University of Jordan
Faculty of Medicine
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Medical Committee
The University of Jordan

Genetics & Molecular Biology

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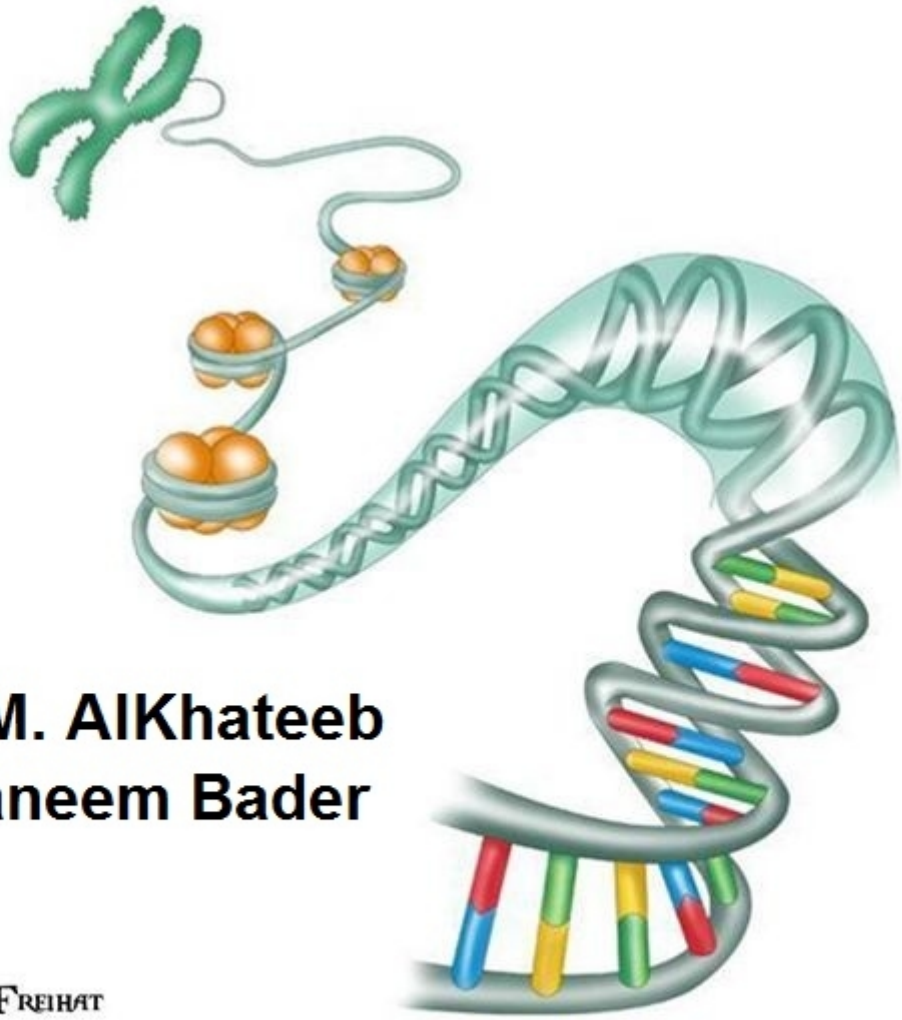

Sheet#: 1

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" اللهم إني أسألك فهم النبيين وحفظ المرسلين والملائكة المقربين، اللهم أخرجنا من ظلمات الوهن، وأكرمنا بنور الفهم، وافتح علينا بمعرفة العلم،

وحسن اخلاقنا بالحلم، وافتح علينا أبواب جودك وخزائن رحمتك يا أرحم الراحمين . اللهم اجعل السنتنا عامرة بذكرك وقلوبنا بخشيتك وأسرارنا بطاعتك انك على كل شيء قدير . وحسبنا الله ونعم الوكيل "

Medical Genetics

- **Genetics**: (1) Is the branch of biology that deals with heredity, how characteristics and diseases pass from one generation to another in all living organisms.
  (2) study of individual genes and their effects. It includes studies of inheritance, mapping disease, genes, diagnosis, treatment, and genetic counseling
- Animals, plants and humans have the same genes but have different sequence.
- **Medical genetics** : Is the science or study of biological variation as it pertains to **health** (normal , tall , short , blue or green eyes, curly or straight hair and so on) and **disease** (why someone has a disease while the other doesn't, why a person is susceptible or resistant to the disease?). Any application of genetic principles to medical practice.

History of Medical Genetics:

Note: the first person who started to talk about heredity was Dawrin (evolution theory) we stared from simple animals till we reach human being, but that was not true, later on several studies were done and end up with that there is variation within the same species, and we found that these characteristics are not genetically pure, sometimes enviorenmt might

interfere and cause many changes that can interfere with the genetic makeup of the person

- **Early Genetics**
  - In the 1860s Mendel started to do some experiments on pees.
  - Mandel tested in his experiments 8 characteristics (flower color (purple or white) , flower position (lateral or at the end), seed color (black or green) , seed shape (wrinkled or smooth) , pod shape , pod color , stem length)
  - He used to mix between the 8 characteristics.
  - Mendel deduced 3 main patterns from his experiments. these principles are :

1) The law of Segregation: The law of segregation refers to the observation that each individual possesses two genes for a particular characteristic, only one of which can be transmitted at any one time. Each characteristic is segregated differently. This segregation is independent; for example the color has nothing to do with the seed's shape (each characteristic is inherited or segregated alone independent of any other characteristics) the characteristics are inherited in a mathematical way.

2) Dominance: It has to do with dominant and recessive alleles and how some characteristics overcome the others (e.g. blood groups)

3) Independent assortment: The law of independent assortment refers to the fact that members of different gene pairs segregate to offspring independently of one another.

- **Modern Experimental Genetics** - 1900s
  - Maize, drosophila , mouse
- **Medical Genetics** - 1960s to the present

- For each characteristic there are 2 genetic materials (alleles) that do control it
- Polydactyl id a dominant characteristics
- Sometimes the urine will became black because of the reaction of some enzymes. These abnormalities are discovered in very early in the infants.

- Anticipation: is a phenomenon whereby the symptoms of a **genetic** disorder become apparent at an earlier age as it is passed on to the next generation (with generations the disease becomes more severe). In most cases, an increase of severity of symptoms is also noted.
- When we talk about inheritance, we talk about mitochondrial inheritance, not nuclear.
- Some diseases are linked with some inherited characteristics (e.g. if you have character x you will be more susceptible to disease y).

- The First one that has talked about genetics is Darwin in this theory about evolution.
- There are some Variations between the same species because of heredity and selection.
- Characteristics heredity depends on genetics and the environment.

All Variations and Differences are important in making the severity of the diseases less, since some individuals will die from the disease and some will carry the genes of it.

DNA Genetics

- 1953 - Watson and Crick's Double Helix

- 1992 –2003 Human Genome Project

2003 -> the future of medical diagnosis and treatment generated from tis human project

Why it is important in medicine?

- 10% of the patients seen in GP have a disorder with a genetic component
- 80% of mental retardation due to genetic component
- 2-3% background population risk for a major birth defect 15% overall miscarriage risk for any pregnancy
- 25-50% first trimester miscarriage risk
- 30-50% first trimester losses due to chromosome anomalies
- >30% pediatric hospital admissions due to genetic diseases
- Genetic diseases affect all major systems, any age, any race, male or female
- Changing focus of medicine**:**
    - Primary care physicians vs. specialists: the diseases and genetic abnormalities are diagnosed from the beginning (primary care).
    - Prevention vs. treatment: for vast majority of genetic diseases there's no treatment so prevention is very important.
    - Genetic causation for both rare and common diseases: 20% of our population is a carrier for familial Mediterranean fever; however 5% are carriers for thalassemia. Even though the prevalence of Mediterranean fever is much more than thalassemia,

screening is only available for thalassemia and that because Mediterranean fever is not a killing disease (it's mild) whereas thalassemia is very serious, it costs a lot of money.

- Human Genome Project
- Designer drugs

- Variation and selection

- Genetics and genetic variations are the link between basic research & clinical observation.
- All living organism start from single cell organism 3.4 billion years ago, and then they develop and variation occur along time.
- Evolution: if we compare the human being now and before millions of years would we find any differences? These differences along time we call them evolution.
- 2 butterflies, they are genetically identical, the only difference that one hatches in the spring, the other in winter, this is because of variation among them (same genes but variation).
- Tomato has many colors.
- **Roses have different colors because of variation.**
- **Eyes and skin are different among people because of genetic variation.**
- **Even identical twins are not exactly the same.**
- **Variations occur as a mutation or during fertilization (recombination of chromosomes) and development of fetus. (this gives us diversity)**

- **We can see variations in 4 levels :**
  - Nucleus level
  - Chromosomal level
  - Gene level
  - DNA and protein level (same protein but different structures of protein (tertiary or quaternary structure)

- Some variations are physiological e.g. Lactose intolerance (60% of population).
- In our area blood group A is prominent and in other areas group blood B is prominent.
- Jews are more susceptible to some diseases like Tay-Sachs Disease.
- Sickle cell anemia is more susceptible in black people.

- Why Variations are important?

Variations are a way of survival. If all individuals have the same structures and mutations then if the mutation causes death, all individuals will die. However if we have some variations among individual then there will be more resistance for mutations.

- Variation are related to :
  - ALLELES
  - LOCUS (place or address of the gene , location)
  - HOMOZYGOTE
  - HETEROZYGOTE
  - GENOTYPE
  - PHENOTYPE
  - PLYMORPHIC
  - POLYMORPHISM

- Variations are simply differences in genetic sequence.

- Variation can be seen at every genetic level:

- In the DNA
- In the genes
- In the chromosomes
- In the proteins
- In the function of proteins

- **Character :** a structure, function, or attribute determined by a gene or group of genes i.e. the appearance of the seed coat in Mendel's garden pea studies (1 allele)

- **Trait :** the alternative forms of the character i.e. "smooth" or "wrinkled" peas (2 alleles, one maternal and one paternal)

- **Phenotype:** the observable and physical description of the character in an individual organism i.e. a green pea**.** An organism's physical appearance based on an interaction of its genes and environment ex: fur color, eye color, # toes, hair texture, speed, intelligence.

- **Genotype** : the genetic constitution of the organism

- **Mutation** : a change in the genetic material, usually rare and pathological (bb , Bb) an organism has • Ex: BB or Bb or bb for eye color

- **Polymorphism:** a change in the genetic material, maybe single nucleotide is different, usually common and not pathological. (to be a polymorphism, its prevalence should be more than 1% in population)
- **Locus:** location of a gene/marker on the chromosome.
- **Allele:** one variant form of a gene/marker at a particular locus.
- Blood groups are polymorphic.

- **Homozygote** : an organism with two identical alleles

- **Heterozygote**: an organism with two different alleles, same function but genetically different.

  - **Hemizygote** : (hemi: half) having only one copy of a gene (only one allele)
    • Males are hemizygous for most genes on the sex chromosomes.
  - **Dominant trait**: a trait that shows in a heterozygote.
  - **Recessive trait** : a trait that is hidden in a heterozygote
  - Gene: a sequence of nucleotides.
  - Genome: all nucleotides as a whole.
  - Haploid: Half the chromosomes.
  - Diploid: All the chromosomes

  [Remember, in mitosis the chromosomes are diploid (2 copies), while in meiosis they're haploid (Half the number).]

- The Causes of Genetic Variations are

  - Evolution
  - Gene Flow and Drift Gene Frequency
  - Adaptation
  - Natural Selection
  - Mutation

- **Evolution**: (1) Evolution refers to change in characteristics over time, or transformation over time. Evolution assumes that all natural forms arose from their ancestors and adapted over time to their environments, leading to variation. In evolution, there are many rules the environment places upon the survival of a species. There are also numerous ways in which evolution occurs, the most noted are: Adaptation & Natural Selection.

- Due to evolution there is adaptation.

- **(2) Evolution**: changing characteristics through time. For example, almost every two years, theoretically, there should be a change that's noticed between one and another, and that could be due to environmental factors (Wars, Radioactive materials, etc.)
  → Evolutions vary depending on the changes in gene frequency in a population, and can be categorized into:

  -Macro-evolutions: due to the emergence of a new race.
  [HIV has appeared recently due to evolutions.]
  [Certain type of fish lives in very low temperatures (below zero) and for that reason they have no RBCs so they won't be damaged.]
  [Some Parasites –like tape worms- don't have GI tract so they take nutrients through the skin.]

  -Micro-evolutions: developed during a certain period of time.
  [The prevalence of a certain disease among Jordanians of age 25 years differs from that in 50 years old Jordanians.]
  [Thalassemia is caused be 400 different mutations, now if you look for these mutations in Greeks and Mediterranean people, you will find 10 mutations that are repeated there predominantly, in the Far East there're other 10 mutations that predominate, and among Jordanians there're other 20 ones, but why do that variation occurs? Due to the interactions and mixing between generations and different nations during past times and these

made your gene pool impure.]

- **Gene frequency**

  - **Gene drift:** Random changes in the sequence of genes to eliminate a characteristic and make another predominates during time. And this needs a closed small population that doesn't mix with others.

  [Mixing two plants with different colors in the first generation, then in the following generation, you keep promoting the fertilization between plants with one color. By that, with time, you'll be having a population of plants with only one color.]

  [80-85% of Bema Indians who live around the Amazon have Diabetes because they're considered a closed population that has almost similar genotype and thus a similar phenotype.]

  [If persons in a population with many different genes keep marry from each other, they will end up having only a specific group of genes, and those differences will be noticed in a limited group of them.]

  → Another term that's similar somehow to gene drift is the: "**Bottle neck**" which indicates also the loss of some genes and the prevalence of others.

  And again let's discuss another example on the effect of environment: Certain kind of white butterflies were living on trees in England, but after the industrial revolution, the people there started to use the hard coal in the industries and produce CO_2 that turned the white butterflies to black ones.]

- **Adaptation**:

  [Sickle cell anemia is an autosomal recessive disorder: Needs 2 mutated alleles to appear.

  Here if there's a patient with only **one** mutated allele and he reaches the Himalaya, he will give exactly the same **clinical picture of the disorder** due to **changing his environment**

[Some Plants change their characteristics according to the environment in which they live, it may be on the sea surface or on top of mountains, accordingly it may be short + stump or long + darkly stained.]

- **Natural selection**
- **Mutations**: they cause diseases and disorders (unlike polymorphism). These disorders are because of radiations, XRay, UV, chemicals, drugs, physical conditions or microbial. In mutations the damage might be beyond repair. It is a permanent change in DNA sequence.

  Types of mutations:

  1) **Missense:** one nucleotide is changed. The amino acid will also change.
  2) **Nonsense:** a stop codon is produced so we will have a short protein.
  3) Frame shift: by insertion or deletion. The whole amino acid sequence will be different. We will have a different protein.

  Source of variation is from mutations or genetic shuffling. Mutations are also seen in chromosomes: different chromosomal number (e.g. 4 instead of 2) or a decrease or increase in a certain part of the chromosome.

  - **Genetic shuffling:** mixing of alleles by re-assortment/ crossing over/ combinations during meiosis. And by that normally some chromosomes shuffle and produce different genotypes.

  Some shuffling is discontinuous: only one gene control the characteristic.

  Some other shuffling is a multi-gene shuffling \ characteristic: more than one gene control the characteristic (e.g. skin color) so you can find a different range of this characteristic. (Continuous) Height is controlled be more than one gene (it ranges from short to long)

- Human genome has 30 000 genes
  - We know about 85% of the genes
  - We don't know a lot about 15% of the genes.
  - 1-2% of the genes code for proteins
  - 25% important for translation (mRNA for example)
  - 75% are junk (polymorphism found in junk genes)
  - Repetitive elements: • Satellites (regular, mini-, micro-) • Transposons • Retrotransposons • Parasites

- 99.9% of the genome in all humans is the same. They are only different in 0.1%.

  - these variations can be:
    - Harmless (change in phenotype)
    - Harmful (diabetes, cancer, heart disease, Huntington's disease, and hemophilia)
    - Latent (variations found in coding and regulatory regions, are not harmful on their own, and the change in each gene only becomes apparent under certain conditions e.g. susceptibility to heart attack)

"اللهم استودعك ما قرأت وما حفظت وتعلمت، فرده لي عند حاجتي إنك على ما تشاء قدير ".

Written by: Raneem Bader