GENETICS

Sheet no. 10

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BLUE: SLIDES, **BLACK**: DOCTOR'S NOTES, **PINK** : EXTRA FROM ME

Intro: in this lecture we will discuss the mode of inheritance or patterns or typical Mendelian inheritance laws , the previous lec was about non-medelian modes. **SIMPLE**

Lecture outline

- Nomenclature of human genes
- Monogenic Versus Multifactorial Inheritance
- Mendelian Pedigree Patterns
- Pedigree drawing

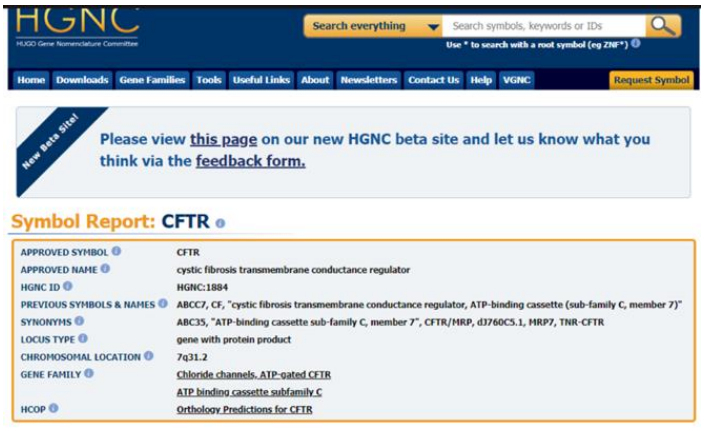
Nomenclature of Human Genes

- Human genes have **upper-case italicized** names; for example: *CFTR* gene
- ***CFTR* :cystic fibrosis transmembrane conductance regulator**
- **(**Another names of the CFTR gene are**) Synonym symbol(s):** ABCC7, MRP7, CFTR/MRP, TNR-CFTR, ABC35, dJ760C5.1

1986). The identification of the human cyst fibrosis transmembrane conductance regula tor (CFTR, also called ABCC7) (Dean et al 2001; Dean and Annilo 2005), reported in 1989 (Riordan et al. 1989), represented an-

- The process of discovery genes & diseases often involves **several competing** research groups, so that the same gene may **initially** be referred to by several different names.
- Eventually an official name is assigned by the HUGO (Human Genome Organization) Nomenclature Committee, and this is the name that should be used henceforth. Now a days we have several database for genes, we can use them in searching for genes' names.

- *Official names can be found on the nomenclature website (http:// www.genenames.org) or from entries in genome browser programs such as Ensembl, UCSC* (These are another examples of databases for laboratory & research needs)



- *Note from the record:* we only need to memorize the name of databases & why we use them.

Monogenic Versus Multifactorial Inheritance

- Monogenic: a disease is caused by one gene, Digeneic: is caused by two genes and etc
- Multifactors: connection between environment & genes that can cause diseases, these are hard to interpret in basic family degree
  - as example mitochondria inheritance which didn't follow Mendel laws,also as we **remember** that mitochondria has 37 gene, only 13 for proteins coding, so the **Mothers** are responsible for mitochondrial inheritance mutation in children
- The **simplest** genetic characters are those whose presence or absence depends on the genotype at a **single** locus.
- That is not to say that the character itself is programmed by only one pair of genes: expression of any human character is likely to **depend on the action** of a large number of genes and environmental factors.
- However, sometimes a particular genotype at one locus is both necessary and sufficient for the character to be expressed, given the normal range of human genetic and environmental backgrounds (Mendelian characters)
  - Mendelian characters can be recognized by the **characteristic pedigree patterns** they give.
- The best starting point **for acquiring information on any such character,** whether pathological or non-pathological, is the Online Mendelian Inheritance in Man (**OMIM**) database. Just another database you can search for genes details (this database is more for clinicians)

BOX 3.2 DATABASES OF HUMAN GENETIC DISEASES AND MENDELIAN CHARACTERS

This is a short selective list of especially useful, reliable, and stable resources; many other useful databases may be found by searching.

OMIM (http://www.ncbi.nlm.nih.gov/omim). The Online Mendelian Inheritance in Man database is the most reliable single source of information on human Mendelian characters and the underlying genes. The index numbers quoted throughout this book (e.g. OMIM 193500) give direct access to the relevant entry. OMIM contains about 20,000 entries, which may be sequenced genes, characters or diseases associated with known sequenced genes, or characters that are inherited in a Mendelian way but for which no gene has yet been identified. Some entries describe characters that are not normally Mendelian. In those cases the OMIM entry will concentrate on any Mendelian or near-Mendelian subset and may therefore not give a balanced picture of the overall etiology. Each entry is a detailed historically ordered review of the genetics of the character, with subsidiary clinical and other information, and a very useful list of references. Entries have accumulated text over many years with only patchy rewrites, so that the early part of an entry may not reflect current understanding.

The **Genetic Association Database** (http://geneticassociationdb.nih.gov), maintained by the US National Institute on Aging, can be searched for a list of genes and publications reporting possible genetic susceptibility factors for multifactorial diseases. At the time of writing it is at an early stage of development, but it should become a valuable resource for accessing information that is otherwise dispersed over many individual publications.

Genecards (http://www.genecards.org), from the Weizmann Institute in Israel, contains about 50,000 automatically generated entries, mostly relating to specific human genes. It gives access to a large amount of biological information about each gene.

GeneTests (http://www.geneclinics.org) is a database of human genetic diseases, maintained by the US National Institutes of Health and aimed mainly at clinicians. It includes brief clinical and genetic reviews of about 500 of the most common Mendelian diseases. There is more clinical information than in OMIM.

Types of Mendelian Pedigree Patterns

There are five typical basic Mendelian pedigree patterns:

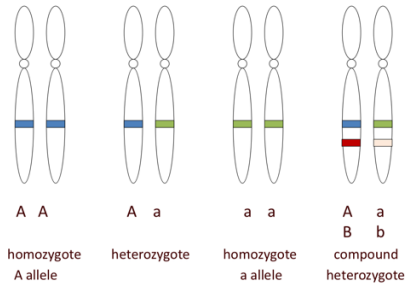
They can be **categorized based** on the location of the gene and how many copies of the mutant allele are required to express the phenotype:

- Autosomal dominant.
- Autosomal recessive.
- Y-linked.
- X-linked recessive
- X-linked dominant
- Mitochondrial inheritance → It has two types of inheritance: Mendelian and non

- Other as (non Mendel modes, genome imprinting, multifactorial, trinucletides ...etc, sometimes theses follow typical Mendel laws)

The Gene is the Unit of Inheritance

- The **location** of a gene on a chromosome is its locus. Loci plural
- **Alternative** forms of a gene at a **particular** locus are referred to as alleles.
- An individual's **genotype or (genetic composition)** at a particular locus is defined by the nature of the alleles at that locus, but **phenotype** = traits & characteristic
- If both alleles are identical, then the individual is **homozygous** at the locus. Homozygosity may refer to the presence of two normal or two mutant alleles.
- If the alleles differ, then the individual is **heterozygous** at the locus.
- If two different heterozygous mutant alleles in the same gene are present, then the individual is a **compound heterozygote.**this feature exists more in recessive genes



- Notice that (A & a) are heterozygous alleles, (B& b) are heterozygous alleles too
- And both alleles are in same gene

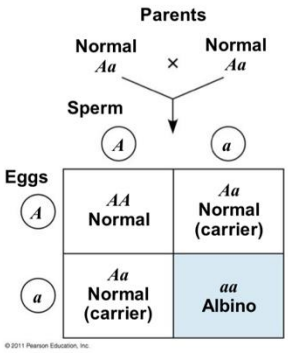
- Traits that are determined by loci on one of the **22 chromosomes are autosomal.** Traits determined by loci on the X chromosome are X-linked, and those determined by loci on the Y chromosome are Y-linked.
- We have more than 15 thousand characters in general population & more than 9 thousand diseases (Autosomal recessive & dominant)
- X-linked genes are more than 1200 gene, Which is greater than Y-linked. Y-linked genes are less than 60 & indeed they are responsible for male characteristics.

Modes of inheritance:

1st: Autosomal recessive inheritance

- Autosomal recessive traits are those traits in which the phenotype is expressed **only if homozygous** for the recessive allele, i.e.,(aa) where a=recessive allele. Two copies of the recessive allele are necessary for expression.
- Recessive alleles are responsible of disease, small (a) is the affected allele, (A) is normal or wild type allele.
- **Patients get diseases due to**: homozygous recessive alleles Or compound heterozygous that result from different mutations in same gene.
- In general, recessive traits are associated with a 1) **reduced level of activity** of a gene product (proteins & enzymes) or 2) **loss of protein's functions** or 3) **abnormal structural protein** in systems that have sufficient reserve function.
- So that loss of half the activity in the **heterozygous** state does **not** perturb the system because the dominant allele is 50% sufficient in producing active proteins.
- The **affected** individual can be of either sex and either a homozygote or compound heterozygote for a single- gene defect.
- Autosomal recessive diseases are for the most part rare and often occur in the context of parental consanguinity.
- So recessive diseases are common within Consanguineous communities مجتمع يكثر فيه زواج الأقارب
- **Heterozygous** carriers of a defective allele are **usually clinically normal**, but they may **display subtle differences in phenotype** that become apparent only with more precise testing or in the context of certain environmental influences (i.e., sickle cell disease, if the oxygen gets lower than normal some signs appear)
- It affects either sex, both have an equal chance in being affected
- Affected persons are **usually** born to **unaffected parents** who have heterozygous genes
- Parents would be described as asymptomatic carriers because they carry one mutant allele without being affected.

- **Punnett square**: give the percentage for offspring probabilities.
- Affected individuals carry two mutant alleles at the disease locus, one inherited from each parent.
- The chance that each future child born to these parents is also affected is normally 25 % (the risk that one parent transmits the mutant allele is 1/2, so the risk that they both transmit the mutant allele to a child is 1/2 × 1/2 = 1/4).



- In this example, offspring probabilities are : 25% affected, 75% is healthy (25% homozygous, 50% heterozygous). These are chances for each pregnancy

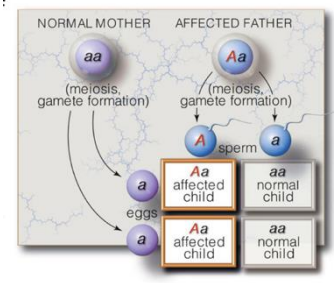
- **Not** all recessive traits are due to enzyme deficiency.

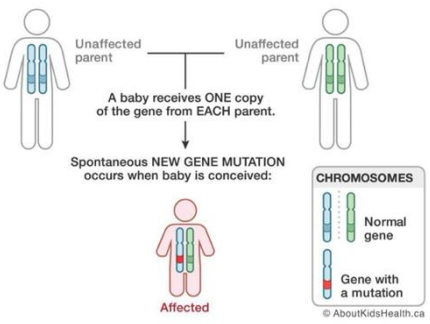
Disease	Effect	Incidence of Disease
Thallassemia (chromosome 16 or 11)	Reduced amounts of hemoglobin; anemia, bone, and spleen enlargement	1/10 in parts of Italy
Sickle-cell anemia (chromosome 11)	Abnormal hemoglobin; sickle-shaped red cells, anemia, blocked circulation; increased resistance to malaria	1/625 African-Americans
Cystic fibrosis (chromosome 7)	Defective cell membrane protein; excessive mucus production; digestive and respiratory failure	1/2000 Caucasians
Tay-Sachs disease (chromosome 15)	Missing enzyme; buildup of fatty deposit in brain; buildup disrupts mental development	1/3000 Eastern European Jews
Phenylketonuria (PKU) (chromosome 12)	Missing enzyme; mental deficiency	1/10,000 Caucasians

From the record: Phynotypes are not required for memorization, just learn some examples of recessive diseases.

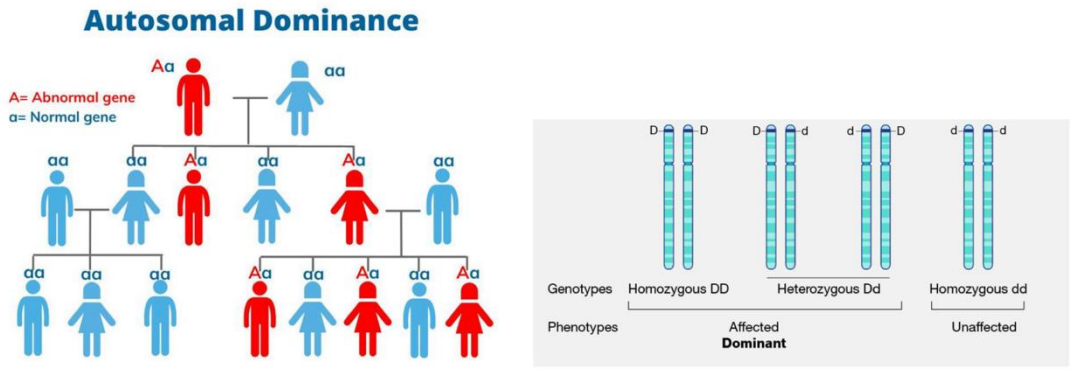
2nd: Autosomal dominant inheritance

- Every affected person has at **least one** affected parent
- **Two affected parents** can have unaffected children, if both are heterozygotes in punnett square the heterozygous affected couples will have a 25% chance of having a normal baby هون العكس يعني
- **One allele** is sufficient to cause the disease.(Aa or AA genotype)
- Two **unaffected** parents **NEVER** have affected offspring
- **De novo** could occur: an affected child is born for healthy with both parents & the mode of inheritance is dominant (as the picture indicates)
- Affected individuals appear in **every** generation عكس الصفات المتنحية
- Transmission of the disease can be from both sexes





- Mutation in only one allele is enough to express the disease
- Heterozygotes much more common than homozygotes, because AA genotype is sever which lead to death before having children
- May see variable **expressivity** and variable **age of onset,** these features are more concerned with dominant disease. (Mentioned in next page too)
- May be due to **new** mutation
- Actually, many human dominant disorders are not pure dominant, the homozygote may actually be more **severely** affected, and even may not survive, so clinically affected individuals will be heterozygote.



https://twitter.com/AllaboutAPDS/status/1597229418388541441

Figure

Example of autosomal dominant inheritance.

• If one parent has the disorder (assumed to be Aa) and the other does not (aa) then there is a 50% chance that the child will inherit the disorder and a 50% chance that they will not.

• If both parents have the disorder (assumed to be Aa x Aa) then there is a 75% chance that their children will inherit the disorder, and a 25% chance that they will not.

- same probability to get affected in both sex

➜ Examples and Features of Autosomal Dominant Inheritance

More than half of Mendelian phenotypes are autosomal dominant, Examples:

• Familial hypercholesterolemia

• Myotonic dystrophy

• Huntington disease

• Neurofibromatosis

• Polycystic kidney disease (dominant & recessive types)

• Achondroplasia (dominant مرض التقزم) all people with this syndrome have Aa genotype; because as we mentioned before AA genotype is very severe & cause early death.

➜ Autosomal Dominant disorders frequently have differences in expression of mutant genes

1. **Penetrance**: probability of any phenotype all or none concept while having genotype

2. **Expressivity**: severity/ onset of the phenotype in individuals with the same genotype

3. **Pleiotropy**: a genetic defect results in diverse phenotypic effects, as different unrelated organs & tissue.

https://youtu.be/L2TNAilLqpI?si=jodoC-xtg0i1ZzGS

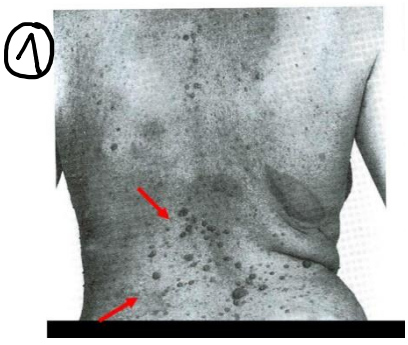
⤴ An extra video to understand first two concepts

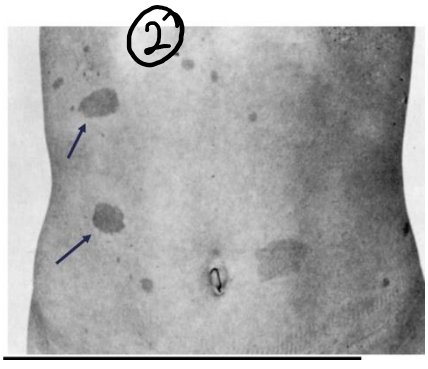
Examples: Neurofibromatosis, SHFM

✱ Neurofibromatosis

(NF1)gene- common disorder of the nervous system, can appear as: 1-4

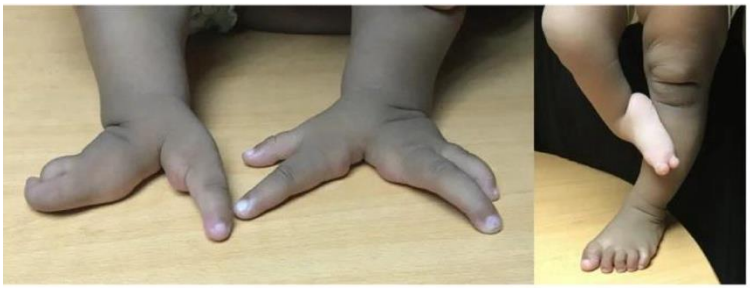
1. Multiple benign **fleshy tumors** (neurofibromas) in the skin
2. Multiple flat, irregular pigmented skin lesions known as **café au lait spots**
3. Small benign tumors (**hamartomas**) on the iris of the eye
4. Less frequently, mental retardation, **CNS tumors,**diffuse plexiform neurofibormas and the development of cancer of the NS or muscle





- Adult heterozygotes almost always demonstrate some sign of the disease → Penetrance is 100% but age-dependent
- Phenotype **ranges** from café au lait spots to tumors of the spinal cord → Variable expressivity
- **Pleiotropic** → affects skin, iris, brain, muscle,= different organs , tissues & signs

✱ Reduced Penetrance



https://bmcmedgenet.biomedcentral.com/articles/10.1186/s12881-019-0839-2

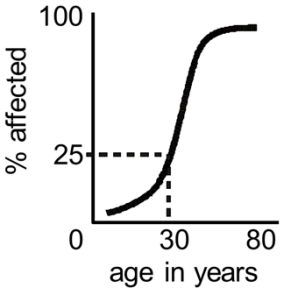
• **Ectrodactyly or split hand/foot malformation (SHFM)** is a group of genetic skeletal disorders with variable phenotypes.

• SHFM is clinically heterogeneous, varying from slight shortening of a single central digit to monodactyly in extreme cases.

• Ectrodactyly may occur as an isolated anomaly affecting only one or more limbs, or in syndromic forms with extra-limb manifestations

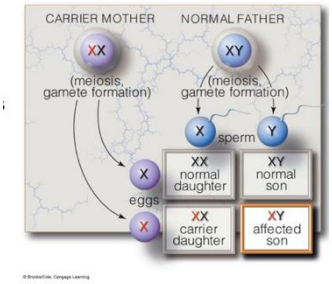
➜ Age of Onset (age-dependent penetrance)

Example: Huntington Disease

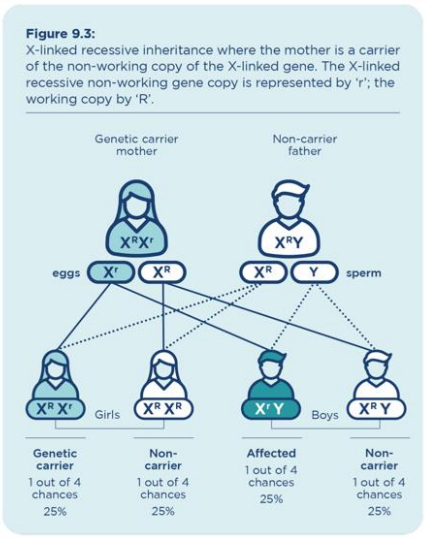


- HD is a **neurodegenerative** disease characterized by progressive dementia and abnormal movements
- HD is an exception in that severity of the disorder (clinical expression) is the samein heterozygotes and homozygotes (onset age?)
- The onset is almost at 30 if the person has a heterozygous gene, in case of homozygous it could appear earlier or cause death.

3rd: X-linked recessive inheritance



- **More males** than females have X-linked recessive genetic disorders
- **Males have only one X-chromosome and can express a single recessive allele hemizygous**
- A female heterozygote has two X chromosomes and may not show symptoms (carrier)
- Hemizygous= X-linked recessive= affected male
- Males **transmit** an X- linked trait only to their **daughters**
- Males **NEVER** transmit an X- linked trait to their **sons**.
- Males who inherit the trait will be affected.
- **Affected males are usually born to unaffected parents;** the mother is normally an asymptomatic carrier but may have affected male relatives.
- **ALL** of daughters of affected male are **carriers (heterozygotes) 100%** if the mother is healthy homozygous
- Females will express the trait ONLY if both her mother and her father have the allele
- Females who inherit the trait will be carrier
- Females may be affected if the father is affected and the mother is a carrier,
  - Female carriers with a single mutant allele can occasionally be quite severely affected and are known as manifesting heterozygotes.
- A female carrier for an X-linked recessive trait faces a **50% risk** of transmission of the trait to **any offspring**
- **Males**: affected/ healthy , **Female**: healthy/carrier/affected

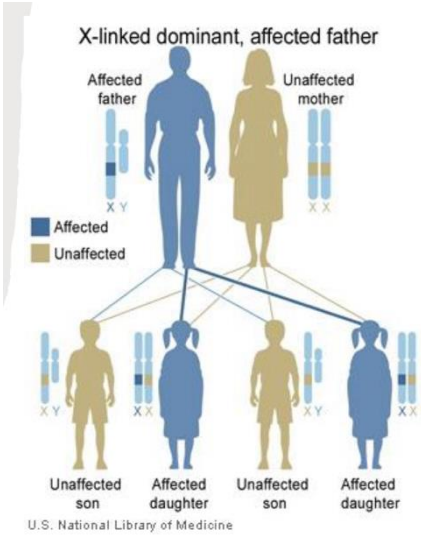


Practice this punnett question & calculate the percentages

Examples of common X-linked recessive disorders are:

1) Hemophilia A
   - One of the most common in Jordan
   - Bleeding caused by lack of blood-clotting protein
   - Gene of factor 8
   - X-linked mutation
2) Duchenne muscular dystrophy
   - Caused by DMD gene mutation
   - Degeneration of muscles caused by lack of the structural protein in muscles= dystrophin

4th: X-linked dominant inheritance



- Males and females are **equally** likely to be affected, single gene can cause defects.
- An affected female has a 50% chance of passing the trait to any offspring,
- Whereas males transmit the trait **to all of their daughter but NON of their son.**
- For an affected male, **all his daughters ,**but none of his sons, **are affected.**

5th: The pattern of inheritance of mitochondria

- Mutations in mitochondrial genes are also the cause of several single gene disorders.
- It affects both sexes.
- It is usually inherited from an **affected mother** (but is often caused by **de novo** mutations, with the mother unaffected).

- It is **not** transmitted by a father to any of his children.
- Either **caused by** a mutation **on one of the 13 gene** in mothers mitochondria (which in this case the disease doesn't follow Mendel laws), or a **nuclear gene** and follow the Mendel laws (recessive & dominant)
- Clinical manifestations are often highly variable, all sons of an affected women will get the disease but in different levels, according to numbers of affected mitochondrial cells in the children.

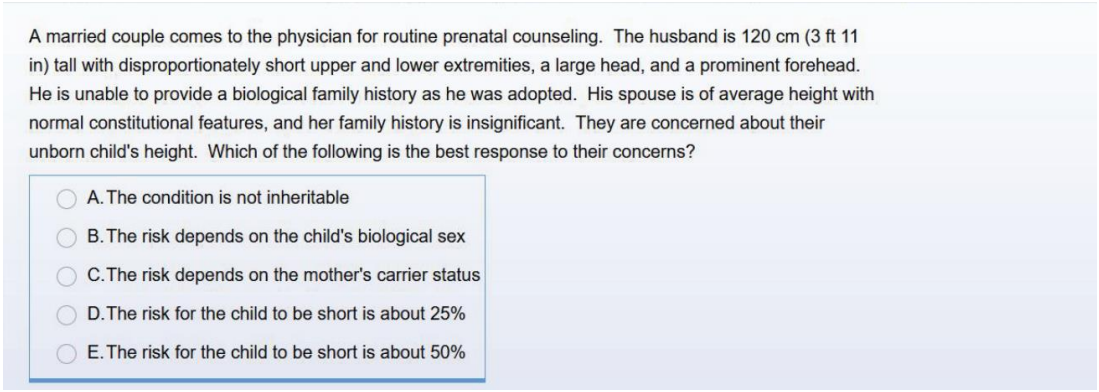
SUMMARY :

1) Human genes are written: by Upper-case & italics letters
2) Monogenic: a disease is caused by a single gene
3) Multifactorial: a disease is caused by genes & environmental factors
4) There are 5 basic typical Mendelian patterns
5) Allele: particular locus in the gene
6) Compound heterozygous gene: different mutated alleles in same genes
7) Autosomal recessive genes: appear only if it homozygous (aa), both sex have equal chance, usually heterozygous people are asymptomatic
8) Autosomal dominant: one allele is sufficient, at least one of the parents is affected, de novo can occur.
9) Penetration vs expressivity vs Pleiotropy concepts
10) Neurofibromatosis & SHEM are examples of autosomal dominant diseases
11) X-linked recessive: males are more affected
12) X-linked dominant: both sexes have equal chances
13) Mitochondria has two inheritance patterns: according to the site of defect, in its gene or nuclear gene. 13 genes out of 37 are proteins coding.

PAST QUESTIONS:

1) A recessive allele in tigers causes the white color tiger. If two normally pigmented tigers are mated and produce a white offspring, what is the percentage of their offspring would be expected to have normal pigmentation?
   a) 25%
   b) 50%
   c) About 66%
   d) 75%
   e) 90%
2) One form of hemophilia is caused by sex-linked recessive gene. Assume that a man with hemophilia marries a phenotypically normal woman whose father had hemophilia. What is the probability of having a daughter is affected with hemophilia?
   a) ¼
   b) 1/8
   c) ½
   d) 1/16
   e) ¾
3) Mitochondrial disease are clinically heterogeneous groups of disorders. If the causitve gene is located in the nuclear genome, it may be inherited:
   a) In recessive manner
   b) In dominant manner
   c) By material inheritance
   d) A & B
   e) All of above

Answers: D – A – D



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"إنما يفسد الناس نصف متكلم ونصف فقيه ونصف نحوي ونصف طبيب؛ هذا يفسد الأديان وهذا يفسد البلدان وهذا يفسد اللسان **وهذا يفسد الأبدان**."

V1

V2 : highlighted