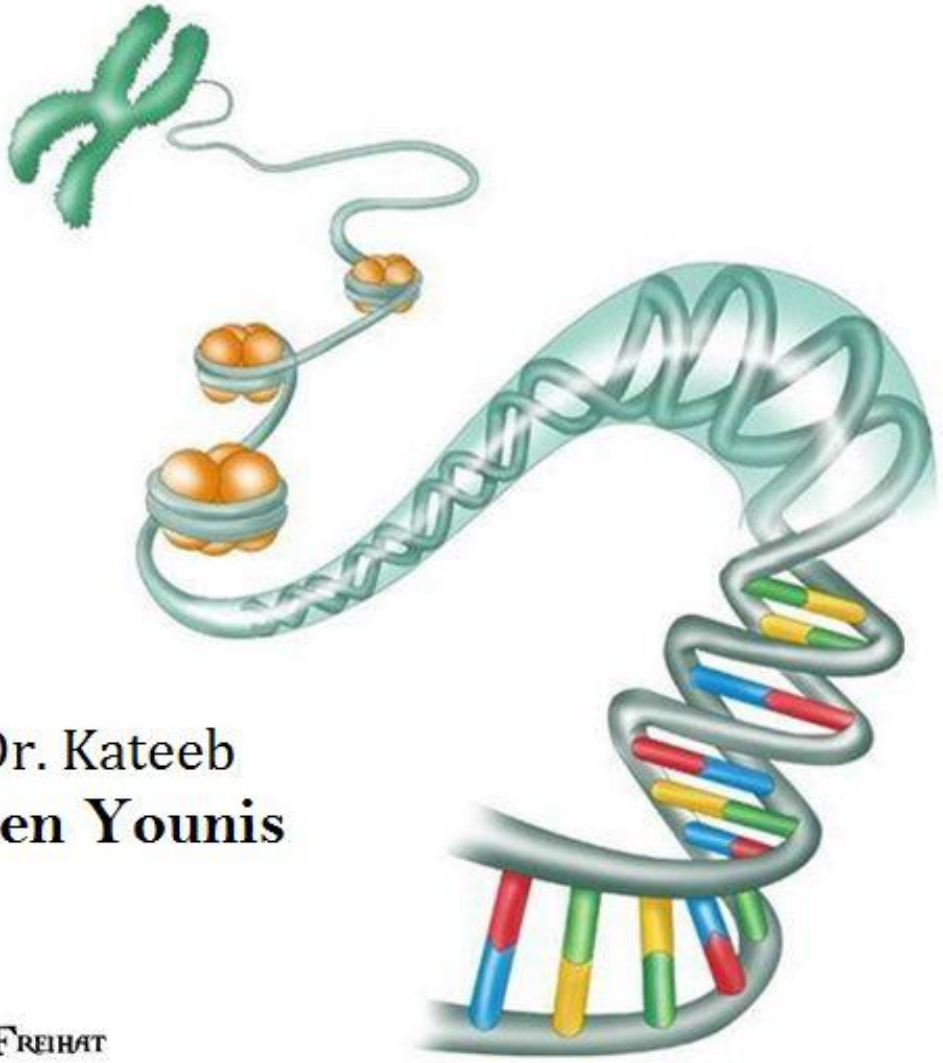
University of Jordan
Faculty of Medicine
Batch 2013-2019

Medical Committee
The University of Jordan

Genetics & Molecular Biology

○ Slides ○ Sheet ○ Handout ○ other.....



Sheet#: 6
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Designed by Nadeen Al-Freihat

Mendelian Inheritance

- Sex linked disorders

These genes are located on the X and Y chromosomes. Those found on the Y chromosomes belong and function in males only.

If you look at the X chromosome: it's a large chromosome, contains 5% of the human genome and it has 160 mb (mega bases), it also has 700 genes and a few of them cause dominant type of diseases while most diseases that are related to the X chromosome are recessive.

*What are the possible genotypes in the x inherited types of diseases?

It has 2 alleles, like any other autosomal chromosome. In females:

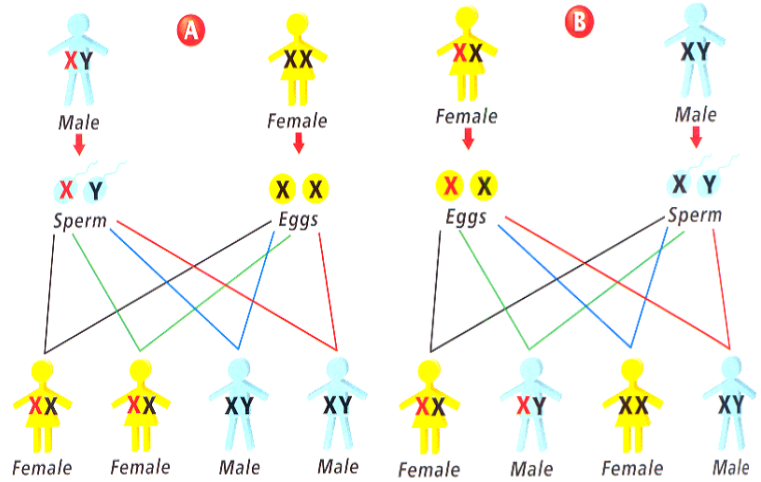
- They can be the same → homozygous, which is the normal wild type.
- One of them can be mutated → heterozygous, a female carrier.
- Or both can be mutated → homozygous mutant female.

While in XY male they can be homozygous wild type or heterozygous mutant.

In the inheritance of these types of diseases, if the mother is a carrier and the father is normal there's a chance that 50% of the children, whether males or females, will be affected since the X chromosome comes from the mother.

If the x chromosome of the father is mutated, only females will get the disease because the males won't inherent he X chromosome from their father.

X-linked Inheritance

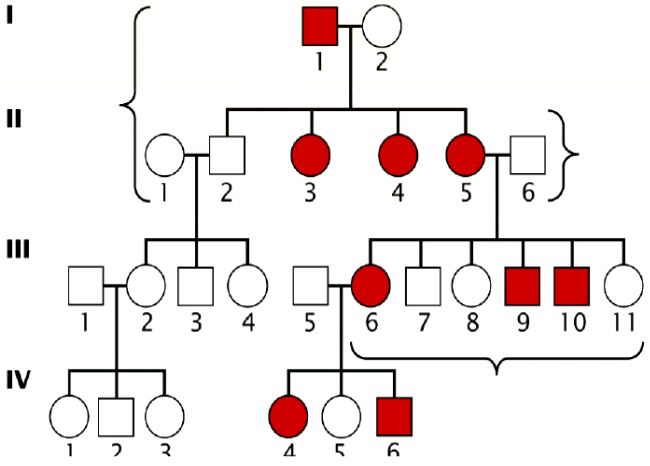


X- Linked diseases are either:

- **X Dominant**

  Where the affected male will transfer the disease to all his daughters, so the male who has hemophilia for example, all his daughters will be affected. In heterozygous females, there's a 50% chance that she will pass it to her children, homozygous females will transfer the disease to all her children whether males or females. High rate of miscarriages in females and also lethal conditions can be seen in males.

  The pedigree of X- linked dominant is similar to the autosomal dominant as we can see an affected person in each generation. How can we differentiate between them?
  In X-linked dominant, he father can only transmit the disease to his daughters, while the sons are normal. The mother can give both sons and daughter. However in autosomal dominant, both the mother and father can transmit it to their children whether male or females.



← X-linked Dominant

There are a few diseases which are x-linked dominant, for example:

1. Dwarfism
2. Incontinentia pigmenti
3. Congenital generalized hypertrichosis (CGH)
4. X-linked hypophoshatemic (Vitamin D-resistant rickets)
5. Congenital bilateral ptosis where the patient has dropped eyes.

*Incontinentia pigmenti:

In heterozygous females there will be a severe type of pigmentation. New born girls generally will have the disease and can live with it and transmit it to their children. In males it's not compatible with life and they die in uterus.

*Congenital generalized hypertrichosis (CGH) "wolf-man"

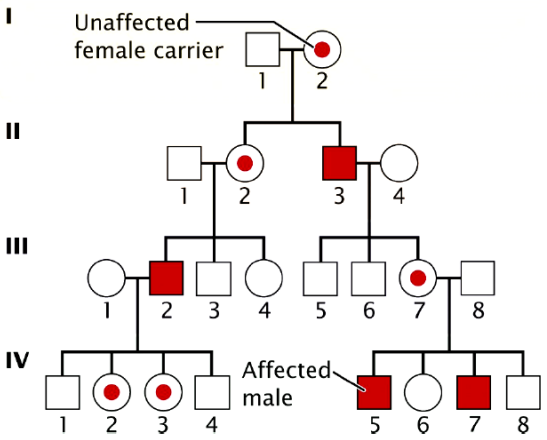
The entire body of the patient will be filled with hair.

- **X Recessive**

It's always expressed in males, not females because in females both X's should be affected to get the disease. So females are usually heterozygous and carriers of the disease.
Affected males get the disease from heterozygous mothers, and they can transmit it to their daughters.
Daughters of affected males are usually heterozygous and there's a 50% chance that the mutant gene of these girls will be transmitted to their own daughters.
If the disease is inherited from the father, all daughters will get the disease. If it's inherited from the mother, both males and females can get the disease. Females are carriers while males get the disease.
It depends on what is the origin of the disease, maternal or paternal.

Looking at the pedigree, the X- linked recessive looks like the autosomal recessive where it can skip generations. Here the ancestor and the 2nd generation is skipped.

To differentiate between them, in x-linked recessive only males are affected.



← X-linked Recessive

There are many diseases that belong to the X-linked recessive type:

1. Hemophilia A & B
2. G6PD
3. Ichethiosis, it's a skin disease that makes it look like fish skin. The patient has a deficiency in an enzyme that removes cholesterol from the skin.

Some conditions might make it more complicated and hard to recognize the pedigree for this,

1. Having a small family of 4-5 people. So when looking for a genetic disease problem, it's more preferable to include the extended family in the pedigree.
2. New mutation in the family, like a problem in the sperm or ovum during embryogenesis.
3. Germ line mosaicism, the sperm or the ovum have 2 cell lines where one is normal and the other is abnormal. In this family, some people have the disease while others don't.

   One of the most famous pedigrees in history for hemophilia where it affected 5 royal families: the British, Greek, Spanish, German and Russian royal families. They all intermarriage between the same family.

Y chromosome

It's the smallest chromosome you can find, has very few genes, 70mb, all of them give the male characteristics (Holandric).

** Holandric: Relating to a trait encoded by a gene or genes specific to the Y-chromosome and therefore occurring only in males.

There are male differentiation genes that we can find in testis-specific spermatogenesis factor, minor histocompatibility genes (HY), several housekeeping genes and SRY gene.
Transmission is from father to son, abnormalities cause infertility.

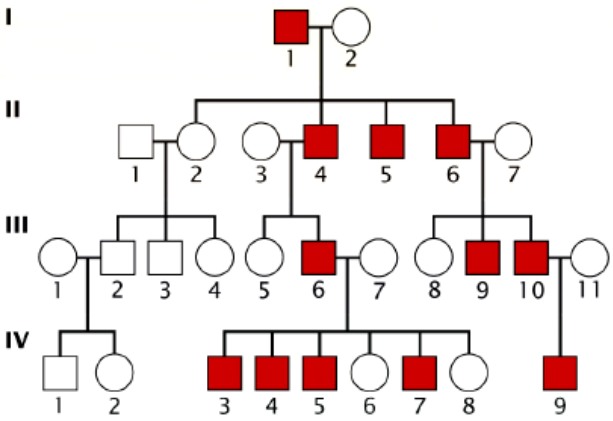
The genes found on the Y chromosome, are in two regions: Pseudoautosomal 1 and 2. These areas are found on the tips of the chromosome. They're called autosomal because these genes have complementary genes on the X chromosome.
They look autosomal because they're found on both, X and Y chromosomes.
The other male specific region that gives the male characteristics have the SRY and ZFY gene which are needed for the production of sperms.

The SRY gene gives a transcription factor for a protein that controls the expression of other genes which are important for the development of males. They're important for testosterone and dihydrotestosterone production which are needed for the males' characteristics and spermatogenesis.

The main three functions of the SRY gene:

- Differentiation of sertoli cells
- Induce migration of cells from mesonephros to the genital ridges
- Induce proliferating cells to produce genitalia ridges

Y-linked diseases are always transmitted to males and the pedigree includes all males in all the generations. There's no females interference which is shown in pedigree.
An example of a disease: hairy ears disease (Hypertrichosis pinnae auris).



SOX gene, housekeeping gene, it's very important to the development of males. If there is a complementary dysplasia there will be a problem in about 70% of individuals. The gene controls the testes and genitalia. (Correction note: I suffered trying to understand what the doctor said here, it is most likely "campomelic dysplasia" with ambiguous genitalia)

Sex limited traits:
Related to the testes in males, uterus in females. Examples:
Growth of beard in males, milk production in females.

Sex influenced traits:
Only that sex will have the disease: like baldness, recessive X type of disease, you never see a bald female, her hair might be light though.

Other conditions…
There can be a translocation between X & Y especially in the SRY gene, if that happens, the female who gets that gene will be genetically a female when doing a genetic analysis (XX) but phenotypically she's a male.

If it happens in males and he loses the SRY gene, he'll be genetically a male (XY) but phenotypically a female.

X Inactivation

Theoretically, any female has 2 X's, which means that she has double the genes. However, functionally only one of these is functional while the other is inactivated.

This inactivation was discovered in 1961 by Lyon and Russell and they called it [Lyon's theory]. The inactivation happens very early in life, after fertilization (After the 1st week of gestation before there's about 24 cells.) this inactivated x is important to keep the dose of any protein or enzyme, since the dosage for them in males and females should be the same.

There's certain location where the X inactivation happens, that area is called XIST (X Inactive Specific Transcription gene) it's found in the q13. This gene is responsible for the production of mRNA that will coat the chromosome, coating will help methylate the chromosome. Methylation will inactivate the genes so they won't function.

This inactivation is completely arbitrary. In cell A, the paternal chromosome could be inactivated, while in cell B the maternal chromosome will be inactivated. That's why the female proteins which are controlled by genes found on the X chromosome are heterogeneous, they're not homogeneous. Some are inherited from the father while others are inherited from the mother.

You can see in any organ, there are two cells which will form a mosaic. Some cells are paternally in origin while others are maternal. These are an example for inactivation.

In calico cat hair color, the female will have 2 colors one brown (X^b) and the other is black and each color is controlled by a different allele from maternal or paternal origin. That's why in males, you'll only see one color only.

Another example is anhidrotic ectodermal dysplasia, some part of skin aren't producing sweat, in females there are areas on the skin where there aren't sweat glands. While in males they're either there or not.
Also G6PD, in males they're homozygous (correction note: I think it is hemizygous) while in females you'll find 2 polymorphic types.
This is also true for melanin, in albinism: males have pinkish eyes with no pigmentation while in albino females you'll find black spots in her eyes because her mother or father aren't albino causing these spots.

Certain areas on X/Y chromosomes are homologous and this happens to compensate; which means that X inactivation won't be completely inactive, almost 15% won't be inactivated because these genes have homology on the Y chromosome. Because if they didn't have this homology and all got inactivated, the male would have more protein for these genes compared to the female.

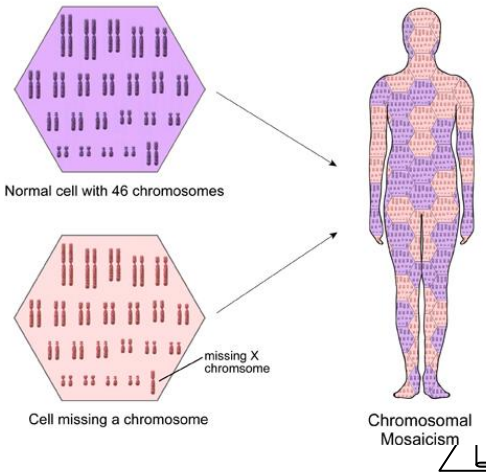
There's 15% of the X chromosome won't be inactivated and it escapes inactivation, to compensate the function of these genes. These genes have Xg blood group, affected with Kallman's syndrome or housekeeping genes like SOX gene.

These are all about Mendelian inheritance.

Non-traditional type of inheritance

We can't apply to them the Mendelian inheritance, and that's why they're called non-traditional.
These include:

1. Mosacisim
2. Imprinting
3. Trinucleotide expansion
4. Uniparental Disomy
5. Mitochondrial inheritance



- Mosaicism

  It's when a person has two cell lines in their body. This is mainly due to a certain mutation happening in their DNA or because of an epigenetic characteristic (where there are certain abnormalities in the environment around the DNA not the DNA itself). Like patients with Down syndrome, where some cells have an extra chromosome while others have the normal number of chromosomes. About 2-4% of Down syndrome patients have mosaicism.

  Types of mosaicism:

- Somatic mosaicism, where it happens in a somatic cells
- Gonadal mosaicism

  Which is restricted to germ line cells and its seen only in certain tissues and defined as: The presence of a mutation in all or part of the germ line but not in the rest of the body. This implies that a mutation occurred in a precursor; a sperm or an egg cell, examples:
  Osteogenesis imperfecta, achondorplasia, Duchene's muscular dystrophy and hemophilia A.
  These germ line mosaicism are usually seen as a new mutation, it is when you see a person presenting with an autosomal dominant disease the first time in the family, and it shows in the same pedigree that more than one person will be affected.

  How are these generated?
  During cell development, at one stage one of the cells get mutated then at the end we'll have two cell lines, one is mutated and the other is normal.

- Imprinting

  It means the differential expression depending on the parent origin. That means that one gene will silence another gene so that only one can be seen. That could be in the sperms or ova, it could be chromosomal where they're marked, and it won't change the nucleotide sequence, only the

gene will be silenced by the other gene. We talked about it in Prader-willi and Angleman syndromes.

This generally happens before fertilization. The sperm or ovum already have this imprinting abnormalities. We can also have transcriptional silencing because the product of activation of one gene will stop the function of the other gene by methylation.

The somatic cells can transmit this abnormality by mitosis, it is reversible, when the fertilization happens again the imprinted gene will be reactivated again.

For most genes, we inherit two working copies -- one from mom and one from dad. But with imprinted genes, we inherit only one working copy. Depending on the gene, either the copy from mom or the copy from dad is epigenetically silenced. Silencing usually happens through the addition of methyl groups during egg or sperm formation.

The epigenetic tags on imprinted genes usually stay put for the life of the organism. But they are reset during egg and sperm formation. Regardless of whether they came from mom or dad, certain genes are always silenced in the egg, and others are always silenced in the sperm.

The imprinting can be transient: like in neonatal diabetes where the new born will be deficient with insulin then after a period of time he'll be normal since other cells' products will compensate the deficiency, this is uniparental disomy and happens at chromosome 6. Also biparental expression can happen at chromosome 11 especially in early age in yolk sac.

The importance of imprinting:
The functions of imprinting is not very well understood. But maybe it's important in development where the genes that will cause abnormalities will be silenced by one way or another. Also they suggest that we need to activate this imprinting in order to get a healthy embryo to silence the non-coding genes.

Other important characteristics that can't be explained by Mendelian inheritance:

- **Copy number of variation**

The same gene should normally have two copies, but sometimes these copies can be increased. That indicates that an oncogene was activated or there was a problem during division or abnormality during replication of DNA.

So the number of the copies of this gene can differ in different people.

Certain diseases which have an extra copies:

Alzheimer, autosomal dominant adrenoleukodystrophy, HIV and drug metabolism.

Drug metabolism, if many people take the same drug for hypertension for example, you can see single drug response. Some people will respond faster and metabolize the drug fast so you need to increase the dose, while some people if you give them the normal dose, it'll be toxic to them this depends on the number of copies of that gene in their genetic makeup.

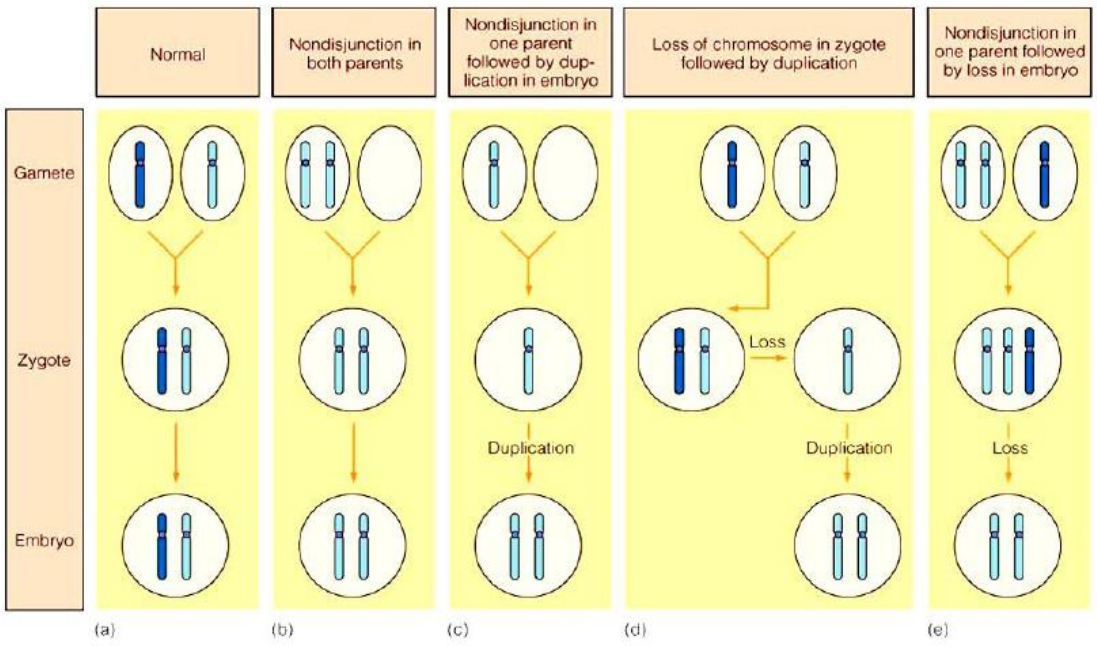
- **Uniparental disomy**

Means that both alleles of the gene are inherited from one parent could be paternal or maternal. Its incidence is around 2-17%.

There are two types:

1. Isodisomy: where the parent passes the two copies of the chromosome to one child.
2. Heterodisomy: the parent gives one copy which can be homologous as a result from non-disjunction in meiosis1.

Look at this figure..



A. It's a normal process of transmission where the two chromosomes are coming from two different gametes.
B. Non-disjunction where both chromosomes stay in one cell for both parents.
C. One will pass normally and it'll duplicate (uniparental disomy)
D. Two chromosomes coming from two different parents. One has a junction (correction note: I think no non-disjunction happened here so no junction), then one of the chromosomes is lost in one way or another when it divides. We end up with one chromosome which will duplicate and we'll have a uniparental disomy.
E. There's triplet, where one is junctional and then loses a chromosome ending up with uniparental disomy.

This can happen for one gene or for segment of a chromosome not only a complete chromosome. And we have many diseases like Prader-Willi, cystic fibrosis and many others.

- **<u>Trinucleotide expansion</u>**

1-3% of the genome are coding areas, while the others are noncoding and can be related to diseases as there are different structures there. In the non-coding areas have Trinucleotide are repeating themselves for a

number of times, the number of these repetitions are related to certain diseases some can be 5, 40, 5000.
If it's the normal DNA, we have normal 7 CAG repeats and that can be increased to 8, 9, and 15 and so on. This is expansion and it's associated with certain diseases.
For example: (in non-coding areas)
CGG expansion → fragile x syndrome
CAG → Huntington disease
CCTG→ Myotonic dystrophy

<u>These expansions might happen at two different areas, in coding and outside the coding areas</u>.

The first one to be discovered was in 1991 (fragile x syndrome), and the last one was a psychiatrist disorder.
These diseases have an association with neurologic disorders, metabolic activity and they cause mitotic abnormality in division.

- The fragile X syndrome
  It's the second disease that cause genetic mental retardation, after trisomy 21 (Down's syndrome), the gene responsible for it has around 17 exons (fragile x area), it involves the expansion of CGG which are normal 6-45 in number, if they increase from 46-60 they're normal but stable, 61-200 then they're permutation and if they're above 200 then have complete mutation and they have mental retardation.

THE END.
SHOUTOUT TO ABU SHAWERMA
& the gorgeous Aseel Ahmad

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