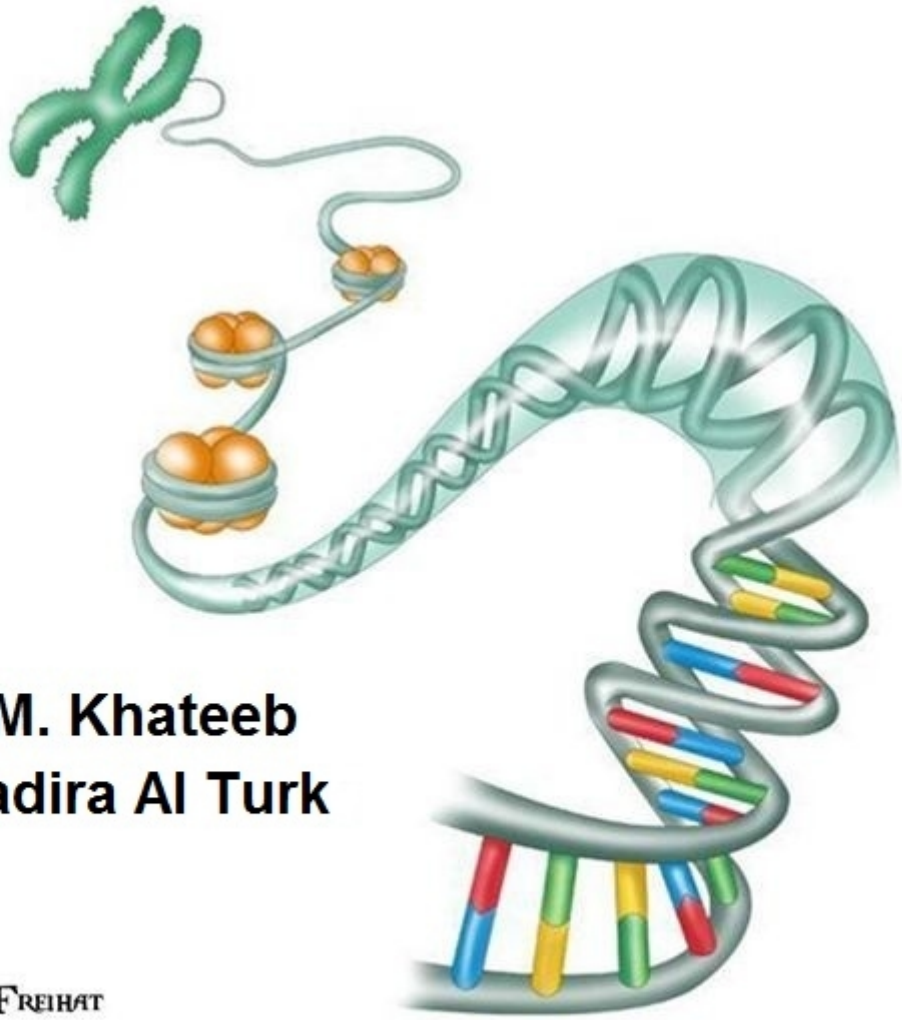
University of Jordan
Faculty of Medicine
Batch 2013-2019

Medical Committee
The University of Jordan

Genetics & Molecular Biology

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



Sheet#: 5

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Mendelian Inheritance

BE PATIENT !!!

This sheet consists many topics:

1-Students questions.

2-Genetic disease: [single gene defects]

3-Pedigree

4-Autosomal Dominant Inheritance

5-Autosomal Recessive Inheritance

6-Factors that may complicate inheritance patterns

1-Students questions:

Question1: Do we have to memorize all the examples about deletions?

Answer: you have to memorize what the doctor has focused on and explained in details.

Question2: what is the difference between Locus and allele?

Answer:

Locus: is the location of the allele on a chromosome ; e.g: allele A presents on" chromosome 1,p arm, region 3"..>>the address of the allele.

Allele: (one of the number of alternative forms of the same gene or same genetic locus), one from father , one from mother=2 alleles only. More than 2 means abnormal problem.

Question3: what do we mean by polymorphism?

Answer: Normally when we talk about a certain characteristics that are found in population in more than 1%. E.g: we have proteins that are different with one amino acid.(instead of Alanine we have tyrosine and bother are normal). They're not directly related to inheritance, not like inheriting an allele.

2-Genetic diseases:

-we classify genetic diseases into 3 main groups:

1-**Unifactorial:** a single gene inheritance, at this category we have autosomal dominant, autosomal recessive, sex-linked and mitochondrial diseases.> the disease is due to single gene.

2-**Chromosomal**: could be numerical or structural or microdeletion.

3-**Multifactorial**: when we have genetic background & environmental effects; (associated with the effects of multiple genes in combination with lifestyles and environmental factors).

-In these types of diseases; generally we will talk about the basic concept of formal genetics, and what do we mean by single gene inheritance. The most common are autosomal dominant and autosomal recessive ,in general the autosomal recessive is far much more than autosomal dominant.

-Probability and how we can calculate the risk of getting a disease in a family and a population.

-There are factors that are not directly autosomal dominant or autosomal recessive or sex-linked, sometimes there will be certain conditions which complicate that.

-In all these types of genetic problems, when we talk about a single gene, the main principle to understand them is to look for family pedigree and how are these genes found in the family to understand how this gene was inherited.

3-Pedigree

-Means how these alleles segregate to daughter cells , so we can understand the type of inheritance

-Another important principle knows how these alleles or genes will segregate, the principle of segregation, in sexual reproduction, we have 2 copies for each gene , they will be segregated during meiosis or mitosis during the division ;these alleles will be segregated to daughter cells, this segregation is independent which means that Gene 1 has nothing to do with Gene 2, each of them will segregate alone{not dependent on each other}.

-These genes remain intact

-Assortment: that genes at different sites transmitted independently; E.g: a gene presents on chromosome1 will be segregated to a daughter cell independently on other gene on chromosome2, even if they are related to same function.

-So why do we do family pedigree?

1) The most common tool for understanding genetic diseases.

2) Illustrate the relationship among the family, we can show which family members can affected which are carriers & so forth.

3) We can determine the type of inheritance: dominant, recessive or sex-linked.

4) We can determine the probability for an offspring and how many will end up with certain disease or not.

-There are basic questions you must ask about them to construct family pedigree:

1) Ask whether relatives have a similar problem.

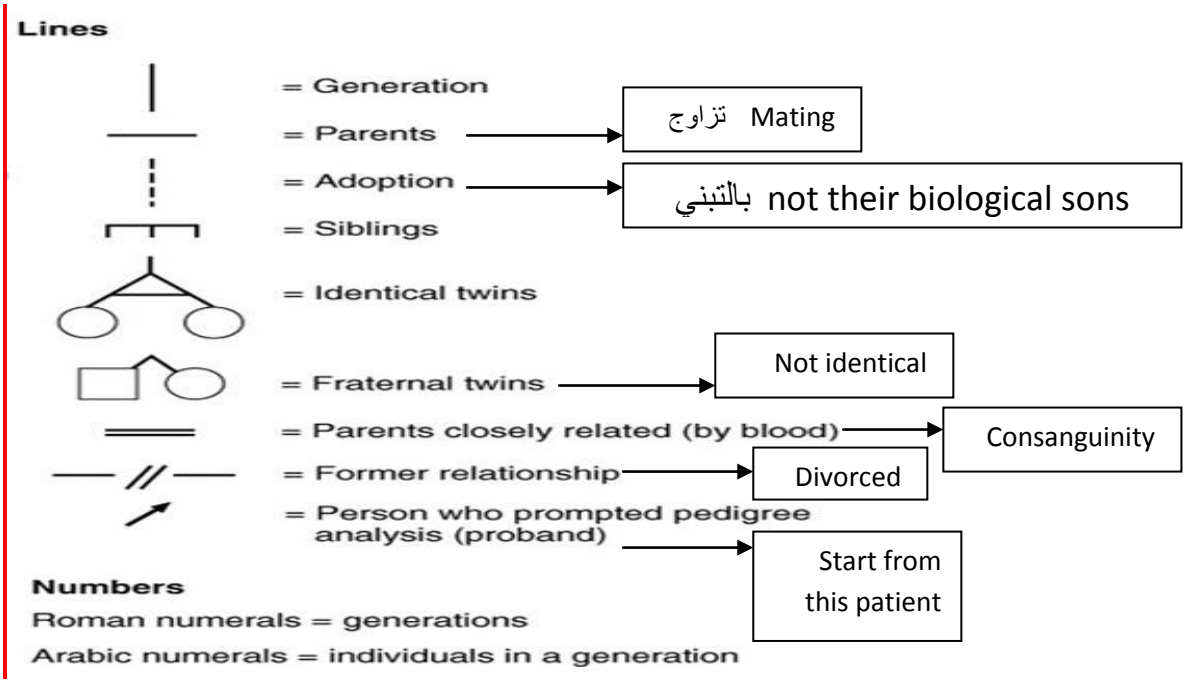
2) Ask if there were siblings who have died.

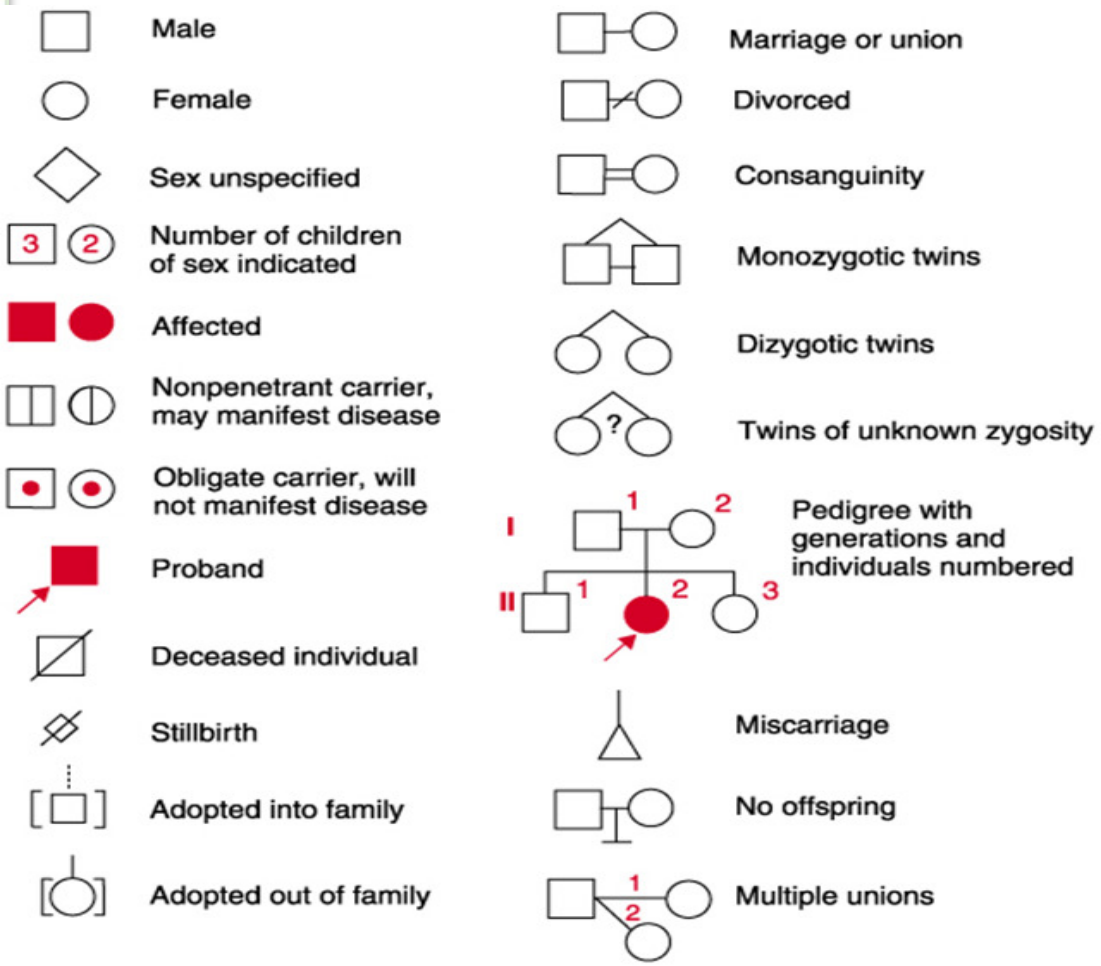
3) Inquire about miscarriages, if there is neonatal deaths.

4) Be aware of siblings with different parents (p:تعدد الزوجات).

5) Ask about consanguinity (صلة قرابة).nowadays nearly 20% marriage first degree relatives.

-Now here is a table with important symbols you should memorize them to construct a pedigree:

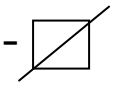




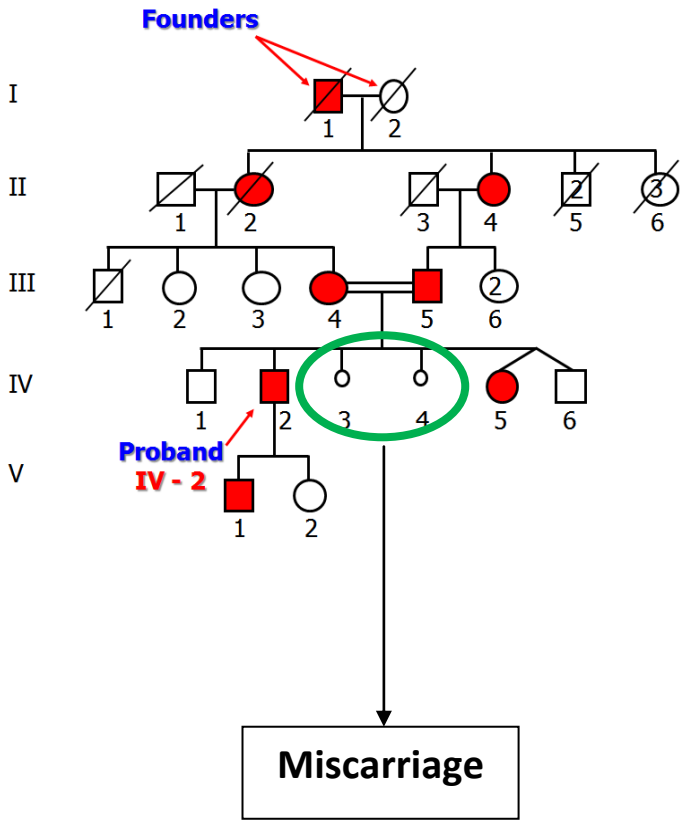
-Sex unspecified: could be male or female we don't know.

-Half filled: they are carrier for a disease.

-Dot inside the square: sex inherited disease

-  : dead

-Adopted out of family: a child placed for adoption by his or her biological family.



-we have some terms:

Dominant trait, Recessive trait, Allele, Punnett square, Genotype, Phenotype, Homozygous, Heterozygous, Probability.

-Punnett square: (diagram that is used to predict an outcome of a particular cross or breeding experiment)

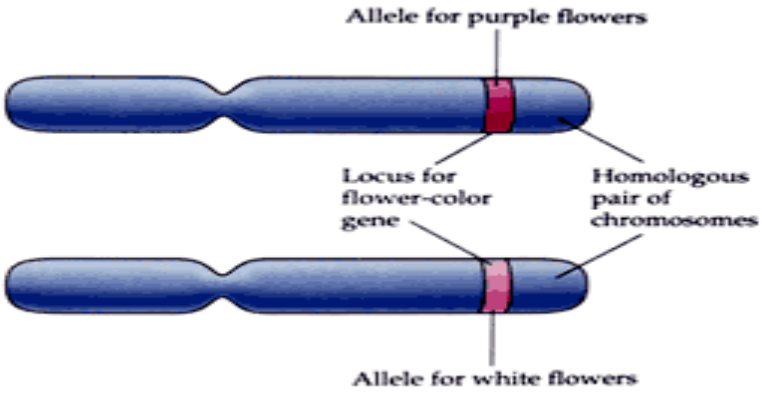
-Genotype: about alleles and genes, 2 alleles that code for the phenotype, green eyes for example .

-Phenotype: my blood group is A for example, tall, short, green eyes ,etc. The characteristics that we observe.

-Homozygous: the two alleles are identical.

-Heterozygous: Not identical alleles.

-Probability: possibility of that gene to pass to the next generation.



Punnett Square: phenotypic characteristics because we are observing the end result of mating.

	X	X
X	XX	XX
Y	XY	XY

-As you know XX female and XX male so it gives the possibilities that it'll be a male/female; 50% could be male and 50% could be female.

-If we want to talk about genotype, then we will talk about alleles, either dominant or recessive

e.g: 1) 25% TT ,25% tt, 50% Tt

	T	t
T	TT Tall	Tt Tall
t	Tt Tall	tt Short

2) 100% TT, when the two parents have dominant alleles (TT)

3) 100% tt, when the two parents have recessive alleles (tt).

4) 50% Tt , 50% tt , when the one parent has(Tt) heterozygous, and the other has(tt).

4) Autosomal dominant inheritance:

-If there is one allele is dominant that will mask the other allele and take the phenotypic characteristics.

-Here, there is no sex difference; males and females are equally affected.

-The characteristics of autosomal dominant:

1) A gene is dominant if it is expressed when heterozygous; the phenotypic characteristic will be seen. Like dwarfism.

2) No masking in each generation=no skipping.

3) Recurrence is 50%

-when we draw the pedigree, you can see in each generation there is an affected person, the mother could give her sons / daughters also the father could give his sons /daughters so there is no differential to give this or that.

-Examples:

1)Waardenburg Syndrome:

-Usually the patient has white tress (خصلة شعر) which is a phenotypic characteristic, could be in skin , hair and eyes, and there are three types of this.

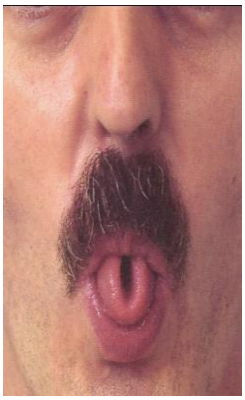
-We can look for the genotype in the pedigree to detect the alleles.

2)Marfan's syndrome 3)Huntington's Chorea

4) Osteogensis imperfecta 5)Neurofibromatosis

6)Familial Hypercholesterolemia 7) Porphyria and others

-We can see Normal physiological conditions autosomal dominant characteristics for example:



-pulling your thumb (dominant), straight or bending

-please {look at the above pictures}

-Polydactyly(either in hands or feets) زيادة في عدد الاصابع, there's an affected person in each generation.

5)Autosomal recessive inheritance:

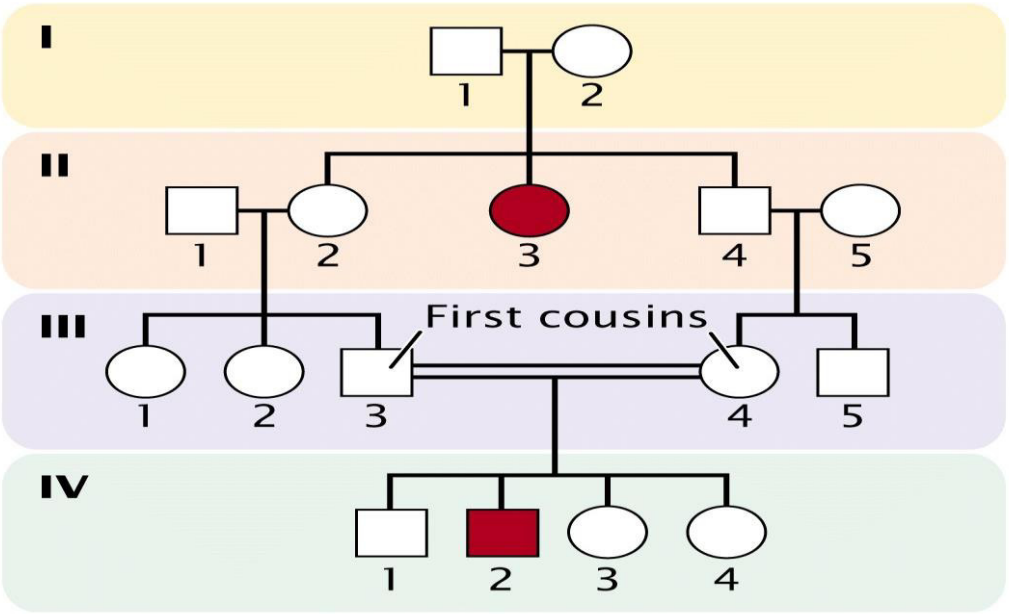
-Means to get the phenotypic characteristics when both alleles are defected.

-One allele is not enough to give the physiological or phenotypic characteristics which we can see.

-If the mother is a carrier and the father is a carrier, you will get 25% affected (have the disease), 25% normal, 50% carriers like their parents.

-Generally we call these diseases: Inborn error metabolism, generally they are enzymes defective and metabolic abnormality like: sickle cell anemia, cystic fibrosis, beta thalassemia, congenital adrenal hyperplasia, etc.

-When we draw the pedigree, we can see skip some generations= no affected person in those generations.



-if you have consanguinity mating, the possibility of having affected children is increased.

-the carrier stage can be detected by doing test otherwise there is no clinical features in carrier person.

-Concentrate here please: the doctor talked that carrier person has no clinical manifestation but as we know there are characteristics that determine by many genes we called that

"polygenic" characteristics like skin color [not a disease] where the skin color is controlled by more than one genes. Some have intermediate character for the carrier ,e.g: if you have black (BB) chicken and the other is white (WW), the intermediate has heterozygous so different color will appear, blue (BW) , [25% black ,25%white ,50% blue.]

-These heterozygous of what we are talking about, has some benefit effects, e.g: carrier for {thalassemia/sickle cell anemia/G-6-PD deficiency} he is resistant to malaria.

-How can we calculate the probability??

Biostatistics issue

-multiplication rule: two events occur together, e.g: green eyes and tall. So this equal = Probability (Green) * Probability (tall)

-Additive rule: e.g: tall or short, so this can be calculated = Probability (tall) +Probability (short).

-To know the frequency of that is important to know how spread is it in a population and how many are carriers are there for the gene. It's important for policy makers so if they know that the possibility that a carrier is 40%, they'll know that there's a high chance of people getting the disease, and they'll know how to prevent it.

	T	t
T	TT	Tt
t	Tt	tt

- The sum of the probability (alleles) in a population is constant =1
- If we have a probability of a separate gene frequency =p, the other probability of the other gene =q
- p+q=1

- when mating happens in this example: Tt x Tt
  the results : p^2 ,2pq, q^2.

-p^2*2pq*q^2=1

-p^2=pp=homozygous (normal)

-q^2=qq=homozygous (abnormal)

-2pq= 2 persons have heterozygous (carrier)

For example:

If we know that 1/2500 people has cystic fibrosis (qq) that means q^2=1/2500, >> q= 1/50 =0.02 ,

From the equation p+q=1>> p=0.98

Carrier rate= 2pq = 1/25 =0.04

6) Factors that may complicate inheritance.

-sometimes these inheritance are not always straight forward autosomal dominant or autosomal recessive, there are some conditions where we have problems:

A) Co-dominance B) germline mosaicism C)Epistasis

D) delayed age of onset E) reduced penetrance F)variable expression

Co-dominance: like in blood group, where there are two alleles and both of them show phenotypic characteristics.

*Epistasis :

-means one gene or allele can mask the function of other allele or gene, respectively.

-Epistatic allele that masks the other one. (Yes function)

-Hypostatic allele the one which has been masked. (No function)

-The best example when we talk about blood groups

-The basic structure of blood groups include: H material binds to the RBC membrane, then Glycosamines, including N-acetylglucosamine and N-acetylgalactoseamie unite with H, which will produce A substance or B substance or O.

-If the H is absent and the gene responsible for A or B is there so although we have A or B but without H material which is needed to synthesize them then no functional appearance will take place, there won't be binding; here H is epistatic allele.

-Here we can't say this is autosomal dominant or recessive.

*pleiotropy:

-One gene, the same one gene separates apparently unrelated phenotypic by a single gene.

-Means the same gene when it become defected in the liver e.g >clinical picture that is different from the same gene when it be defected in other tissue

-same gene gives different clinical manifestations.

-Examples:

1-Marfan's syndrome: AD, Affects EYE, Skeleton and Cardiovascular.

2-Cystic fibrosis: AR, affects sweat glands, pancreas, lungs.

3-Osteogenesis imperfecta : Bones, sclera ,teeth.

Genetic Heterogeneity:

-It's the opposite of pleiotropy.

-To get that characteristic you need more than one gene.

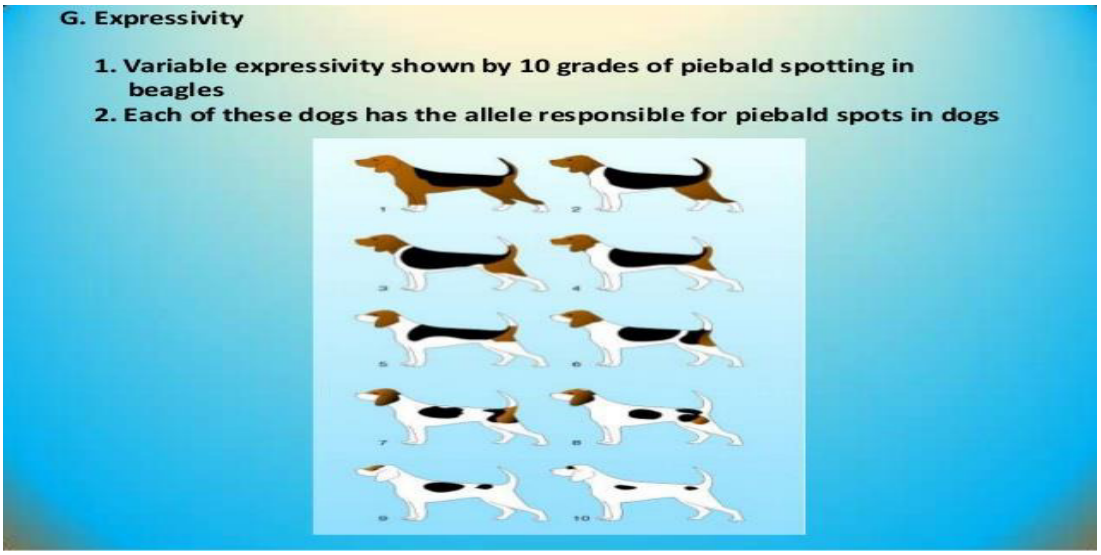
-These heterozygsity could happen due to genetic causes: like deafness, albinism, cleft palate, poor blood clotting

Or could happen on different loci; like retinitis pigmentosa ,w where more than different alleles ,more than 20 different alleles can end up with the same disease.

Variable expressivity:

-The same gene, the same character but the end results are different between the siblings, for example: dogs here are the result of the same pregnancy and same genes but different expression, genotypically they are the same.

-Variable penetrance; the clinical picture from that gene is different from one to other.



delayed age of onset:

-the clinical picture appears later and is associated with diseases like: Alzheimer disease, hemochromatosis

-في ظلمة الجهل و المحن تذكر دوماً ما من أحد أعطى إلا كافأه الله حتى و لم يكافأه أحد , أخلص النية لمن سترد روحك إليه

☺-موفقين جميعاً

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