



University of Jordan
Faculty of Medicine



GENETICS & Molecular Biology



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Hi all, the first lecture in medical genetics is only an introduction and revision for basics of genetics.

Our reference for this course is: ***Medical genetics Jorde, Carey, Bamshad) 5th edition***

This lecture will cover Chapter 1, 2 (briefly) + few pages from chapter 3.. let's go.

In this lecture we will review cell biology history of genetics and genetic variations. we will talk also about cytogenetics , biochemical genetics.

What's genetics ?

- Genetics: is the study of gene, genetic variants and hereditary in living organism, Medical genetics involves any application of genetics to medical practice.
- Medical genetics is now becoming a central component of our understanding of most major diseases. These include not only the paediatric diseases (like Thalassemia, sickle cell anemia, cystic fibrosis, etc...) but also common adult diseases such as heart disease, diabetes, many cancers, and many psychiatric disorders.
- so, why should we care about genetic diseases?
 - *Simply because genetic diseases are much more prevalent than we think they are*, genetic diseases can be as prevalent as three to seven percent of all diagnosed diseases
 - This includes the *autosomal dominant, autosomal recessive X-linked chromosomal disorders and congenital malformations*.
 - so, medical genetics is not a small part of life, regardless of which of the disciplines that you go into. You will come across a genetic disease at one point or another in your career .
 - so you do need to understand when to think of genetic conditions, what kind of tests are required, and how the changes genes affect the disease course.

Multigenic diseases

what do we mean by complex multigenic diseases?

- multiple genes that produce one disease, complex also means that many genes also modify the disease like *cystic fibrosis* which is caused by one mutation but there are multiple modifier genes that change the course of the disease.
- environment also can change the course of the disease .

A brief history

- Gregor Mendel, an Austrian monk who is usually considered the father of genetics, advanced this field significantly by performing a series of cleverly designed experiments on living organisms (*garden peas*). He then used this experimental information to formulate a series of fundamental principles of heredity.

- Mendel found out that :

- 1- phenotype is controlled by some things that are inherited, so they are unique inherited traits from parents to progeny.
- 2- he figured out that the phenotype is produced by two alleles only(no more, no less):
 - Two alleles: one from the mother and one from the father (*independent segregation*)
 - at that time, the prevalent theory was the theory of mixing (*traits from the father and traits from the mother are mixed together to produce genetic material of the progeny*).
 - also, he figured out that the two alleles are segregated independently (*each allele is passed into the progeny independent from the other*)

- Oswald Avery showed that genes are composed of **deoxyribonucleic acid (DNA)**, by a very smart experiment on Pneumococci:

- Pneumococci is either pathogenic or non pathogenic, they wanted to figure out why was one pathogenic and the other not.
- so, they chopped off the pathogenic bacteria and divided it into basic pieces(nucleic acids ,proteins ,lipids ,etc), and they started injecting these into the non-pathogenic bacteria, they figured out that the nucleic acid compartment(DNA) is responsible for transmitting the pathogenicity.
- They figured out that the DNA was the basic building blocks for inheritance.

- The most significant achievement of the 1950s was the specification of the physical structure of DNA by James Watson, Francis Crick and **Rosaline franklin**.

Rosaline franklin was an x-ray crystallographer who deserved the Nobel prize (but she died before getting it), she took different materials, crystallized them, looked at them on x-ray, she produced an image (you can check it on the slides).

[End of chapter 1]

Very quick revision of cell biology

- **DNA structure:** DNA is a polymer of deoxynucleotides (A,G,C,T), A binds T (2 H-bonds) and C binds G 3 H-bonds) to form a double helix and this double helix is bound by proteins (mainly histones) to form chromatin.

- DNA is too long, if you unfold it, it's 2 meters long molecule.

- **Somatic cells Vs Gametes:**

- **Somatic cells:** diploid cells, with full set of chromosomes, resulting from mitoses. And having two sex chromosomes.
- **gamete cells:** haploid cells, with half number of chromosomes, resulting from meiosis. and having only one sex chromosome.

- **Autosome Vs sex chromosome:**

- **Sex chromosomes:** X and Y chromosome that determine the gender of the individual (genetically).
- **Autosome** : any chromosome other than X and Y.
- Sex chromosomes in males are XY, but females have two X chromosomes, it's not fair to have two active X chromosomes in females, so one of these chromosomes will undergo *silencing*.
- X-chromosome silencing is a random process, so in female one cell may have the paternal X chromosome active, other cell may have the maternal one. That's why all females are *mosaics*.
- If we need only one copy of all X-linked genes, why do females have 2 copies of it?

*Actually, some X-linked genes will escape inactivation (silencing), because some genes require two alleles to give me normal female, that why having X on the one sex chromosome, and it's called **Turner syndrome**.*

- **Homologous chromosomes:** are a set of one maternal and one paternal chromosomes that pair up with each other inside a cell during meiosis.

- **mitoses Vs meiosis:**

- Mitoses: diploid to diploid.
- Meiosis: diploid to haploid.
- During meiosis tetrad of homologues chromosomes occur, that leads to *crossing over* of genetic material, contributing in the genetic diversity.
- The difference between meiosis in males and females, that meiosis produces 4 sperms in males, but in females it produces only 1 ovum and 3 polar bodies (Inactive X chromosome).

- Other difference that in males, sperms are continuously produced through meiosis all over the life. in females , meiosis is almost over at birth ,so the number of eggs has been determined, most of meiosis end out. there is a small part of second meiosis start just before ovulation.

●TranscriptionVs Translation:

- **transcription** : DNA to mRNA
- **translation** : mRNA to protein.

●in mRNA, **exons** *contain the coding genetic material* and **introns** *contain the non-coding material*.

● in order produce mature mRNA, a process called *splicing* occur to separate exons from introns. Actually the coding genetic material is only 1-2% out of our genome.

● Some mutations in a non-coding part of DNA may produce a disease like introns, promoters and enhancers.

● Epigenetics

- Remember that we have mentioned in neoplasia lectures that are our cells have the same genetic material, but some cells have closed areas in DNA,due to DNA packaging by histones, this may affect available genes and therefore transcription.
- remember that we talked also about transcription factors (ex: MYC), that can turn on and turn of the transcription of certain genes.
- As a result, even if you have exposed gene, it is not necessarily going to be transcribed because in addition to RNA polymerase II you have to have a whole host of other proteins that bind to DNA and make transcription possible, these are controllable by signals coming from outside the cell.

● miRNA binds to mRNA, it: degrades mRNA and inhibit mRNA translation.

●**codons**: are triplet repeats of nucleotides (3 nucleotides per amino acid)

- we have 20 amino acids, and 64 codon, that means more than one codon can produce the same amino acid. The other thing about genetic code is that it is universal, necessary for all organisms(with the exception of mitochondrial codons)

we have just reviewed cell biology , these are the first two chapters in the book , we are not supposed to know all details related to them

[End of chapter 2]

Genetic Variation & Mutation

- genetic variation means *diversity*, there is nobody looks like the others. Despite the fact that we share 99% of our genetic material !

- so less than 1% makes us different.

- that remarkable diversity, like when we talk about humans, carrots or snails, it is only small difference in DNA and this is produced by various difference we talked about.

- before talking about mutations, we have to review some terms:

- locus**:a particular location in the DNA that contains gene.

- allele**: one of two copies of the gene (either maternal or paternal).

- we have two copies for almost all genes.
- which genes don't we have two copies for them?
- *some genes on Y chromosome and some genes on X chromosome.*

- Homozygous**: the same two alleles.

- Heterozygous**: different alleles.

- Hemizygous**: one allele only, *Where can we find it?*

- It's found on the x-chromosome , because only one x-chromosome is active while the other is inactivated.

- Genotype**: the DNA sequence.

- Phenotype**: the result of the sequence(the result of expression)

●Mutation Vs Polymorphism :

- We have studied that mutation has a prevalence of less than 1% while the polymorphism has a prevalence of more than 1%.
- Well, forget about this, They both are a change in DNA code.
- It was classically known that polymorphisms don't cause diseases while mutations cause diseases, polymorphisms occur in non-coding regions while mutations are in coding regions.
- But the fact is that polymorphisms can be found in coding regions and even if they were in non-coding regions they can still cause diseases. Also, polymorphisms are called polymorphisms even if their prevalence was less than 1%.
- So, polymorphisms and mutations are *essentially the same*.

●A mutation in germ cells: transmitted to progeny.

●A mutation in somatic cells: Not transmitted to progeny ,but they can cause cancer for example.

● **Point mutation:** a mutation in a single base of a nucleotide.

They could be:

- **silent:** no change in the amino acid.
- **missense:** change in the amino acid.
- **non-sence:** facing a stop codon(causes the translation to stop).
- Important note: not all non-sence mutations are non-functional, it depends where the mutations occurs on the mRNA (some proteins may retain their function even if they are shorter).

●Insertions and deletions:

- Do all insertions and deletions cause frame-shift mutations?
- Answer: *No, if you insert or delete a codon you don't necessarily get a frame-shift mutation(the doctor didn't talk about details).*
- Keep in mind: this doesn't mean that frame-shift mutations are bad and non-frame-shift mutations are good, even the non-frame-shift mutations can cause massive changes.

● **Gene Amplification:** breast cancer is an example (amplification in HER2 receptor).

● **Consequences of mutations:**

- you may gain a function → *dominant disease*.
- you may lose a function *recessive disease*, one allele is not enough, Except in case of *Haploinsufficiency*.
- *Haploinsufficiency*: when you have one normal allele and one abnormal allele, however this abnormal allele causes problems, ex: sickle cell trait.

● Q: how does sickle cell trait differ from sickle cell anemia?

- Answer: in sickle cell trait the patient is heterozygous (one normal allele and one abnormal allele), however, this abnormal allele causes a mild version of sickle cell anemia.
- One abnormal allele is not enough to give you the complete disease but you will have symptoms (phenotype)

● Another example is atherosclerosis which results from hyperlipidaemia because the patient has a missing LDL receptor gene.

- People with one abnormal copy have abnormal lipids and have atherosclerosis and get heart attacks and strokes earlier than normal people, while people with two abnormal copies get heart attacks even earlier, and have considerably high cholesterol level compared to the heterozygotes.
- Dominant negative: when the abnormal protein affects the function of the normal protein or the protein in complex, ex: sickle cell anemia.

● How is sickle cell anemia an example?

- Because one subunit of haemoglobin is abnormal and it affects the function of the normal subunits (alpha subunits are normal but beta subunits aren't).

- What causes mutations?

- We have induced mutations and spontaneous mutations, first let's talk about induced mutations:

- *Induced mutations* are caused by radiation, chemicals,...etc.

- Note: In Hiroshima and Nagasaki we saw an increase in cancers among population, however, frequent studies on the populations that were exposed to massive doses of radiation did not show a long lasting effect.
- It means that there wasn't a major effect on the health of later generations, *but Why?*
 1. the repair enzymes are very active in germ cells.
 2. there weren't enough survivors to see the effect
 3. spontaneous miscarriages.
- In the past it was thought that miscarriages were rare events, but nowadays with more accurate pregnancy tests that can detect pregnancy very early, we knew that miscarriages are common events, and it's a way to protect the progeny from inheriting defective genetic material, so the mutations that can majorly affect the progeny will be miscarried.

- **spontaneous mutations:**

- Every single gamete produced has 30 mutations on average, and these mutations are not caused by radiation or chemicals or any mutagen (they are spontaneous).
- it's just that the repair machinery is not able to fix everything that goes wrong, it only fixes the important ones (ex: those mutations that can affect the cell cycle are detected by p53).
- Some genes are more mutated than others, *why?*
Well, not all genes have the same size, *the bigger the gene, the more likely it will be randomly mutated.*
- Also, C-G dinucleotides are more likely to be mutated, because they are heavily methylated and when methylated cytosine is delaminated (by a mutation) it will be read as thymine (C-G → T-A)

- Note: we induce the deamination of methylated cytosine in cells that produce antibodies in order to have more variety of antibodies.

-The end

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