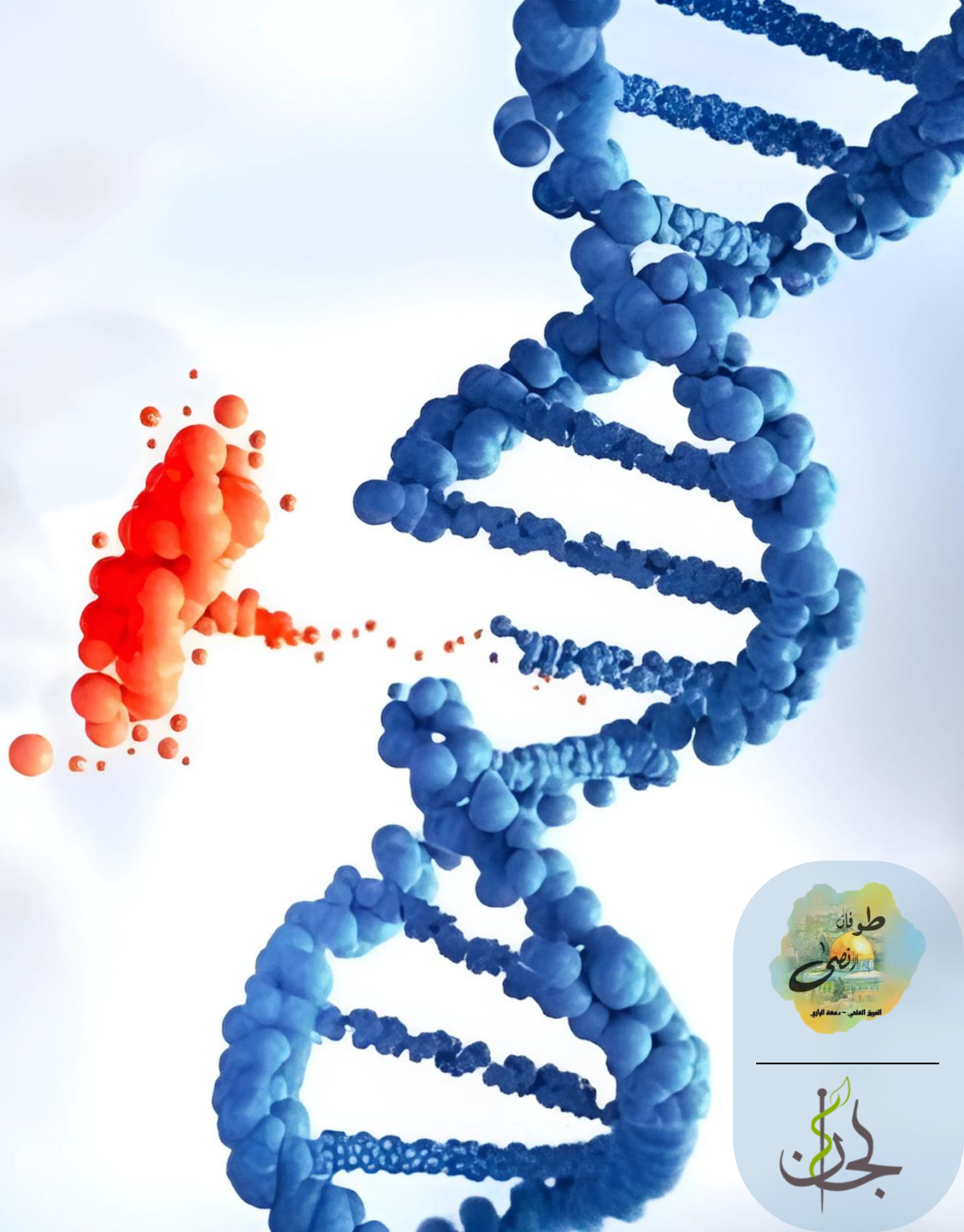
Genetics

Modified no.

Writer: لمى أبو إسماعيل وسارة عمر

Editor: خديجة ناصر وسديل مأمون

Doctor: زيد أبو ربيحة



welcome to genetics 4th lecture

To make it easier, I wrote summaries at the end of each long box to go through it if you want (but make sure to read doctor's words for exam purposes 😊)

Say بسم الله and let's start

Table of content

Color code

- Slides
- Doctor
- Additional info
- Important

Genetic Variation

Talking about human beings in general, there is a remarkable degree of variation, meaning that the gene sequences of each individual are not identical to those of others, and we can see this in different genetic traits. You can observe it in eye color, height, skin color, etc. This is because of the variations in our genome.
But if we talk about gene coding regions that are involved in our biological processes, genetic variations could be the cause of genetic diseases like cystic fibrosis and neurofibromatosis.

So changes in DNA sequence result in different traits and genetic diseases if present.

=> To sum up: our genetic variations contribute to the differences between us in different traits like skin color, and these variations might cause diseases

All genetic variation originates from the process known as mutation, which is defined as a change in DNA sequence.

Mutations can affect either somatic or germline cells (cells that produce gametes).

Mutations in **somatic cells** (all cells other than germline cells) can lead to cancer and are thus of significant concern. These mutations often occur later in life due to exposure to chemicals that cause changes in the DNA sequence (mutations).

Our attention will be directed to **germline mutations** because these can be transmitted from one generation to the next.

As a result of mutations, a gene may differ among individuals in terms of its DNA sequence. The differing sequences are referred to as alleles.

A gene location on a chromosome is termed a locus (from the Latin for ”place”). Thus, we might say that an individual has a certain allele at the B-globin locus on chromosome 11.(so the site of B-globin gene is called locus)

If an individual has the same allele on both members of a chromosome pair, he or she is said to be a homozygote. If the alleles differ in DNA sequence, the individual is heterozygote. (check the next slide)

The alleles that are present at a given locus are referred to as the individual's genotype (it is the composition of a gene at 2 chromosomes in specific loci)

Some loci vary considerably among individuals. If a locus has two or more alleles whose frequencies each exceed 1% in a population (means if this region sequence differ between 2 human by more than 1% in a population), the locus is said to be polymorphic (many forms- different nucleotide sequences). The polymorphic locus is often termed a polymorphism. (polymorphic= the site of a specific nitrogenous base in a specific site in a locus of a gene can be A or C,etc)

let's continue with the previous example

This locus will be at chromosome 11 from the father & mother. If the sequence of the gene differs between maternal & paternal chromosomes, this will lead to 2 different alleles (heterozygote" while if the sequence is the same then the 2 alleles are similar "homozygote")

!!… keep in mind: here "homo/heterozygote" doesn't indicate disease presence or absence but only the DNA sequence

⇒ If there is a difference but in a non-coding area => no problem
⇒ If there is a difference in a coding area => It is possible that a mutation is leading to disease.

!!.. Keep in mind: polymorphism refers to a change at a locus, while polymorphic describes a locus that has the chang

---

⇒ To sum up, homozygote = no difference in alleles between paternal & maternal copies for a specific locus
⇒ Heterozygote = difference in alleles between the 2 chromosome copies

⇒ About the last point in the previous slide, if variability in a specific locus is more than 1% then we say this locus is polymorphic = has different forms

- Everyone has two alleles for any given locus.
- Let's say we are studying height, where tall = H and short = h.
- Based on the Punnett square here, Parent 1 is tall (genotype: HH) => homozygous for tall height,
- while the other parent is short (genotype: hh) => homozygous for short height.
- As a result, all of their offspring will inherit one H allele and one h allele, making their genotype Hh (heterozygous for height).
- Since H is dominant, all the children will be tall, but their genotype is heterozygous, meaning they carry one tall allele (H) and one short allele (h) at the height locus.

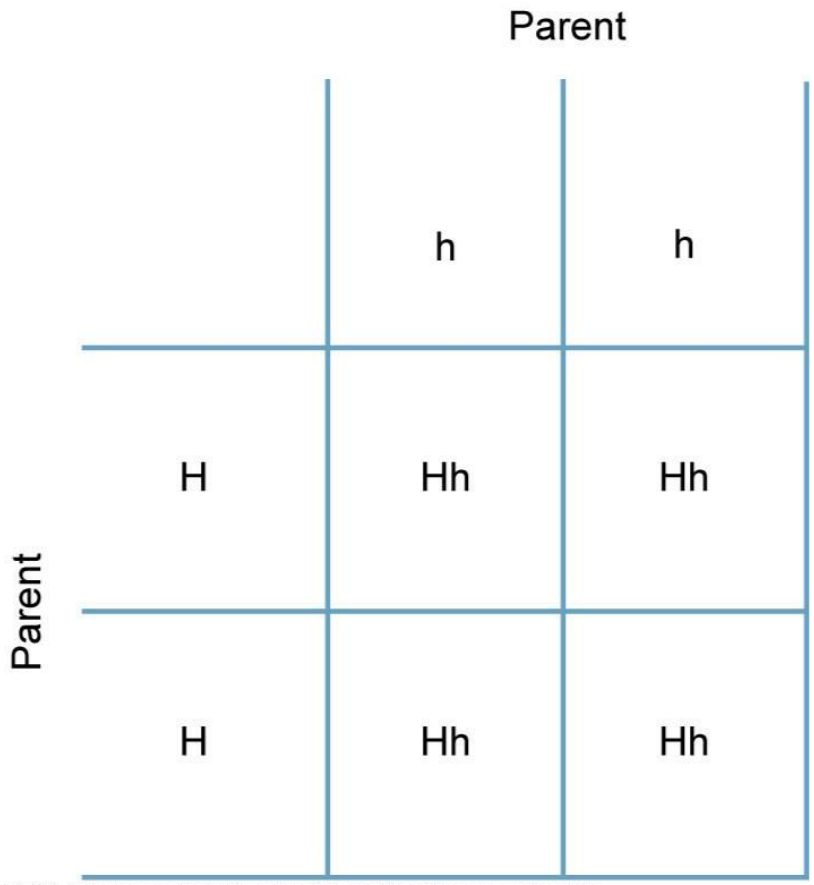


Fig. 3-1. Punnett square illustrating a cross between *HH* and *hh* homozygote parents.

In this example, both parents are heterozygous for tall height.
- Parents' genotype: Hh
- Parents' phenotype: Tall

Each parent has two different alleles at the height locus:
- H on one chromosome
- h on the other chromosome

When these parents reproduce, their offspring will have the following possible genotypes (based on a Punnett square):
- HH (¼ or 25%) → Homozygous tall
- Hh (½ or 50%) → Heterozygous tall
- hh (¼ or 25%) → Homozygous short

Phenotypically:
- 75% (¾) of the offspring will be tall (HH or Hh).
- 25% (¼) of the offspring will be short (hh).

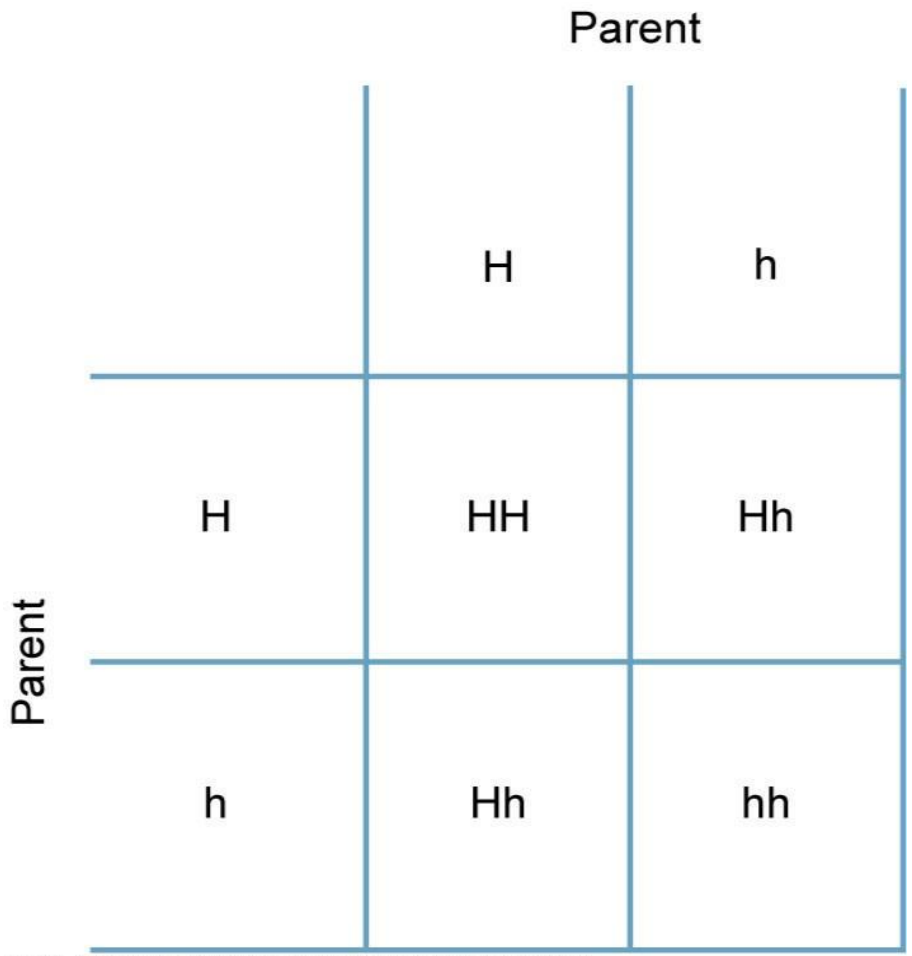


Fig. 3-2. Punnett square illustrating a cross between two *Hh* heterozygotes.

MUTATI0N—THE SOURCE OF GENETIC VARIATION

Types of Mutation

A. Base pair substitution:

- **Silent substitution**: do not change the aa sequence **even if DNA sequence had a base pair changed, amino acids will remain the same = no change in genotype (no change in the protein, enzymatic activity and so on)**
- **Non silent**:

→ **Missense mutations**: produce a change in a single aa ** even though it's 1 mutation in 1 aa but outcomes may be devastating as in thalassemia and sickle cell anemia

→ **Nonsense mutations**: produce one of the three stop codons in the mRNA (UAA, UAG, or UGA) if they've shown up in the middle of protein production, the process will stop and the protein will not be functioning (premature protein).Also, the opposite may happen (mutation leads to longer mRNA than it should be)

B. Deletions or Insertions of one or more base pairs

→ **Frameshift mutations**

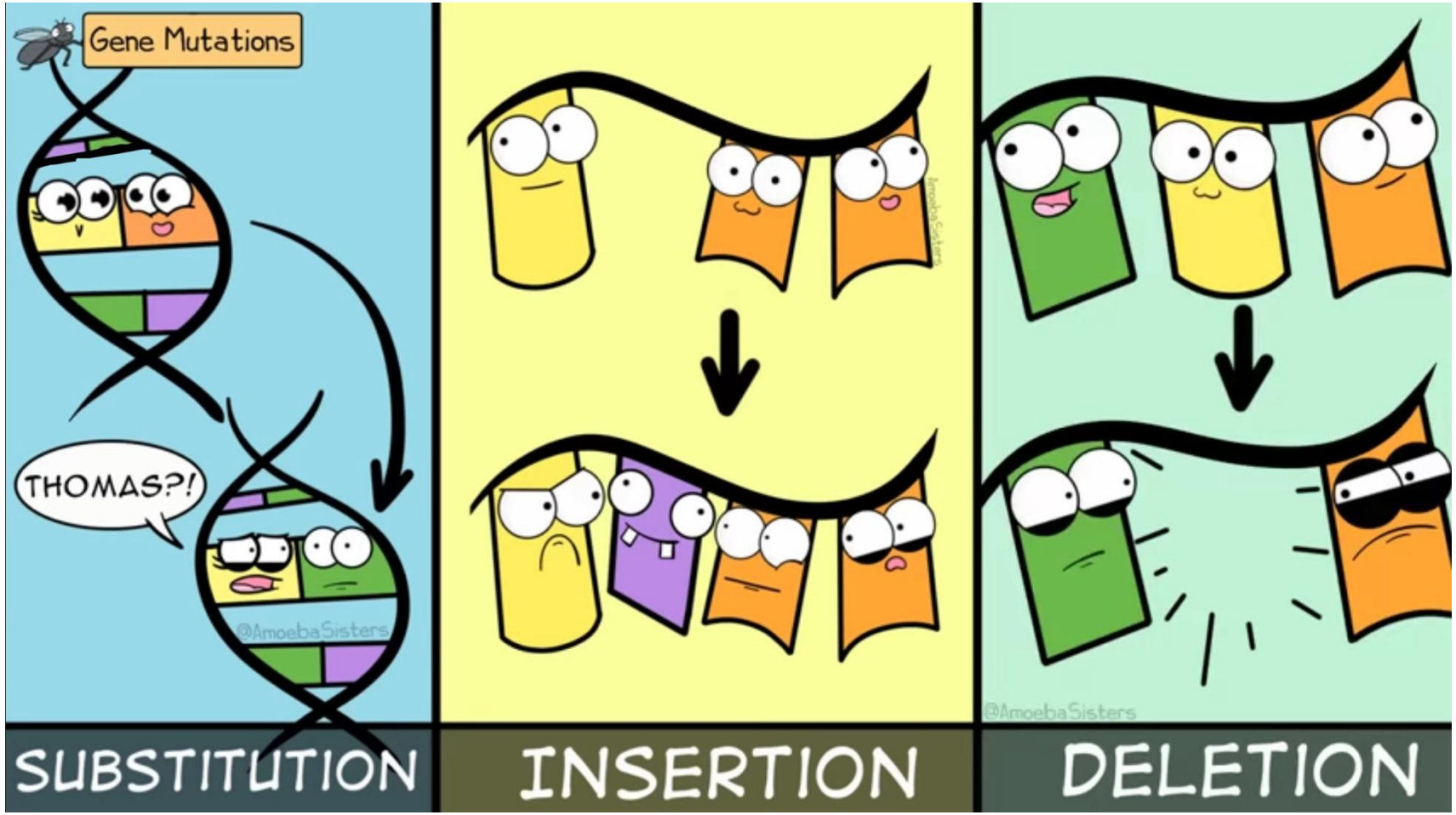
5'-ACT GAT TGC GTT-3' to 5'-ACT GA A TTG CGT-3'

Thr-Asp-Cys-Val to Thr-Glu-Leu-Arg

- **Here we're discussing mutations at molecular level NOT at cellular level**

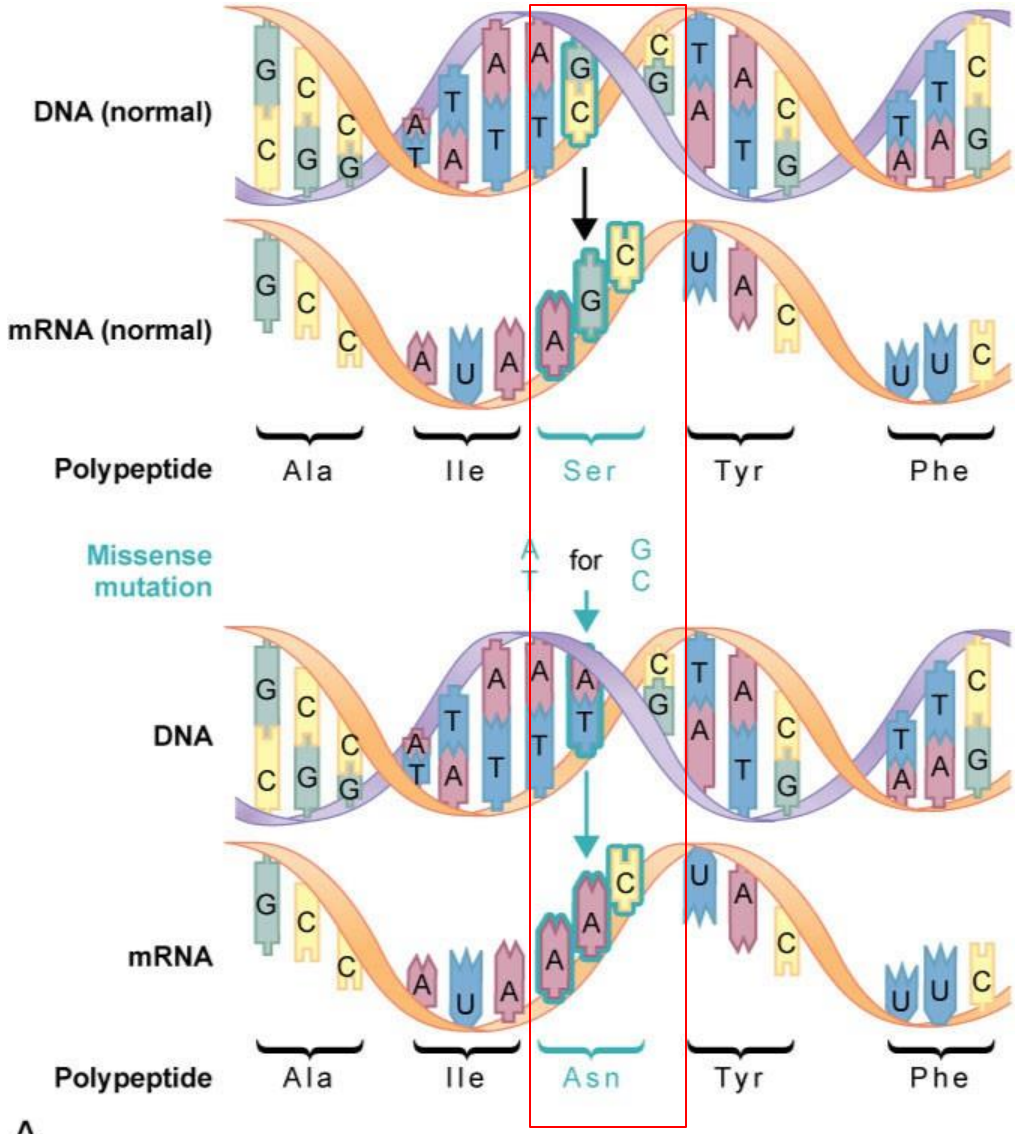
Extra image for fun

check this link from 4:05 for mutation types : https://youtu.be/3jwDl7nYBPM?feature=shared



- In the first raw, there's a normal DNA
- In the second: mRNA which is a copy of a single DNA strand and differs from DNA by the presence of U (uracil) instead of T (thiamine)

- In 3rd raw, (A,T) has replaced (G,C), so **aa will differ** (from Ser => Asn) => this is a **missense** mutation



A

Fig. 3-3. Base pair substitution. Missense mutations **(A)** produce a single amino acid change, whereas nonsense mutations **(B)** produce a stop codon in the mRNA. Stop codons terminate translation of the polypeptide.

- **Non sense mutation**
- (A T) is replaced by (CG) at DNA level
- At the m RNA level it is transcribed into a **Stop codon (UAA)**

This leads to an earlier termination of translation, producing a shorter protein sequence. In some cases, however, it may result in longer proteins under certain conditions. Both the longer and shorter peptides are nonfunctional.

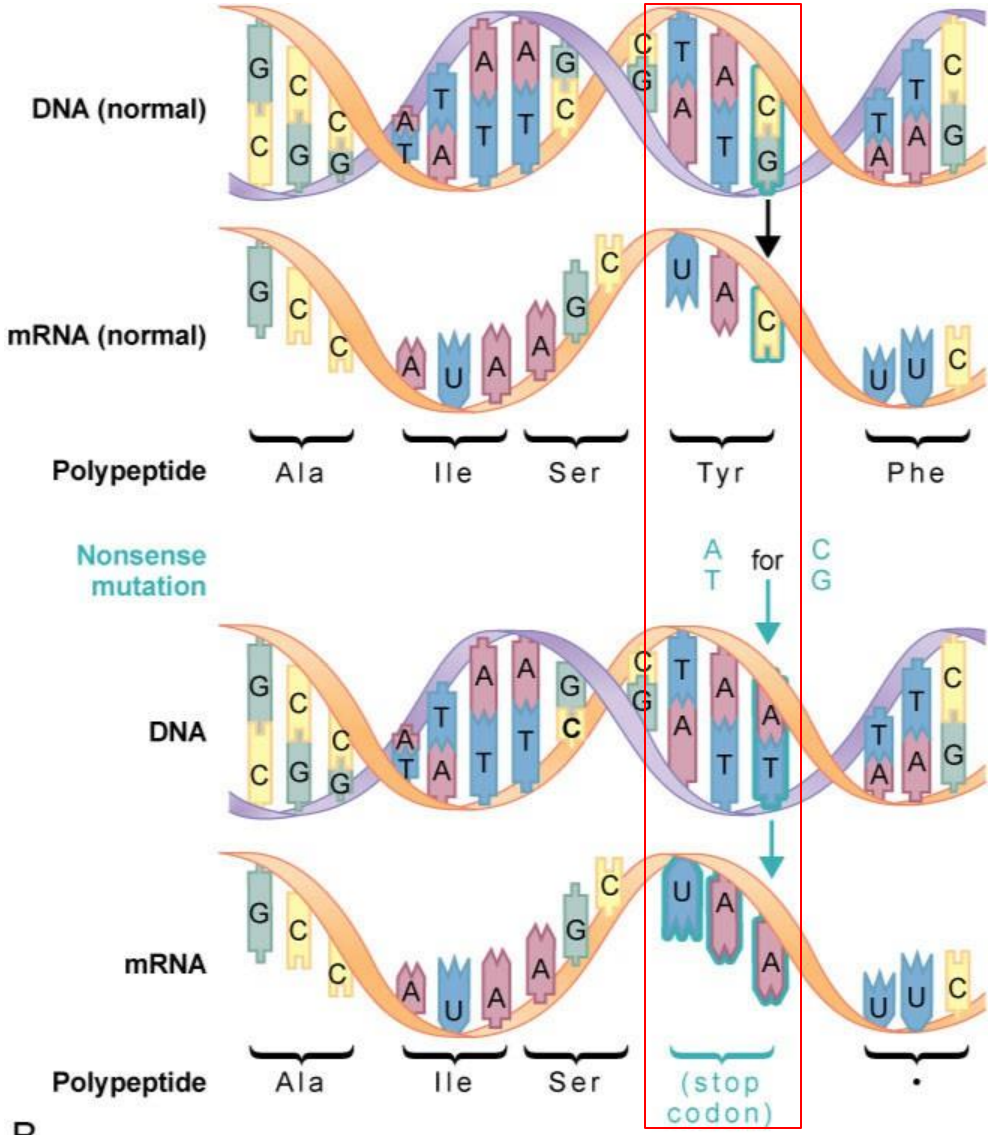


Fig. 3-3. Base pair substitution. Missense mutations **(A)** produce a single amino acid change, whereas nonsense mutations **(B)** produce a stop codon in the mRNA. Stop codons terminate translation of the polypeptide.

- **Frameshift mutation**
- Results from the addition or deletion of a number of bases which shifts the reading frame

- This alters all of the codons downstream from the site of insertion or deletion, then the amino acids as a subsequence

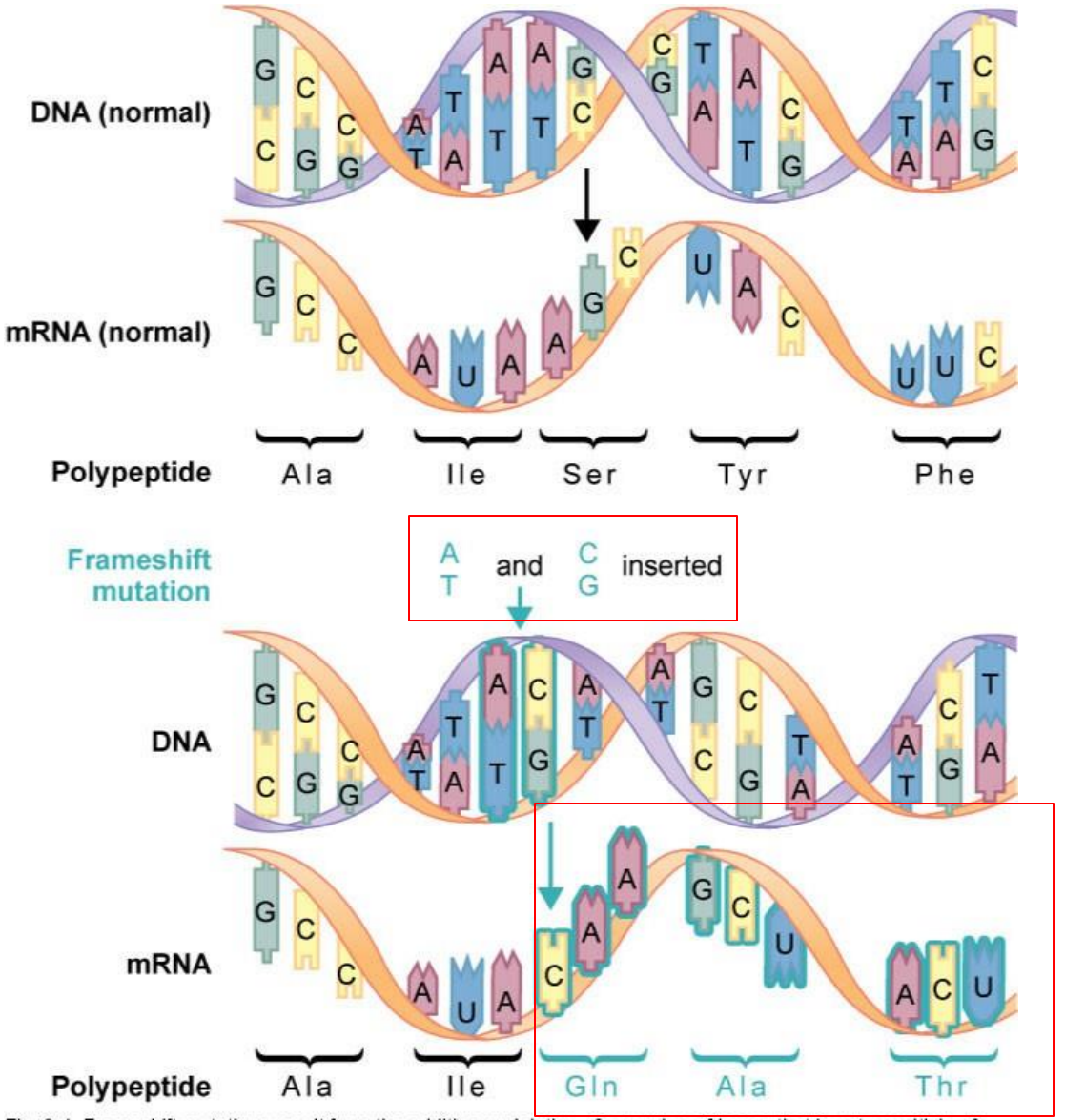


Fig. 3-4. Frameshift mutations result from the addition or deletion of a number of bases that is not a multiple of three. This alters all of the codons downstream from the site of insertion or deletion.

Types of Mutation

C . **Duplications** of whole genes also lead to genetic disease

- or duplication of few bases , Since the genome is large, with only a small portion being coding regions and much of it consisting of duplicated sequences, these types of mutations are relatively common

- Example:
- Charcot-Marie-Tooth disease
  - → Type I: 1.5 million bp duplication on one copy of Chrom. 7
  - → Dosage sensitivity: peripheral myelin protein (PMP22 gene)

Charcot-Marie-Tooth disease type 1 (CMT)

- An Inherited neurological disorder that affects the peripheral nerves, which causes muscle atrophy in lower limb. It is caused by the duplication of the PMP22 gene, this duplication increases the production of PMP22 in the cells leading **to dosage sensitivity, which means that the excess PMP22 protein disrupts normal myelin sheath formation,** leading to the phenotype of demyelination and impaired nerve signal transmission.
- **However, a deletion of one copy of this gene results in a different disorder, highlighting that having either more or fewer copies than normal of a certain gene can have negative effects.**

D. Other types of mutations can alter the regulation of transcription or translation.

1. A **promoter mutation** can decrease the affinity of RNA polymerase for a promoter site, often **resulting** in reduced production of mRNA. The final result is decreased production of a protein.

> A **promoter** is a specific DNA sequence located upstream (before) a gene that serves as a binding site for RNA polymerase and other transcription factors to initiate transcription

2. Mutations of transcription factor genes or enhancer sequences can have similar effects.

> **Regulatory sequences** are specific DNA regions that control gene expression, like enhancers which are found before the promoter

E. Mutations may also interfere with the splicing of introns as mature mRNA is formed from the primary mRNA transcript.

Splice site mutations, occurring at intron-exon boundaries, alter the splicing signal necessary for proper excision of an intron.

These may **occur at:**

- the GT sequence that always defines the 5' donor site
- or at the AG sequence that defines the 3' acceptor site.
- They may also take place in the sequences that lie near the donor and acceptor sites.

When such mutations occur, the excision will often be made within the next exon, at a splice site located in the exon.

Splice site mutations can also **result** in the abnormal inclusion of part or all of an intron in the mature mRNA.

Remember; Exons are coding sequences that remain in the final mRNA and are translated into proteins. **Introns are** non-coding sequences that are removed during RNA splicing.
Check the next slide For further explanation

A. A mutation in the GT sequence (GT→AT) at the beginning of an intron can cause a splicing error, leading to the removal of part of the previous exon. This occurs when an alternative GT sequence in the preceding exon is mistakenly recognized as the original splice site. As a result, the mature mRNA is affected, leading to a shorter peptide.

Similarly, a mutation in the AG sequence at the end of an intron can cause incorrect splicing, removing part of the next exon as well. This further disrupts mRNA processing and affects protein production.

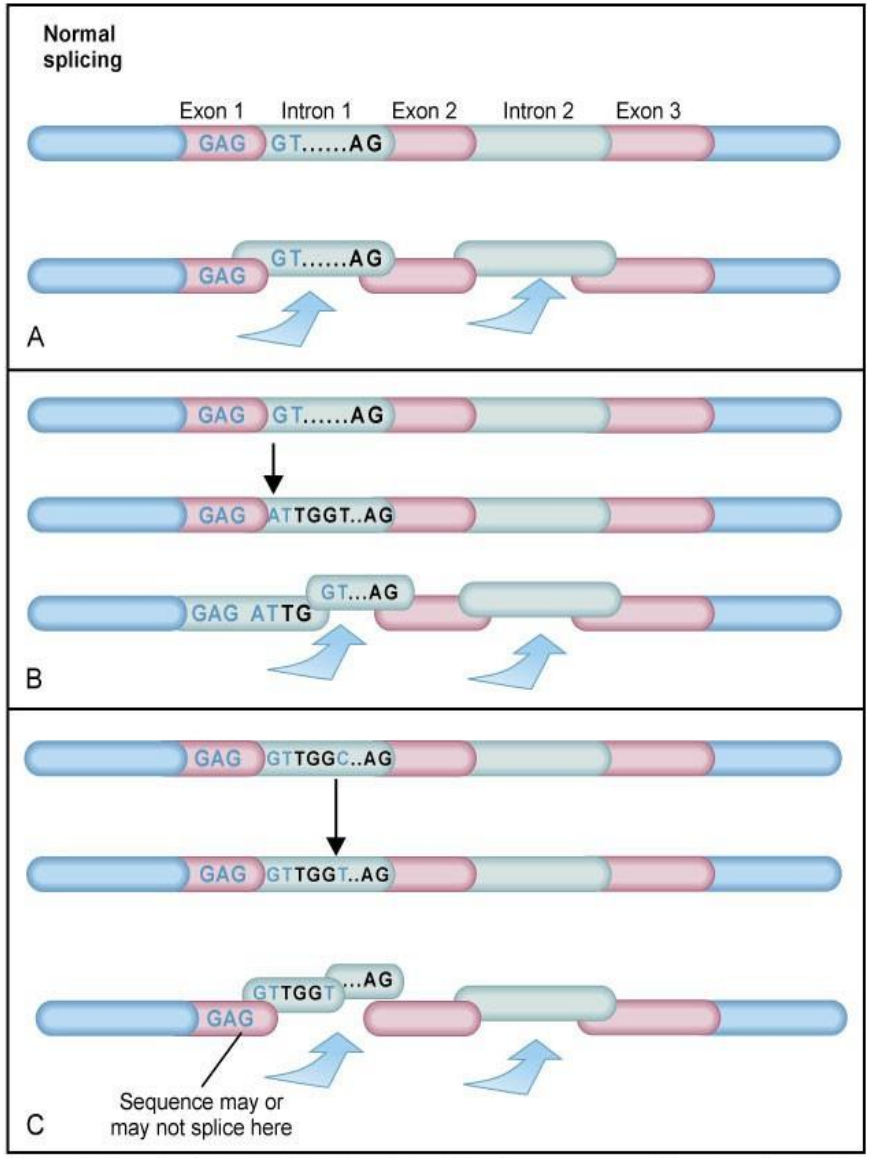


Fig. 3-5. **A,** Normal splicing. **B,** Splice-site mutation. The donor sequence, GT, is replaced with AT. This results in an incorrect splice that leaves part of the intron in the mature mRNA transcript. In another example of splice-site mutation **(C),** a second GT donor site is created within the first intron, resulting in a combination of abnormally and normally spliced mRNA products.

F. Several types of DNA sequences are capable of **propagating copies of themselves;** these copies are then inserted in other locations on chromosomes.

The insertion of these transposons (or mobile elements) can cause frameshift mutations. Until recently, it was not clear whether this phenomenon, which has been well documented in experimental animals such as fruit flies, occurred in humans.

The insertion of mobile elements has now been shown to cause :

1. isolated cases of type 1 neurofibromatosis
2. familial breast cancer,
3. familial polyposis (colon cancer),
4. and hemophilia A and B (clotting disorders) **in humans.**

- Factor 8 in hemophilia A, and factor 9 in hemophilia B.
- Factor 8 which is a large gene has a higher chance to be mutated, by transposons insertions as an example

G. The final type of mutation has been discovered quite recently and **affects tandem repeated DNA sequences** that occur within or near certain disease genes.

- The repeat units are three bases long, so a typical example would be CAGCAGCAG
- A normal individual will have a relatively small number of these tandem repeats (eg, 20 to 30) at a specific chromosome location.
- For reasons that are not yet understood, **the number of repeats can increase dramatically during meiosis or possibly during early fetal development**, so that a newborn may have hundreds or even thousands of repeats.
- When this occurs in certain regions of the genome, it causes genetic disease.

- Like other mutations, **these expanded repeats** can be transmitted to the patients offspring. More than a dozen genetic diseases are now known to be caused by expanded repeats.

Examples : Fragile X syndrome, Myotonic dystrophy, and Ataxia

Molecular Consequences of Mutation

- Mutations can result in either a [1]**gain of function or [2] loss of function** of the protein product.

1. **Gain of function mutations** occasionally result in a completely novel protein product.They result in over-expression of the product or inappropriate expression (i.e., in the wrong tissue or in the wrong stage of development).

This topic will be discussed more in the developmental genetic chapter. Developmental genes occupied during the development of the embryo , switching on and off

- **Gain-of-function** mutations produce a **dominant disorder.**

- **examples**

Charcot-Marie-Tooth disease, results from overexpression of the protein product and is considered a gain-of-function mutation.
Huntington disease is another example.

2a. **Loss-of-function** mutations are often seen **in recessive diseases**. Here, a mutation results in the loss of 50% of the protein product (e.g., a metabolic enzyme) but the 50% that remains **is sufficient** for normal function. The heterozygote is thus **unaffected**.

- In some cases, however, 50% of the protein product is **not sufficient** for normal function **(haploinsufficiency), and a dominant disorder can result.** Haploinsufficiency is seen, for example, in the autosomal dominant disorder familial hypercholesterolemia.

Normally, a person has **two alleles for the LDL receptor (LDLR) gene**, both contributing to LDL receptor production. In familial hypercholesterolemia (FH), a **mutation** in one allele leads to only **50% of the normal LDL receptors being produced**. This **insufficient** receptor count reduces cholesterol clearance from the blood, **causing cholesterol accumulation**

- **Both haploinsufficiency and gain-of-function mutations are examples of dosage sensitivity.**

Dosage sensitivity means باختصار، وجود الشيء أكثر من ما يجب، أو وجوده أقل ما يجب، ويؤثر سلبا

2b. Another type of **loss of function** is seen in **the dominant negative mutation**. This type of mutation results in a protein product that is not only **nonfunctional** but also **inhibits** the function of the protein produced by the normal allele in the heterozygote.

- Dominant negative mutations are seen in genes that encode **multimeric proteins** (i.e., proteins composed of two or more subunits).
- **Example**

Type 1 collagen, which is composed of three helical subunits, is an example of such a protein. An abnormal helix, created by **a single mutation**, may combine with the other helices, **distorting** them and producing a seriously compromised **triple helix protein.**

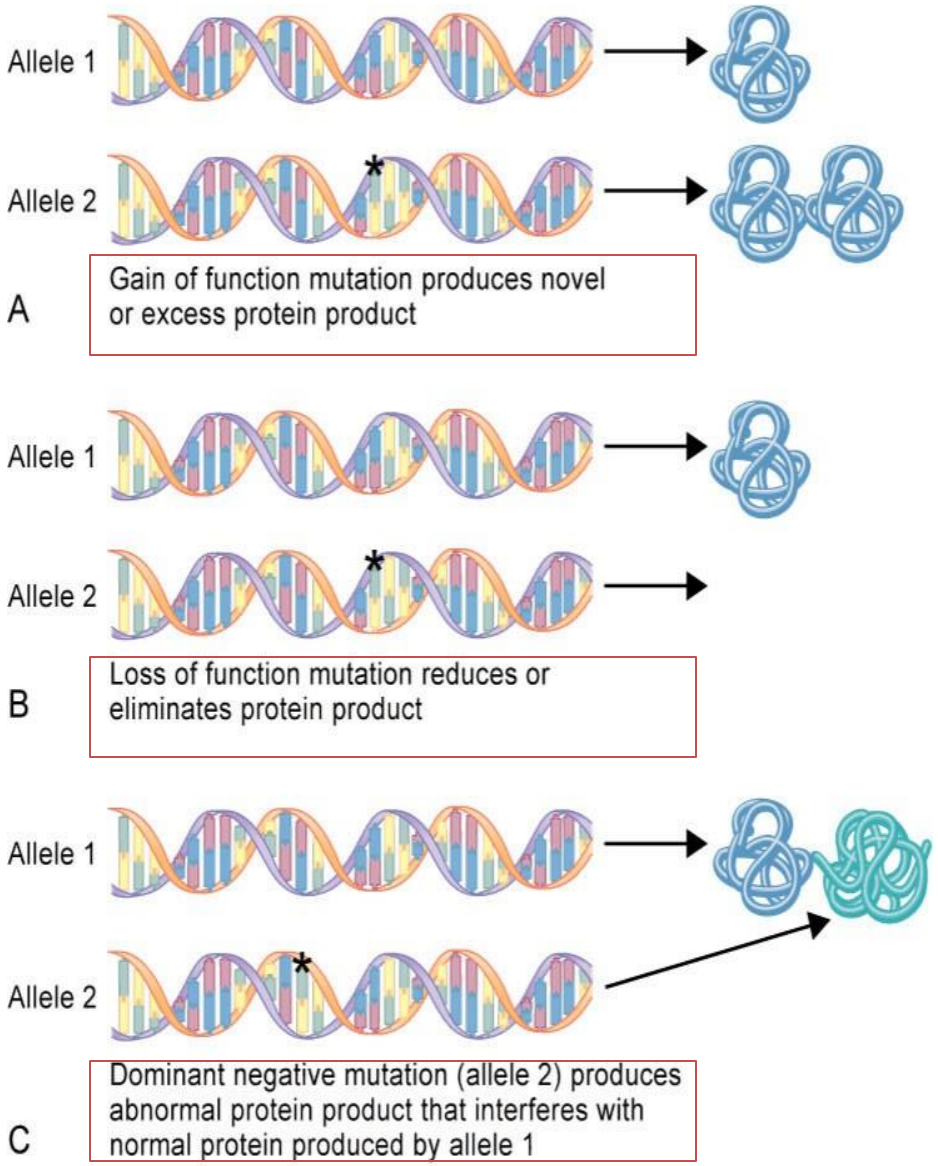
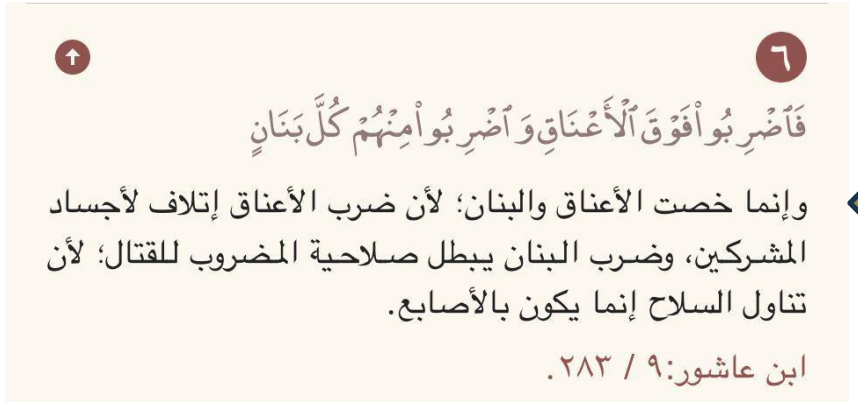


Fig. 3-6. **A,** Gain-of-function mutations produce a novel protein product or an increased amount of protein product. **B,** Loss-of-function mutations decrease the amount of protein product. **C,** Dominant negative mutations produce an abnormal protein product that interferes with the otherwise normal protein product of the normal allele in a heterozygote.

Additional sources

1. Book pages
2. Youtube videos
3. Webpages…etc

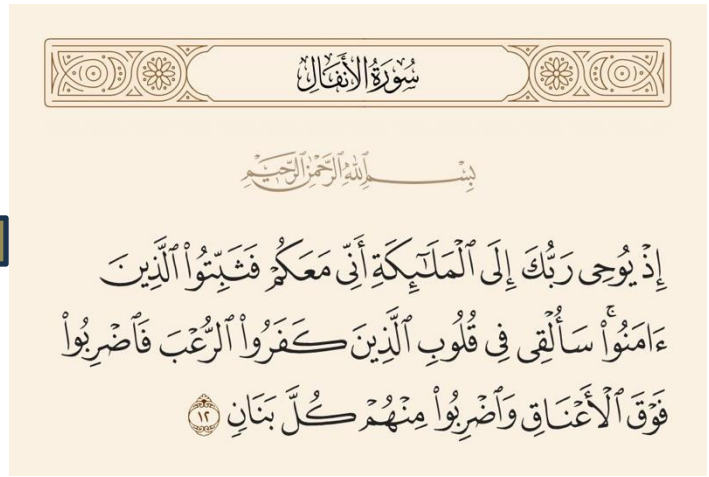


٦

فَٱضۡرِبُواْ فَوۡقَ ٱلۡأَعۡنَاقِ وَٱضۡرِبُواْ مِنۡهُمۡ كُلَّ بَنَانٍ

وإنما خصت الأعناق والبنان؛ لأن ضرب الأعناق إتلاف لأجساد المشركين، وضرب البنان يبطل صلاحية المضروب للقتال؛ لأن تناول السلاح إنما يكون بالأصابع.

ابن عاشور: ٩ / ٢٨٣.



سُورَةُ الأَنفَالِ

بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

إِذۡ يُوحِي رَبُّكَ إِلَى ٱلۡمَلَٰٓئِكَةِ أَنِّي مَعَكُمۡ فَثَبِّتُواْ ٱلَّذِينَ ءَامَنُواْۚ سَأُلۡقِي فِي قُلُوبِ ٱلَّذِينَ كَفَرُواْ ٱلرُّعۡبَ فَٱضۡرِبُواْ فَوۡقَ ٱلۡأَعۡنَاقِ وَٱضۡرِبُواْ مِنۡهُمۡ كُلَّ بَنَانٖ ١٢

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

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!