What are mutations?
- They are changes in the genetic material resulting in abnormal phenotypes. They can occur at a specific gene (part of a chromosome) or involve a whole chromosome! Notice that most of mutations are harmful.

There are two types of mutations:

<table>
<thead>
<tr>
<th>Somatic</th>
<th>Gonadal</th>
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<tbody>
<tr>
<td>Genetic alterations acquired by cells after the formation of the zygote.</td>
<td>Genetic alterations acquired by germ cells.</td>
</tr>
<tr>
<td>They are not transmitted to offspring (not inherited).</td>
<td>They are transmitted to offspring (inherited).</td>
</tr>
</tbody>
</table>

Mutations can be spontaneous or induced:
- Spontaneous mutations (most common): occurring naturally in the absence of mutagens (agents which cause mutations).
- Induced mutations: occurring due to exposure to mutagens:
  - Chemicals:
    - Base analogs: derivatives of normal bases incorporated in the DNA, substitute for normal nucleotide and alter base pairing properties.
    - Intercalating agents: can be inserted between bases in the DNA, resulting in structural changes of the DNA
    - Base modifiers: change the structure of DNA bases resulting in mismatch pairing (e.g. metals or Reactive Oxygen Species).
  - Radiation: X-ray (causing breaks in double stranded DNA) or UV-light (causing cross link of thymidine).

Gene mutations:
- Single base substitution:
  - Substitution of a single nucleotide with a different one:
    - Transition: substitution of one base with a different base of the same chemical category (i.e. purine to purine or pyrimidine to pyrimidine).
    - Transversion: substitution of one base with a different base of other chemical category (i.e. purine to pyrimidine or pyrimidine to purine).
  - Types of mutations which can result:
    - Missense mutation: translation of a different amino acid. Example include: galactosemia and sickle cell disease (valine instead of glutamic acid in the 6th amino acid position of β-globin chain).
    - Nonsense mutation: resulting in a stop codon (UAG or UGA or UAA). Example: β-thalassemia.
    - Silent mutation: doesn’t cause any changes in amino acid sequence.
• **Insertions or deletions:**
  ✓ Extra base pairs might be added (insertion) or removed (deletion) from the DNA sequence of a gene and this can result in what is known as “frameshift mutation”.

![Diagram showing DNA and mRNA sequences with insertions and deletions](image)

• **Triplet repeat expansion:**
  ✓ DNA mutation caused by expansion of a DNA sequence by the addition of trinucleotides resulting in a trinucleotide repeat.
  ✓ Example: Huntington’s disease in which there is excessive repeat of the trinucleotide CAG → adding series of glutamine to the resulting protein.

- **Chromosomal mutations:**
  • **Structural:**
    ✓ Deletion: a segment of the chromosome breaks-off and will be lost.
    ✓ Inversion: a segment of the chromosome breaks-off → flips 180 degrees and then reattaches.
    ✓ Duplication: extra copy of a part of the chromosome is formed.
    ✓ Translocation.
  • **Numerical (aneuploidy):** trisomies are considered as an example.

- **Functional effect of mutations:**
  • Loss of function: reduced activity of the gene product; associated with recessive mutations.
  • Gain of function: confer a new function of gene product; associate with dominant mutations.

- **What are the methods which can be used to detect mutations?**
  • Direct PCR.
  • Real-time PCR.
  • RFLP.
  • Hybridization.
  • DNA sequencing.