University of Jordan
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GENETICS & Molecular Biology

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Subject: Single Gene Disorders (sex chromosomes and non-traditional inheritance)

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Last lecture we talked about single gene disorders, in this lecture we will start with non-mendelian single gene disorders(Sex chromosomes &non-traditional inheritance).

●**Lyonization**: it's a *random* process of X chromosome inactivation in females early in fetal life, because of that, all females are ***genetic mosaics*** since they have two populations of cells ; one population has an active paternally derived X chromosome , and the other has an active maternally derived chromosome.

Hint: mosaicism describes the presence of more than one genetically distinct cell line in the body.

On the other hand, Males, having only one copy of the X chromosome, are not mosaics but are hemizygous for the X chromosome (hemi means "half").

- small percentage of genes that are carried on X chromosome escape inactivation. most of these genes are carried also on Y chromosome.

- The X inactivation centre contains a gene, *XIST,* that is transcribed only on the inactive X chromosome, The RNA transcript, however, is not translated into a protein and it's considered as a **long noncoding RNA**(**lncRNA**).

- The *XIST* RNA transcript remains in the nucleus and coats the inactive X chromosome.

- in addition to incRNA, inactive X chromosome is *hypermethylated* and the histones are *deacetylated*.

Sex-linked inheritance:

1. **X-linked recessive inheritance**:

- General roles (see figure in the slides) :
    1. All males are *Hemizygous*,but females may be *homozygous* or *heterozygous*.
    2. We can't have male carriers.
    3. Only one gene is required in males to have the disease.

●Note #1 : if we have a recessive trait that's carried on X chromosome, but it's also carried on Y chromosome in males, this trait is inherited in a manner similar to *autosomal recessive genes*.

●Note#2 : heterozygous females may have some clinical manifestations of X-linked recessive disease, depending on the fact that Lyonization is a random process, so if a female inactivated a healthy allele in a tissue that expresses this allele, she may have some symptoms.

●Example: type A hemophilia

- In clotting process, we have a cascade of activation processes, ending by activation of fibrin, that's essential in clot formation process.
- In hemophilia A, there's a problem in one of these factors (clotting factor 8).
- Signs and symptoms include: Unexplained and excessive bleeding from cuts or injuries, or after surgery or dental work, many large or deep bruises, unusual bleeding after vaccinations and Pain, swelling or tightness in their joints.
- Treatment: is simply by giving patients the missing clotting factor.
- These clotting factors are obtained from donators, in fact one donator is not enough, so we take blood samples from multiple donators, purifying these clotting factors, and injecting them on the patient.
- The problem here that many of these donators have parenteral diseases, like HIV, so hemophilia patients were at high risk to develop such diseases.
- Nowadays we use other molecular techniques to synthesize these factors in the lab (ex: cloning).
- This disease is inherited as X-linked recessive disease, so males that have only one allele will develop the disease.
- Homozygous females will develop the disease also.
- However, heterozygous females may have some symptoms depending on where healthy allele is inactivated, or if they were unlucky that more than 35% of these cells have activated the bad allele.

2. **X-linked dominant inheritance**:

- Examples: colors blindness, hypophosphatemic rickets. ***Hypophosphatemic rickets*** is a disease in which the kidneys are impaired in their ability to reabsorb phosphate.
- General roles (see figure in the slides) :
    1. If the father has the disease, daughters only will develop the disease.
    2. If the mother has the disease and she is heterozygous, all the progeny have equal chances to develop the disease.

Sex-Limited and Sex- Influenced Traits

●Confusion sometimes exists regarding traits that are sex-linked and those that are ***sex-limited*** or ***sex-influenced*****.**

●A sex-limited trait occurs in only one of the sexes, due, for instance, to anatomical differences. Inherited uterine or testicular defects would be examples.

●A good example of a sex-influenced trait is male-pattern baldness, which occurs in both males and females but much more commonly in males. This is related in part to sex differences in hormone levels. Contrary to oft-stated belief, male-pattern baldness is not strictly X-linked, although variation in the X-linked androgen receptor gene is associated with baldness. Autosomal genes are also thought to influence male-pattern baldness, helping to explain apparent father-to-son transmission of this trait.

Mitochondrial Inheritance

●Males do not transmit mtDNA to their offspring because sperm cells contain only a small number of mtDNA molecules, which are not incorporated into the developing embryo.

- **Note**: One isolated case of paternal transmission of a mitochondrial DNA mutation has been reported, but such events appear to be extremely rare.

● Mitochondrial genome is a multiple copy circular double stranded DNA.

● Mitochondrial genes encodes for some TCA cycle and ETC proteins, as well as some rRNA and tRNA molecules.

●Because each cell contains more than one type of mtDNA molecules, a single cell can harbour some molecules that have an mtDNA mutation and other molecules that do not. This heterogeneity in DNA composition, termed as ***heteroplasmy.***

●during mitoses, one of the daughter cells may receive diseased mtDNA, and other will not.

●the previous fact affect the pathogenesis and clinical manifestations of the carriers, so if the diseased mitochondria is transmitted to embryonic cells that will give rise to a tissue that's highlydependent on oxidative phosphorylation (like skeletal muscle, heart and brain), the symptoms will be severe.

● examples on mitochondrial inherited diseases are Leber hereditary optic neuropathy, and some types of diabetes.

Genomic Imprinting

●in most genes, both alleles, maternal and paternal, are expressed to give certain phenotype.

●However, in some genes, only one allele (may be maternal or paternal) is expressed, and the other is silenced by Methylation and (or) histone deacetylation, *how??*

- During replication, all epigenetics are copied to the daughter cells.
- But during gametes formation (oogenesis and spermatogenesis) different genes are epigenetically silenced in sperm and eggs.
- So in **sperm**, the **maternal** allele (from the grandmother) is silenced (imprinted), and all imprints are erased and rewritten in a **paternal** pattern.
- In **eggs**, the **paternal** allele (from the grandfather) is silenced (imprinted), and all imprints are erased and rewritten in a **maternal** pattern.

● **Prader-Willi and Angelman Syndromes**:

- both are genetic disease results from deletion of about 4 Mb of the long arm of chromosome 15.

- When this deletion is inherited from the father, the child manifests ***Prader–Willi syndrome***, a disease whose features include short stature, hypotonia (poor muscle tone), small hands and feet, obesity, mild to moderate intellectual disability, and hypogonadism.

- When the same deletion is inherited from the mother, the child develops ***Angelman syndrome***, which is characterized by severe intellectual disability, seizures, and an ataxic gait.

  Further analysis showed that the 4-Mb deletion contains several genes that normally are transcribed only on the chromosome inherited from the father. These genes are transcriptionally ***inactive (imprinted)*** on the copy of chromosome 15 inherited from the mother. Similarly, other genes in the critical region are active only on chromosome inherited from the mother and are ***inactive(imprinted)*** on the chromosome inherited from the father. Thus , several genes in this region (the region on chromosome 15 where the deletion occurs) are normally active on only one chromosome. If the single active copy of one of these genes is lost (whether from mother or father) through a chromosome deletion , then no gene product is produced at all, and the disease results. This explains how genomic imprinting affects the occurrence of distinct diseases originated from deletion of the same region on the chromosome.

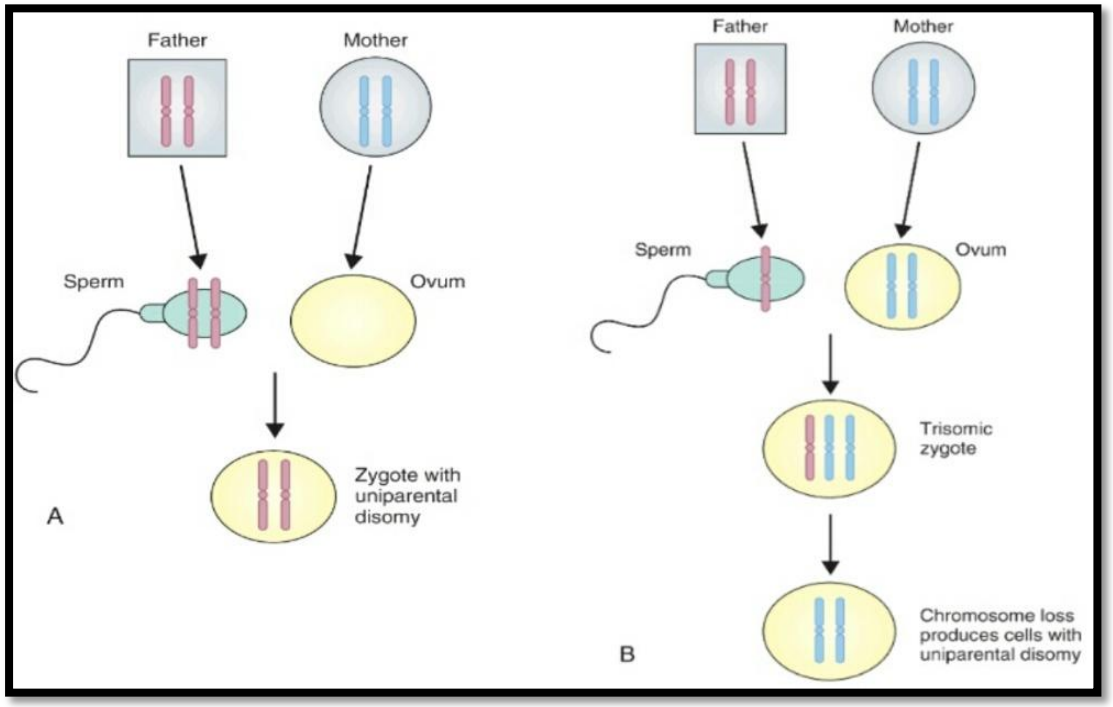
Several mechanisms in addition to chromosome deletion can cause PWS and AS. One of these is uniparental disomy:

- **Uniparental disomy** occurs when a person receives two copies of a chromosome, or of part of a chromosome, from one parent and no copy from the other parent.
- It can be the result of ***heterodisomy***, in which a pair of non-identical chromosomes are inherited from one parent (an earlier stage **meiosis I error**) or ***isodisomy***, in which a single chromosome from one parent is duplicated (a later stage **meiosis II error**).

- Here, if you have ***Prader–Willi syndrome*** you will inherit it from your mother, because two alleles came from your mother(i.e your paternal allele is actually from your maternal grandfather),see figure B.

- on the other hand you will inherit ***Angelman syndrome*** from your father, because two alleles came from your father, see figure A.

  According to the mechanism of deletion or uniparental disomy, the concept remains the same in both which is in PWS , there is no active paternal genes in chromosome 15 and in AS , there is no active maternal genes in chromosome 15.



●Beckwith–Wiedemann & Silver–Russell Syndromes:

- Other example that will clarify the idea of imprinting.
- These disorders result from Uniparental disomy, or changes in methylation status of a region containing IGF2 (Insulin-like growth factor 2).
- **Beckwith–Wiedemann Syndrome** results from *paternal* Uniparental disomy, it's characterized by overgrowth,

predisposition to cancer, enlarged tongue and ear lobe creases, due to ***increased IGF2 expression.***

- **Sliver-Russell syndrome** results from *maternal* Uniparental disomy, it's characterized by growth retardation, proportionate short stature, leg length discrepancy, and a small, triangular- shaped face, due to ***decreased IGF2 expression.***
- So we can conclude that paternal allele is more active than maternal allele due to imprinting, and any disturbance of this balance will change the expression level, this is simply the idea of genetic imprinting (I hope it's clear now).

Anticipation & repeat expansion

●it's the last non-mendelian single gene disorder.

●Anticipation is a genetic phenomenon where each successive generation is getting the disease ***earlier and severer.***

●there are two theories that explain why this occur :

1. Many researchers believed that it was an artifact of better observation and clinical diagnosis in more recent times: a disorder that previously might have remained undiagnosed until age 60 years might now be diagnosed at age 40 years simply because *of better diagnostic tools*. However, this theory can't explain why such disease become more severe on each generation.

2. Others say that the problem here has biological basis.The disease-causing mutation is an expanded tri-nucleotide repeat, The number of these repeats is strongly correlated with severity of the disease. Studies showed that the number of repeats often increases with succeeding generations. (In general, tri-nucleotide repeats are a bit confusing for DNA-polymerse, so it will add some repeats on each replication).

●examples are *Huntington chorea* (number 13 :P) and *myotonia dystrophy* disease.

●**Myotonia dystrophy**:

- It's an autosomal dominant disease that involves progressive muscle deterioration and myotonia (inability to relax muscles after contraction).
- This disorder is typically characterized by cardiac arrhythmias (abnormal heart rhythms), testicular atrophy, insulin resistance, and cataracts.
- Most cases of myotonic dystrophy (termed myotonic dystrophy type 1) are caused by mutations in *DMPK,* a protein kinase gene located on **chromosome 19.**
- Analysis of *DMPK* has shown that the disease-causing mutation is an expanded CTG trinucleotide repeat, that lies in the 3′ untranslated portion of the gene.
- The number of these repeats is strongly correlated with severity of the disease.
- The number of repeats often increases with succeeding generations .
- H*ow does a mutation in an untranslated portion of DMPK produce the many disease features of myotonic dystrophy*?

  The expanded repeat produces an mRNA product that remains in the nucleus of the cell and produces toxic gain-of-function effects. The abnormal mRNA interacts with proteins that normally bind other RNA products to regulate their splicing. As a result , a number of proteins including several that are expressed in heart and skeletal muscle, are abnormally formed. This explains **pleiotropy** of the disease phenotype.

  Note: pleiotropy means multiple phenotypic expressions.

- We have a Second type that occurs in **chromosome 3** that have the same molecular mechanism, with similar features, but it's sometimes due to the fact that it does not affect DMPK itself . This explains **locus heterogeneity.**
- So, Mytonic dystrophy illustrates several important genetic principles : anticipation, pleiotropy and locus heterogeneity.

Fragile X Syndrome

●it is another example on these repeats.

●it results from a duplication in fragile X mental retardation 1 gene (FMR1).

●it occurs usually in males, *why?*

- Because males have only one X chromosomes, so all their cells will be affected, so it can affect females but in less frequency.

●it's the second most common genetic cause of mental retardation, after Down syndrome.

●it's called fragile X syndrome due to the karyotype appearance of X chromosome, the chromosome isn't fragile actually

●it's also subjected to anticipation, each generation it becomes worst.

Fragile X syndrome is also characterized by long face with large mandible, large everted ears and large testicles (macroorchidisim).

-This lecture homework: the ***Sherman paradox*** *(refer to book, page 101).*

-"*when life changes to be harder*, *change yourself to be stronger. What hurts you today, makes you stronger tomorrow*"

-Erza Scarlet

-good luck

-Mohammad Qussay Al-Sabbagh