extranuclear genes (or cytoplasmic genes) are found in the Mitochondria.

Extranuclear genes are inherited maternally because the zygote's cytoplasm comes from the egg (the sperm only contributes with its Nuclear genes)

Some defects in mitochondrial genes prevent cells from making enough ATP and result in diseases that affect the muscular and nervous systems – For example, mitochondrial myopathy (myopathy is a muscular disease) and Leber's hereditary optic neuropathy (damage to nerves).



Best of Luck