Medical Genetics

Sheet: 6 – Patterns of Inheritance

Writer: Odai Bani Monia

Scientific: Ahmad Mashaleh

Final: Mohammad Abu Zalam

Doctor: Bilal Azab

In this Lecture we are going to talk about 5 main topics:

1- Single Gene Inheritance
2- Multiple Alleles
3- Pleiotropy
4- Epistasis
5- Polygenic Inheritance

Please note that I'll put anything in the slides that wasn't mentioned by the professor in Green Boxes like this one.

Single Gene Inheritance

- In Inheritance we have 2 terms through which genetic traits are inherited from parents, these terms are **Dominance** and **Recessiveness**.
- Remember Mendel's experiment on peas when he said that one pea plant color is Dominant (Yellow Color), and the other color is Recessive (Green Color).
- Let's assume that the color gene is "A" for example.
- If the Genotype for the individual is 'aa' then the color (the Phenotype) is Green however if the genotype was 'Aa' then the color is Yellow and if it was 'AA' then the phenotype is Yellow too.
- However, the relationship between Genotype and Phenotype is rarely as simple as in the pea plant characters Mendel Studied.
- Many heritable characters aren't determined by only one gene with 2 alleles.

- The basic principles of segregation and independent assortment apply even to more complex patterns of inheritance.
- Inheritance of characters by a single gene may deviate from simple Mendelian patterns in the following situations:
  1- When alleles aren't completely dominant or recessive.
  2- When a gene has more than 2 alleles.
  3- When a gene produces multiple phenotypes.

- Degrees of Dominance: (will be clarified below)

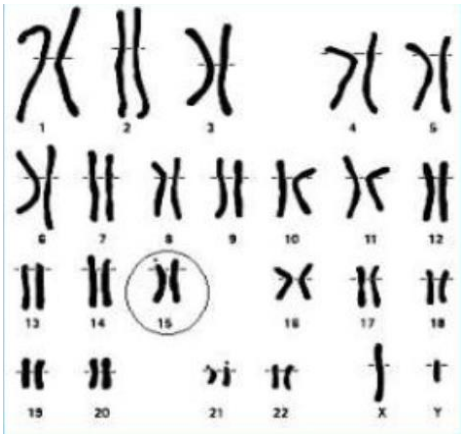
1- **Complete Dominance:** Occurs when phenotypes of the heterozygote and dominant homozygote are identical.
2- **Incomplete Dominance**: The phenotype of F1 hybrids is somewhere between the phenotypes of the 2 parental varieties.
3- **Codominance:** Two dominant alleles affect the phenotype in separate, distinguishable ways.

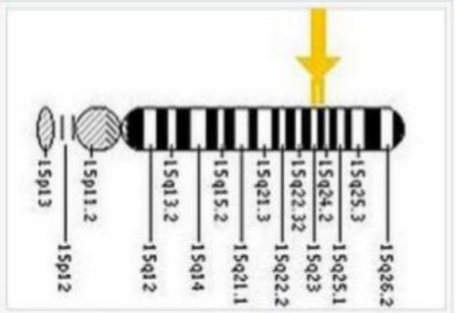
The relation between Dominance and Phenotype:

- A dominant allele doesn't subdue a recessive allele; alleles don't interact that way.
- Alleles are simply variations in a gene's nucleotide sequence.
- For any character, Dominance/Recessiveness relationships of alleles depend on the level at which we examine the phenotype.

Tay-Sachs Disease

- Tay-Sachs is a **Recessive** metabolic disease where the enzyme **Hexosaminidase-A** that metabolizes lipids is defective, therefore there will be lipid accumulation and build up, and eventually will lead to cell damage and Death.
- Tay-Sachs disease is an example of a **Classical lysosomal storage disorder**.
- The gene that encodes for hexosaminidase-A is **HEX-A gene** on chromosome 15 specifically on the q arm (15q – region 14).
- Clinically, due to the build up of lipids in the body, the clinical features start showing in the first months of life and the within the age of 3-4 yrs, the patient will die and during their lifetime they will suffer from neuromotor difficulties in addition to psychomotor impairment seizures, tremors, and other classical features of CNS damage.





The HEXA gene is located on the long (q) arm of chromosome 15 between positions 23 and 24.

Tay Sach's features:
TAY SACHS

- **T**esting recommended
- **A**utosomal recessive
- **Y**oung death (<4 yrs.)
- **S**pot in macula (cherry red spots)
- **A**shkenazi Jews
- **C**NS degeneration
- **H**ex A deficiency
- **S**torage disease

MENDELIAN GENETICS AND HUMANS

Human genetic disorders

Tay Sachs Disease

Inheritance Pattern:

-Autosomal recessive

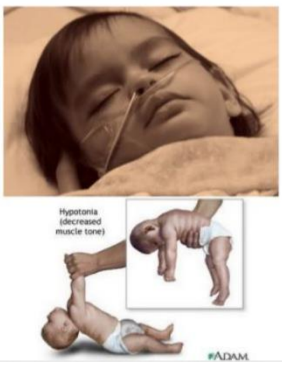
Physical Effects:

-Nerve cells destroyed in brain and spinal cord

-Symptoms appear 3-6 months after birth

-Loss of motor control and atrophy of muscles, seizures

-Death



- Tay-Sachs disease usually occurs in Jewish people.

- If the individual is **Heterozygous** (meaning that he has one abnormal allele), clinically he will be **normal**, so this tells us that the disease is **Recessive** because one abnormal allele didn't cause disease in the individual.
- Now we all know that **hexosaminidase-A** is an enzyme, if we measured the enzymatic activity in a homozygous normal individual vs. heterozygous individual vs. homozygous mutant individual, we would find the following:
  1- In **homozygous mutant** individuals, the enzyme is defective, that is the metabolic activity of the enzyme is ZERO.
  2- In **homozygous normal** individuals, the metabolic activity of the enzyme is 100%.
  3- In **heterozygous** individuals, we expect the metabolic activity to be in between zero and 100% and we call this condition → Incomplete Dominance, because the enzyme is neither fully active nor inactive.
- So, at the **biochemical level**, Tay-Sachs disease is **Incomplete dominant**.
- Now let's talk about it from a Genetic perspective, you have 1 Gene with 2 alleles, right? The 2 alleles lost 2 DNA copies for the same gene, RNA polymerase will then go and use each DNA as a template to transcribe RNA and then RNA will be translated into Proteins (including the enzyme hexosaminidase-A, but it will be defective)
- So, both normal and mutant alleles are expressed in heterozygous individuals.
- Therefore, at the **genetic level** since the 2 alleles are expressed then it's **Codominant**.
- ***TAKE HOME MESSAGE:***

For some diseases you may call it Complete Dominance, Incomplete Dominance, or Codominance based on what level you're examining and looking at the disease (are you looking at the phenotypical, Biochemical, or Molecular Level).

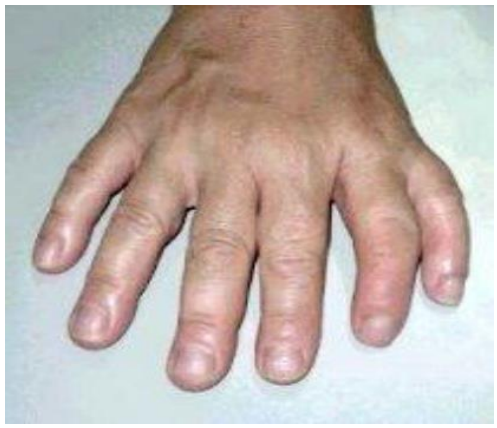
- In the Exam, the question may specify to you whether it's looking at the Phenotypical, Biochemical or Molecular level, if it doesn't specify then you always take the Phenotype.
- For example, if the question asked you: Is Sickle Cell Anemia complete dominant, Incomplete Dominant or Codominant disease?
  Well in this case the question didn't specify at what level he is examining the disease, so you directly look at the **phenotype** and the answer would be **Complete Dominance**.
  (at **biochemical level**, the disease is **Incomplete dominant** and at **molecular level** the disease **Codominant**).

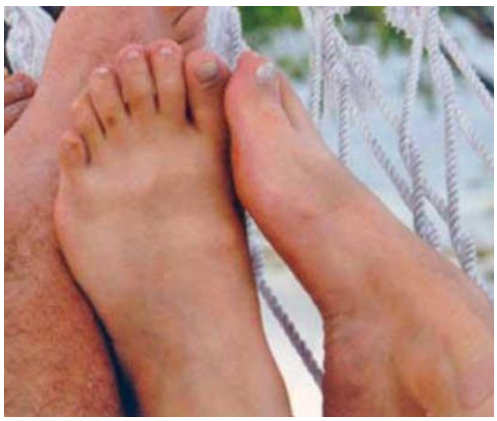
- Tay-Sachs Disease:

1- At Organismal Level → the allele is Recessive.
2- At Biochemical Level → the phenotype is incompletely dominant.
3- At Molecular Level → the alleles are codominant.

Frequency of Dominant Alleles

- Now the question is: is the mutant allele Dominant or Recessive?
  The answer is that it's not necessarily Dominant or Recessive, because in some diseases the disease-causing allele is Dominant while in other diseases the disease-causing allele is Recessive.
- Another Question is that in the population for the same Gene, which is more common, the dominant or the recessive alleles?
  The answer is that there is no correlation between the percentage of dominant or recessive alleles in the population – in other words, we can't say that dominant alleles are more common than recessive alleles or the opposite.
- For example, Polydactyly (Extra Digit), it's a dominant allele but it's less prevalent in the population (so basically it depends on the disease).
- ***TAKE HOME MESSAGES:***
  1- In some diseases the dominant allele is more common while in others the recessive is more common.
  2- In some diseases the dominant allele is disease-causing while in others the recessive is the disease-causing.





Multiple Alleles

- We said that in humans at the individual level each gene has 2 alleles except the sex chromosomes.
- In population wise, you can have more than 2 alleles for a single gene.
- For example, Blood Groups, in the population level we might have A or B or O (multiple alleles), However each individual is carrying only 2 alleles.

(a) The three alleles for the ABO blood groups and their carbohydrates

Allele	I^A	I^B	i
Carbohydrate	A △	B ○	none

(b) Blood group genotypes and phenotypes

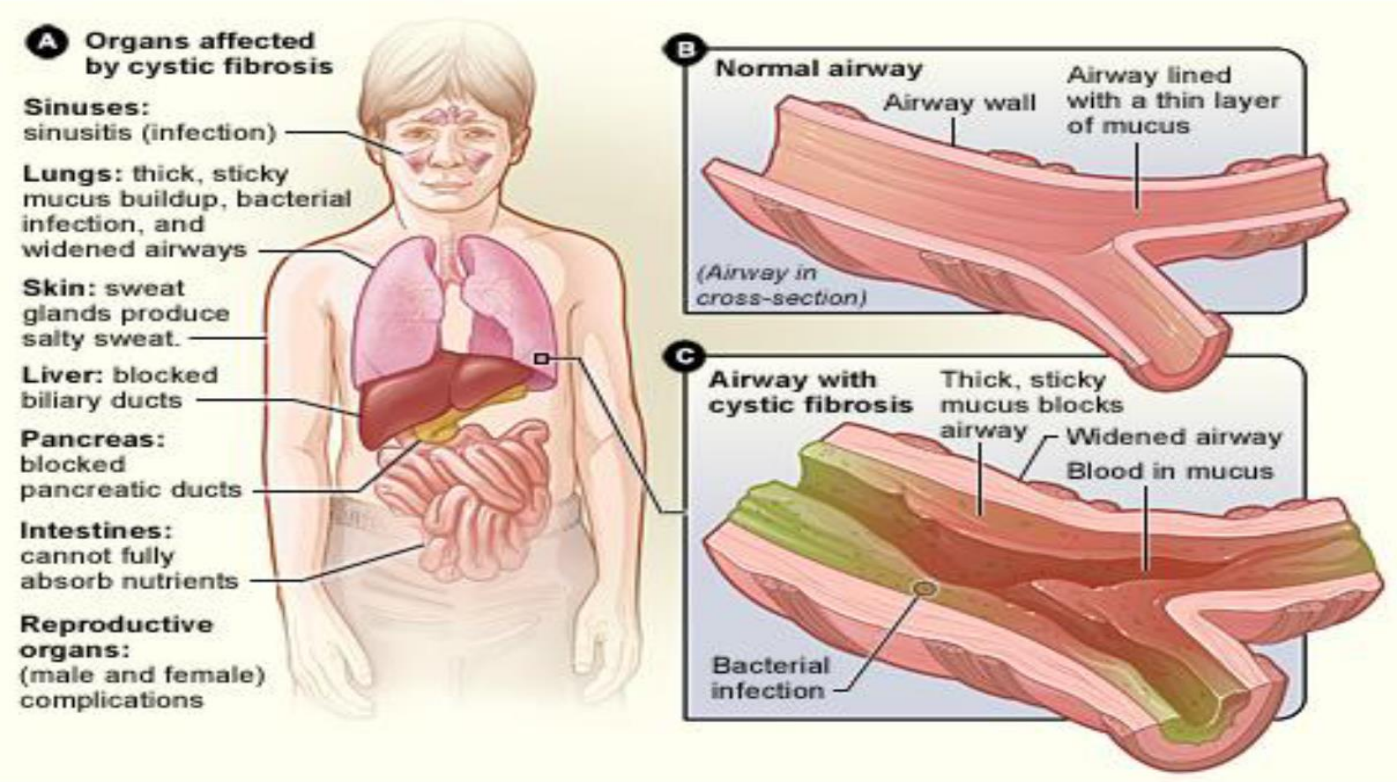
Genotype	I^AI^A or I^Ai	I^BI^B or I^Bi	I^AI^B	ii
Red blood cell appearance				
Phenotype (blood group)	A	B	A B	O

Pleiotropy

- **Pleiotropy** means that 1 gene defect causes multiple phenotypic effects.
- To understand this let's take **Cystic fibrosis** as an example:
- Cystic fibrosis is **an autosomal recessive disorder** caused by a mutation in a Gene which mainly affects a membrane protein which is a chloride ion channel where it becomes defective (so chloride will accumulate outside the cell and is accompanied with mucous build ups).
- Eventually, most of the lumens in our body (including the Trachea and the Lungs) will be filled with mucous, and the problem is that this mucous blocks the lumen and is prone to infection (mostly Bacterial infection).
- The Gene for Cystic Fibrosis known as **CFTR Gene** and the phenotypic effects include:

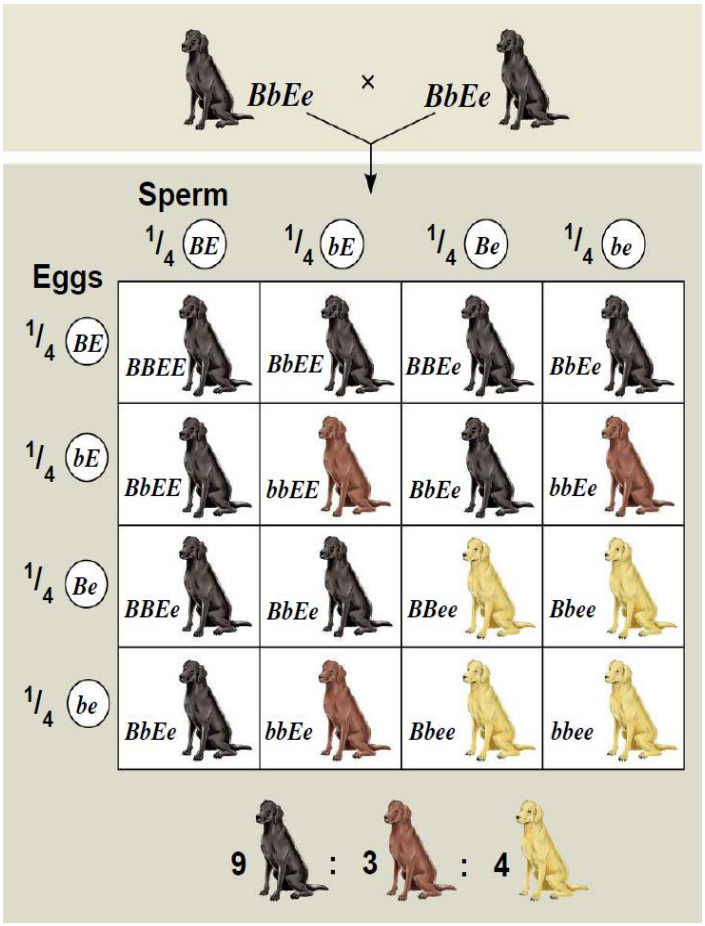
1- Infection of air sinuses (sinusitis).
2- Mucous Build up and bacterial infection in the lungs.
3- Salty Sweating (more NaCl in sweat) → this is the easiest and the typical test to start with to detect cystic fibrosis.
4- Biliary duct will be filled with mucous thus it's going to be blocked.
5- Pancreatic duct will also be blocked thus rendering the pancreatic function.
6- Intestines filled with mucous therefore the GI is incapable of absorbing food.
7- Complications in Males and Females reproductive organs.

- So, we can notice that one gene (**CFTR**) is causing multiple phenotypic effects attacking multiple organs and tissues.
- In fact, most Genes have multiple phenotypic effects, therefore most genes have pleiotropic effects.
- If the mutation is restricted to one phenotype then it's not pleiotropy.



Epistasis

- **Epistasis** is kind of complex topic, to understand it we'll take Dogs as an Example:
- So basically, there is a gene that has to do with black and brown colors of the dogs (**black** color is dominant over the brown color, so 'BB' is black, 'Bb' is black too, 'bb' is **brown**).
- There is another gene, let's assume it's "E", if this gene is homozygous recessive (that is 'ee') it will prevent black-brown color gene from functioning.
- So, if the gene is 'ee', neither black nor brown will manifest.
- If it's 'EE', it allows the other gene to function.
- Epistasis means that a gene at one locus alters the phenotypic expression of a gene on another locus.
- So, 'E' gene either allows or prevents 'B' gene from expressing its phenotype and that is epistasis in its simplest form.

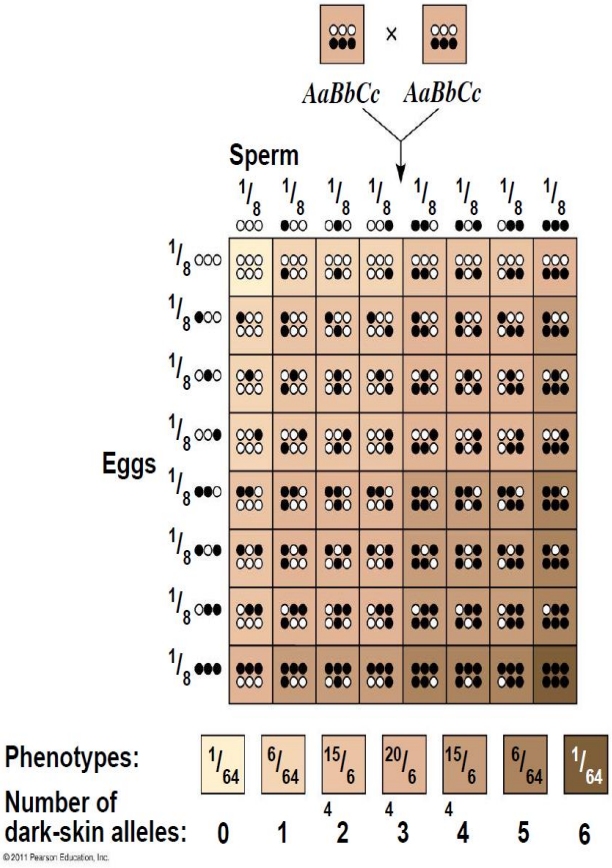


Polygenic Inheritance

- So far, we talked about **Cystic fibrosis** and **Tay-Sachs diseases** which are Single Gene Disorders (Cystic fibrosis caused by **CFTR** gene, and Tay-Sachs is caused by **HEX-A** gene).
- There are other phenotypes that are contributed by more than one gene, and as a matter of fact those phenotypes are the most common phenotypes in the population (these are the most common disorders).

- Quantitative characters are those that vary in the population along a continuum.
- Quantitative variations usually indicate Polygenic inheritance, an additive effect of two or more genes on a single phenotype.

- There is no single gene that can cause cancer by itself, there should be multiple defective genes to cause cancer.
- The same thing applies to DM and Cardiovascular diseases → This is what is called **Polygenetic inheritance.**
- The simplest example is **Skin Color**:
- Skin color has a normal curve distribution which means there is no one phenotype (we don't have just black and white, we have brown, tan, black, etc.).
- Let's assume that we have 3 genes and each of these genes has 2 alleles and each allele contributes to the degree of skin color, so if the 6 alleles are toward the light skin color then you'll have light skin color, and if they were toward the dark skin color, you'll have dark skin color.
- Any combination between the 6 alleles will give a degree in between black and white skin colors.



- One thing that is linked to polygenetic inheritance is **Multifactorial Inheritance**, which is a Gene-Environment Interaction, so the appearance of the phenotype is contributed by the gene as well as the environment.

- For example, **Alcoholism** (addiction to alcohol) is contributed by both the individual's genes as well as his environment, because you must be exposed to heavy alcohol drinking in order to have a chance for your genes to be addicted to it.

- **Sex orientation** and **Lung cancer** also have genetic and environmental components.

WORK HARD IN SILENCE, LET YOUR SUCCESS BE YOUR NOISE.