Genetics

Modified no.9

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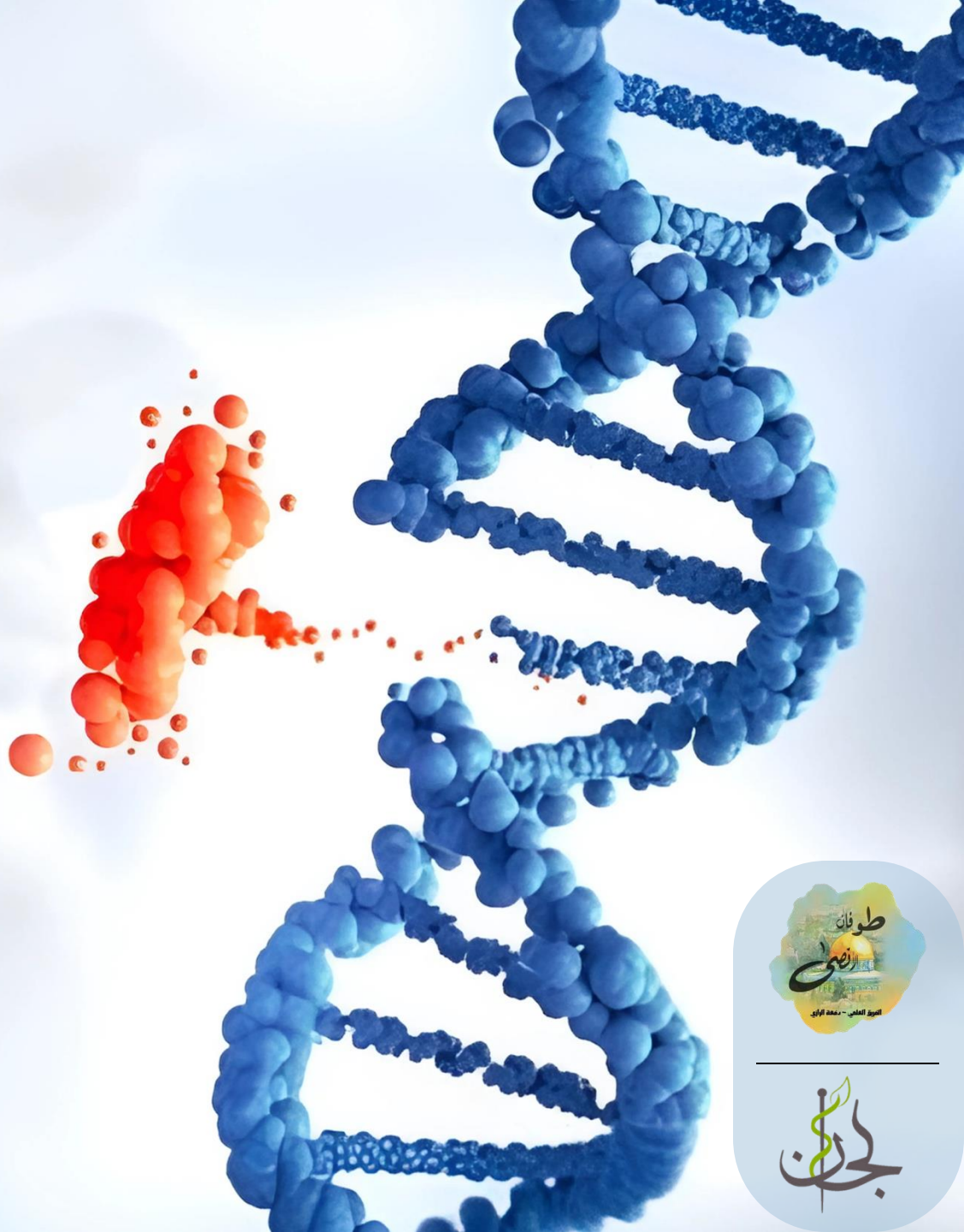


Color code

Slides
Doctor
Additional info
Important

X-Linked Dominant Inheritance

- Are fewer in number and prevalence than are X-linked recessive
- **Hypophosphatemic rickets**, a disease in which the kidneys are impaired in their ability to reabsorb phosphate.
- **Incontinentia pigmenti type 1**, a disorder characterized by abnormal skin pigmentation, conical or missing teeth, and ocular and neurological abnormalities.

→ seen **only in females** (it's severe and fatal in males they die directly after birth)

→ **Heterozygous females** (most common), having one normal X chromosome, tend generally to have **milder expression of X-linked dominant traits.** (homozygous is rare & shows severe symptoms.)

X-Linked Dominant Inheritance

- **Rett syndrome**, a **neurodevelopmental disorder** (mental retardation) seen in **1/10,000 to 1/15,000** females and in a smaller proportion of males.

→ mutations in a gene, MECP2, whose protein product binds to methylated CG sequences (almost at 5 prime region)

→ the protein helps to bring about repression of the transcription of the downstream genes

The MeCP2 protein binds to methylated CpG sequences in DNA and helps repress the transcription of nearby genes by altering the chromatin structure. Mutations in the MECP2 gene disrupt this process, leading to severe neurological disorders like Rett syndrome. So, while the mutation itself doesn't directly increase gene expression, it leads to a loss of repression, resulting in increased activity of certain genes and decrease expression of the genes that responsible for brain development. (ChatGPT)

X-Linked Dominant Inheritance

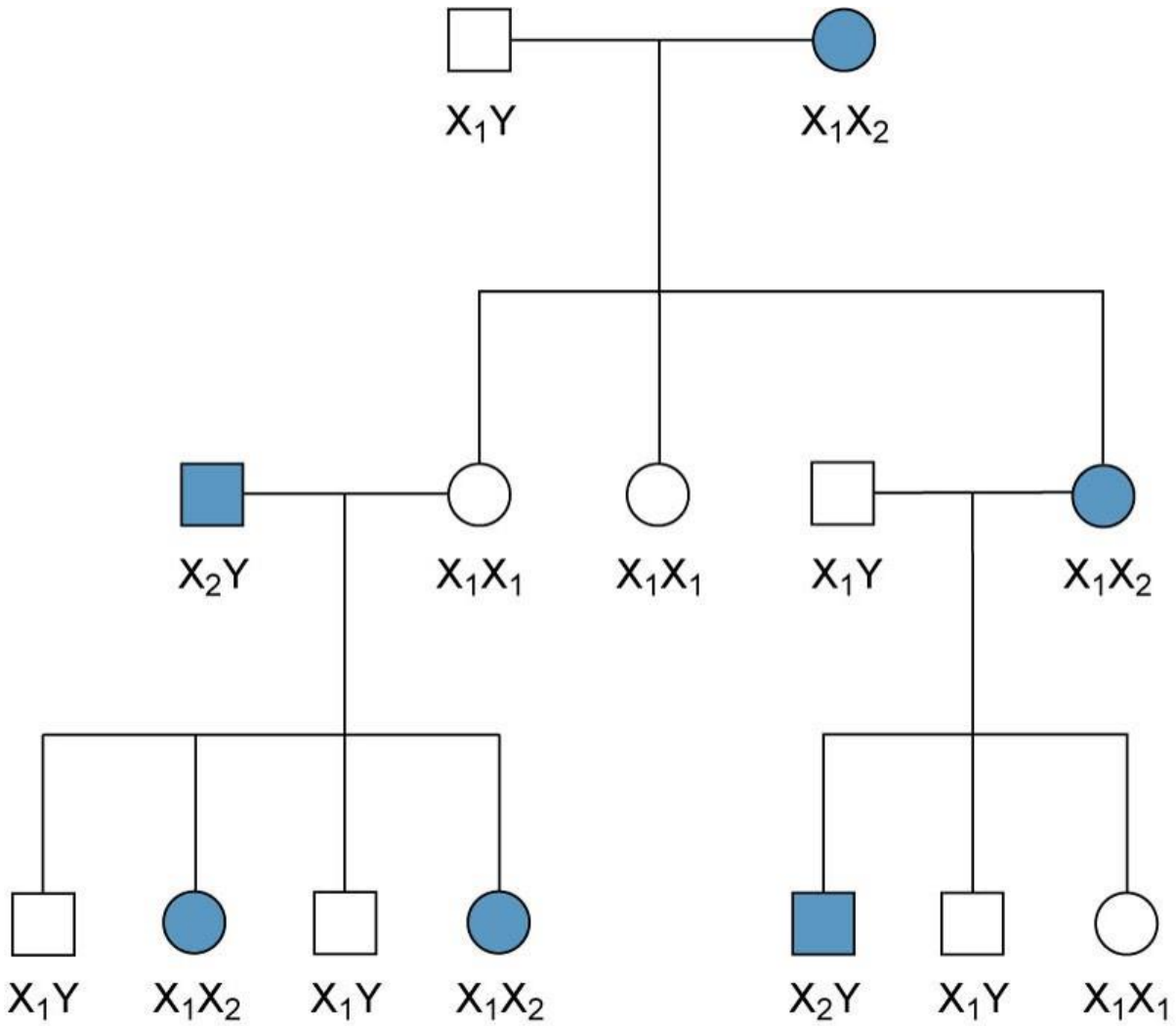


Fig. 5-7. Pedigree demonstrating the inheritance of an X-linked dominant trait. X_1, chromosome with normal allele; X_2, chromosome with disease allele.

This pedigree of X dominant inheritance looks like autosomal dominant trait. Individuals need a single copy of X linked Dominant disease to manifest the disorder.

* It's more common in females since they have two X chromosomes.

*Affected mothers pass the disease genes to some sons and daughters, while affected father only pass it for all daughters.

*If the father is only affected, 50% is the chance to get normal male of all kids not of only males, 50% is the chance to get affected female of all kids.

Very important & easy table, Dr has explained it. Take care of these differences!!

TABLE 5-2 Comparison of the Major Attributes of X-Linked Dominant and X-Linked Recessive Inheritance Patterns*

ATTRIBUTE	X-LINKED DOMINANT	X-LINKED RECESSIVE
Recurrence risk for heterozygous female × normal male mating	50% of sons affected; 50% of daughters affected	50% of sons affected; 50% of daughters heterozygous carriers
Recurrence risk for affected male × normal female mating	0% of sons affected; 100% of daughters affected	0% of sons affected; 100% of daughters heterozygous carriers
Transmission pattern	Vertical; disease phenotype seen in generation after generation	Skipped generations may be seen, representing transmission through carrier females
Sex ratio	Twice as many affected females as affected males (unless disease is lethal in males)	Much greater prevalence of affected males; affected homozygous females are rare
Other	Male-to-male transmission is not seen; expression is less severe in female heterozygotes than in affected males	Male-to-male transmission not seen; manifesting heterozygotes may be seen in females

*Compare with the inheritance patterns for autosomal diseases shown in Table 4-1.

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

(non mendelian mode of inheritance. We said that repeats expansion leads to diseases like fragile x disease.)

- 40% of all cases of X-linked mental retardation (Fragile X is the most **common** inherited disease regard mental disorder) while **Down** syndrome is more common but **not inherited**.

- Distinctive facial appearance, with large ears and long face, hypermobile joints, and macroorchidism.

- Mental retardation tends to be milder and more variable in females

(It's observed that males perform 25% excess severity of symptoms more than females.)

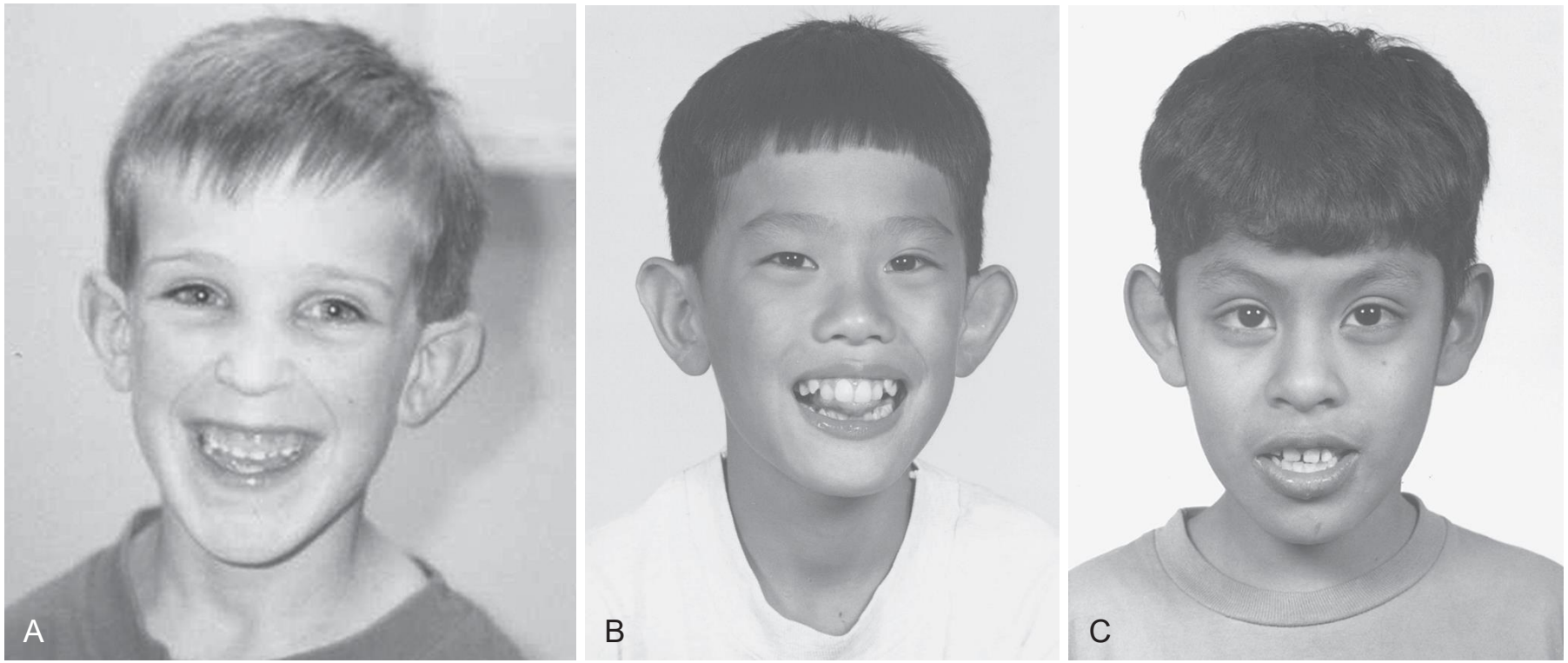


FIG 5-20 Boys with fragile X syndrome. Note the long faces, prominent jaws, and large ears and the similar characteristics of children from different ethnic groups: European **(A),** Asian **(B),** and Latin American **(C).**

FIG 5-21 An X chromosome from a male with fragile X syndrome, showing an elongated, condensed region near the tip of the long arm. (From Stein CK. Applications of cytogenetics in modern pathology. In: McPherson RA, Pincus MR, eds. *Henrys Clinical Diagnosis and Management by Laboratory Methods*. 21st ed. Philadelphia: Saunders; 2006.)

Fragile X syndrome (FXS) is named after the appearance of the X chromosome, which appears 'fragile' or 'broken' under a microscope. This characteristic fragility is observed when the X chromosome is cultured in a medium lacking folate. To study chromosomes, scientists culture lymphocytes and arrest them at the metaphase stage. In the absence of folate, fragile sites on the X chromosome become visible.

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

- Although the presence of a single fragile X mutation is sufficient to cause disease in either males or females, the prevalence of this condition is higher in males (1/4,000) than in females (1/8,000)

- Males who have affected descendants but are not affected themselves are termed "normal transmitting males''

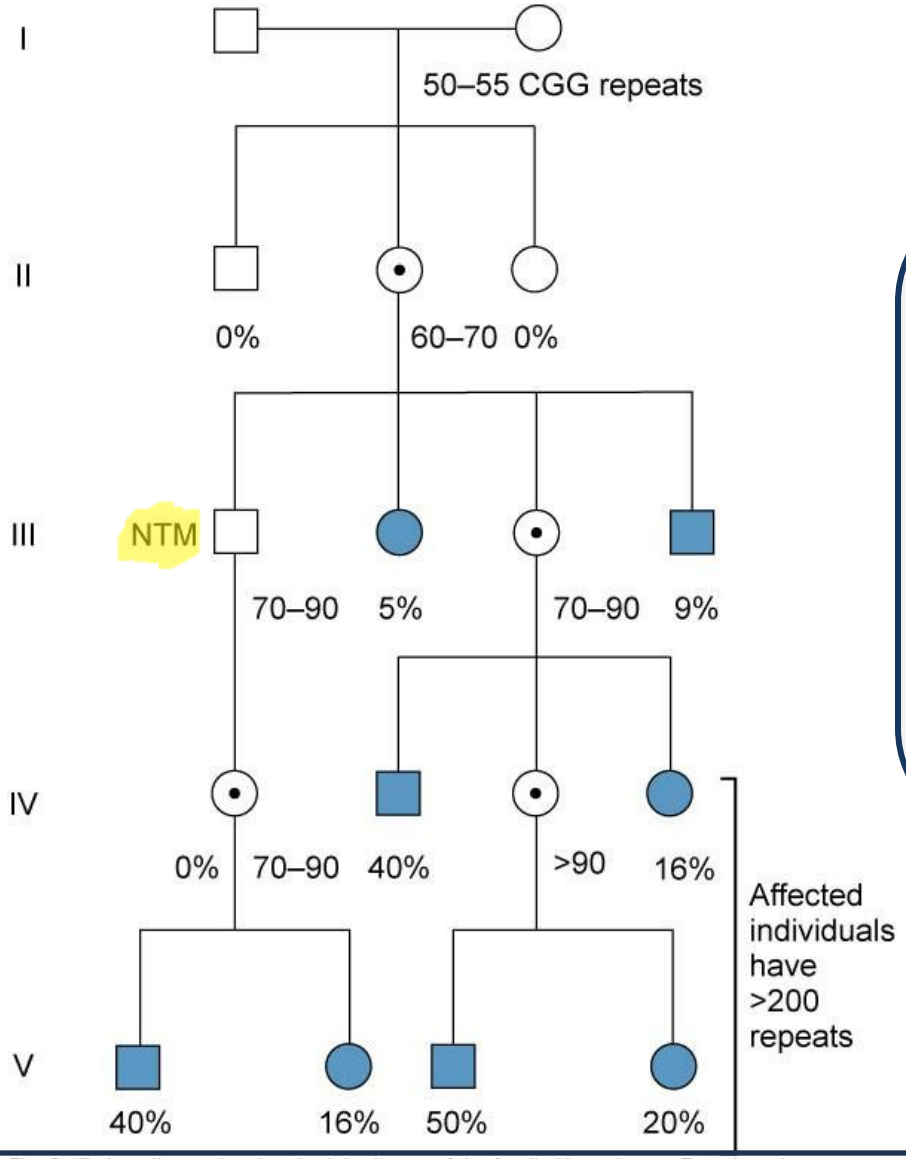


Fig. 5-17. A pedigree showing the inheritance of the fragile X syndrome. Females who carry a premutation (50 to 230 CGG repeats) are shown by *dotted* lines. Affected individuals are represented by *solid* symbols. A normal transmitting male, who carries a premutation of 70 to 90 repeat units, is designated NTM. Note that the number of repeats increases each time the mutation is passed through another female. Also, only 5% of the NTM's sisters are affected, and only 9% of his brothers are affected, but 40% of his grandsons and 16% of his granddaughters are affected. This is the Sherman paradox.

In succeeding generations, the number of CGG repeats increases compared to the parents. Females tend to expand the repeats, leading to earlier onset of disease, while males typically do not expand the repeats, and the disease does not appear early in their children. A repeat range of 50–230 is referred to as a premutation or normal transmitting allele (indicated by dotted lines), whereas solid symbols represent affected individuals.

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

(The syndrome is caused by a mutation in the FMR1 gene, leading to an expansion of CGG trinucleotide repeats The excessive CGG repeats lead to hypermethylation of the CGG island near the FMR1 gene. This methylation inhibits the transcription of the gene and lower the production of mRNA , preventing the production of the fragile X mental retardation protein (FMRP), which is essential for normal neural development)

- ***FMR1***
- the 5' untranslated region of the gene contains a CGG repeat unit that is present in 6 to 50 copies in normal individuals

- Those **with fragile X syndrome have 230 to 1,000 or more** CGG repeats (a **"full mutation"**)

- An intermediate number of repeats, ranging approximately from 50 to 230 copies, is seen in normal transmitting (carriers) males and their female offspring.

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

(In ***less*** than 5% the disease is caused by loss of FMR1 gene function rather than Having expansion of CGG repeats.)

- Those with full mutations have no FMR1 mRNA in their cells

(Premutation individuals have enough FMR1 mRNA expression, while affected ones don't have enough mRNA.)

- The degree of methylation is correlated with severity of expression of the disorder

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

- Another fragile site distal to the fragile X site
- ***FRAXE***
- associated with an **expansion of a CGG trinucleotide** repeat in the 5' region of a **gene labeled *FMR2***
- subsequent **hypermethylation, and a phenotype that includes mental retardation**
- **the CGG repeat at this locus can expand when transmitted through either males or females.**

- **advances have also improved diagnostic accuracy**

With modern technology we can detect size of CGG repeats.

Y-Linked Inheritance

Although it consists of approximately 60 Mb of DNA, the Y chromosome contains relatively few genes.

Y chromosome is the smallest one

Only a few dozen Y-linked, or holandric, genes have been identified. These include the gene that initiates differentiation of the embryo into a male, several genes that encode testis-specific spermatogenesis factors, and a minor histocompatibility antigen (termed HY).

SRY gene that is responsible for initiation of male sex determination. It is located on the short arm of Y chromosome

Azoospermia factors that are present on the long arm of Y chromosome

Several housekeeping genes are located on the Y chromosome,

and they all have inactivation-escaping homologs on the X chromosome.

Transmission of Y-linked traits is strictly from father to son.

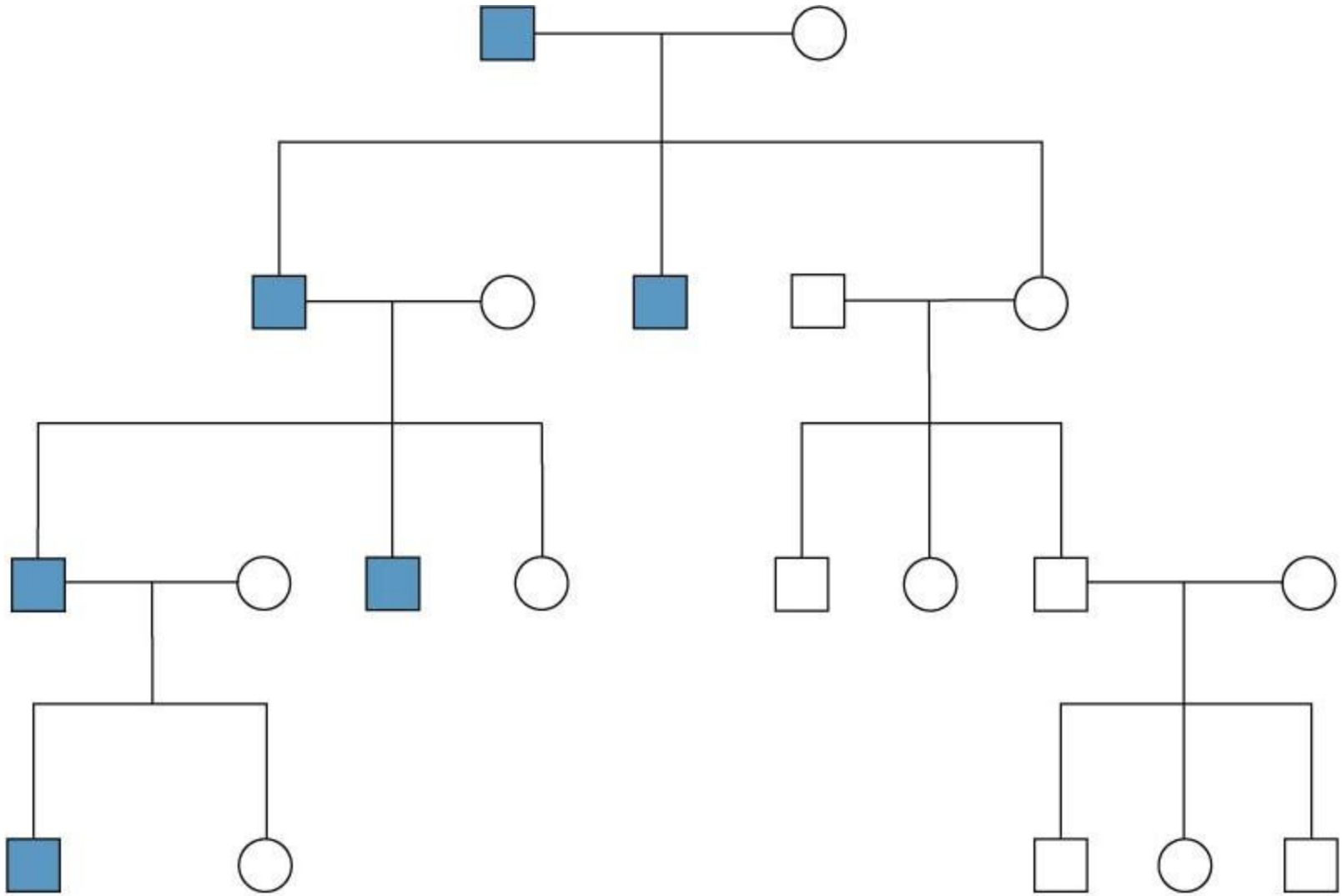


Fig. 5-8. Pedigree demonstrating the inheritance of a Y-linked trait. Transmission is exclusively male to male.

SEX-LIMITED AND SEX-INFLUENCED TRAITS

A sex-limited trait occurs in only one of the sexes-due, for instance, to anatomical differences. Inherited uterine or testicular defects would be examples.

An example of a sex-influenced trait is male-pattern baldness, which occurs in both males and females but much more commonly in males.

Contrary to oft-stated belief, male-pattern baldness is not X-linked; It is thought to be inherited as an autosomal dominant trait in males, whereas in females it is inherited as an autosomal recessive trait.

Female heterozygotes can transmit the trait to their off-spring but do not manifest it.

Females display the trait only if they inherit two copies of the gene. Even then, they are more likely to display marked thinning of the hair, rather than complete baldness.

MITOCHONDRIAL INHERITANCE

- A small but significant number of diseases are the result of mitochondrial mutations
- Each human cell contains several hundred or more mitochondria in its cytoplasm
- Oxidative phosphorylation: ATP: cell survival

MITOCHONDRIAL INHERITANCE

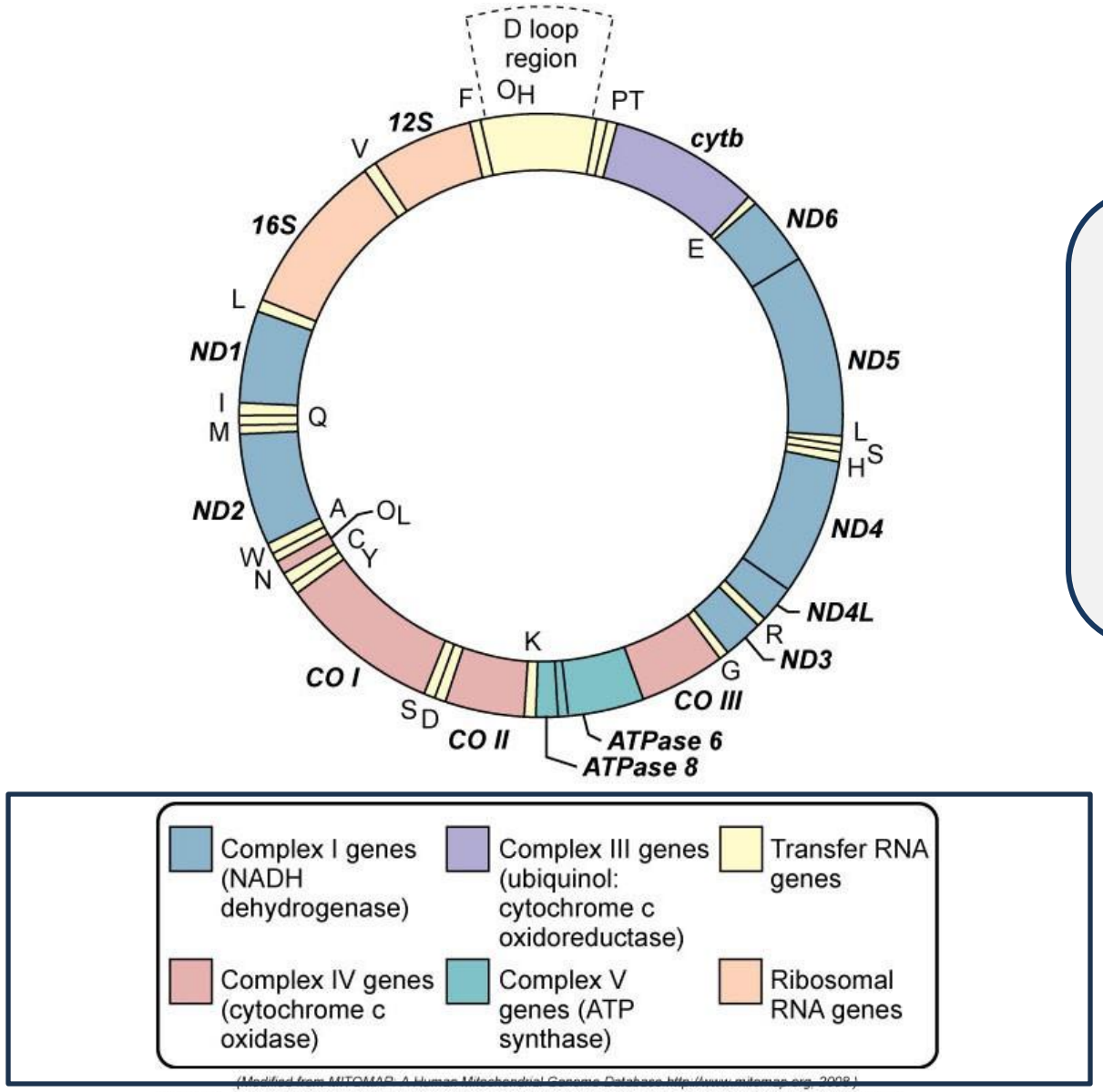
- several copies per organelle
- 16,569 base pairs arranged on a double-stranded circular molecule
- Encodes two ribosomal RNAs, 22 transfer RNAs (tRNAs), and 13 polypeptides involved in oxidative phosphorylation.

Oxidative phosphorylation doesn't need only 13 poly peptides, there are 90 or more produced in nuclear genome and transferred into mitochondria to be involved in oxidative phosphorylation. So most oxidative phosphorylation peptides arise from nuclear genome.

- Transcription of mitochondrial DNA (mtDNA) takes place in the mitochondrion
- mtDNA contains no introns
- mtDNA is inherited exclusively through the maternal line

Sperm contain only a few mitochondria that help in fertilization but do not reach the fertilized oocyte or contribute to embryo development.

During fertilization, **only the head of the sperm (with the nuclear DNA)** enters the egg.
The midpiece, which contains most of the mitochondria, usually does **not enter the egg**



(Modified from MITOMAP: A Human Mitochondrial Genome Database http://www.mitomap.org, 2008.)

Fig. 5-9. The circular mitochondrial DNA genome. Locations of protein-encoding genes (for reduced nicotinamide adenine dinucleotide [NADH] dehydrogenase, cytochrome c oxidase, cytochrome c oxidoreductase, and adenosine triphosphate [ATP] synthase) are shown, as are the locations of the two ribosomal RNA genes and 22 transfer RNA genes (designated by single letters). The replication origins of the heavy (OH) and light (OL) chains and the noncoding D loop (also known as the control region) are shown.

Mitochondria contain copies of double-stranded circular DNA, which include genes for dehydrogenase enzymes, cytochrome enzymes, and ribosomal RNA.

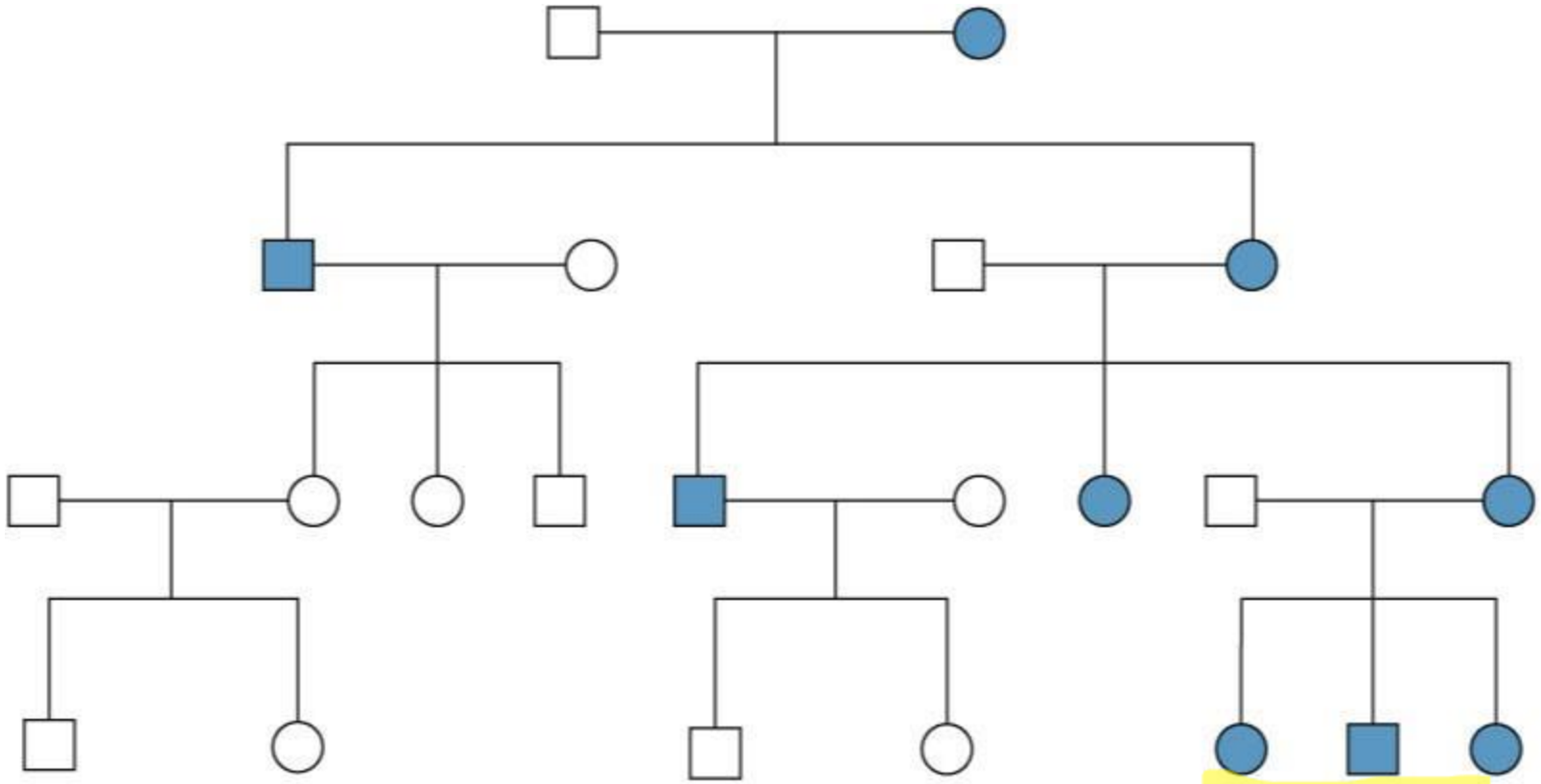


Fig. 5-10. A pedigree showing the inheritance of a disease caused by a mitochondrial DNA mutation. Only females can transmit the disease mutation to their offspring. Complete penetrance of the disease-causing mutation is shown in this pedigree, but heteroplasmy often results in incomplete penetrance for mitochondrial diseases.

MITOCHONDRIAL INHERITANCE

- 10 times higher mutation rate (than nuclear mutations) because mitochondrial DNA does not contain repair mechanism. Also, radicals from oxidative phosphorylation can harm mitochondrial genome and cause mutations.

- Heteroplasmy: a single cell can harbor some molecules that have an mtDNA mutation and other molecules that do not.
- The larger the proportion of mutant mtDNA molecules, the more severe the expression of the disease.

- As cells divide, changes in the proportion of mutant alleles can occur through chance variation or because of a selective advantage.

Chance variation occurs when mutant mitochondrial genomes are passed to the next generation. Mutations such as deletions in mitochondrial DNA may confer a selective advantage by shortening the genome, which increases the replication rate.

MITOCHONDRIAL INHERITANCE

- Each tissue type requires a certain amount of mitochondrially produced ATP for normal function.
- The central nervous system consumes about 20% of the body's ATP production and therefore is often affected by mtDNA mutations.

- Mitochondrial disorders can be classified according to the type of mutation that causes them.

- Missense mutations in protein-coding mtDNA genes cause one of the best-known mtDNA diseases, Leber hereditary optic neuropathy (LHON). individuals experience rapid, irreversible vision loss beginning in the third decade of life.

MITOCHONDRIAL INHERITANCE

- Single-base mutations in a tRNA gene can result in myoclonic epilepsy with ragged-red fiber syndrome (MERRF) related to epilepsy ,ataxia, seizures & myopathy
- MERRF is heteroplasmic and thus highly variable in its expression.
- Another example of a mitochondrial disease caused by a single-base tRNA mutation is mitochondrial encephalomyo- pathy and stroke-like episodes (MELAS). This mutation 1-2% is related to deafness.

(Mitochondrial defects may also be associated with some cases of Diabetis Mellitus and Alzheimer disease, as mitochondrial mutations leads to aging).

- Duplications and deletions: Keams-Sayre disease (muscle weakness, cerebellar damage, and heart failure), Pearson syndrome (infantile pancreatic insufficiency, pancytopenia, and lactic acidosis), and chronic progressive external ophthalmoplegia (CPEO).

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!