4. Mutation

The topic of today's lecture is gene mutations, their characteristics and types. This lecture is part of Module 1: Animal Genetics, which is part of the ISAGREED project. This presentation was supported by an Erasmus^{+} KA2 - Partnerships for Cooperation grant: "Innovating the structure and content of programs in the management of animal genetic and food resources using digitalization".

The term mutation was first used by Hugo de Vries in his work "Mutation Theory". Vries characterized mutations as heritable changes in the genotype that are not due to recombination. Mutations are sudden changes at the level of genetic material, such as DNA in the case of eukaryotic and prokaryotic organisms or RNA in the case of RNA viruses. They are always associated with a change in genotype, but may not be expressed phenotypically. Mutations are not chosen by the organism, they arise randomly. Thus, they are not the result of the organism adapting to its environment. Mutations can be classified according to several aspects. One of the classification criteria for mutations is the level of DNA structure affected by the mutation. According to this aspect, we distinguish:

- gene mutations causing changes in the structure of the gene;
- chromosomal mutations causing changes in the structure of chromosomes;
- genomic mutations causing changes in the number of chromosomes.

In this lecture, we will focus on gene mutations. A gene mutation is a change in the DNA sequence of a gene. This mutation has caused a change in the order or number of nucleotides. We classify gene mutations based on several criteria depending on the level at which we observe the change. This classification is hierarchical and encompasses the entire gene expression pathway up to the final product - the protein. On this basis, we distinguish between mutations affecting the DNA sequence, the sequence amino acid sequence, reading frame, and protein function.

Changes at the nucleotide sequence level are the primary changes in gene structure that are directly translated into protein structure. The DNA mutation is transferred by the process of transcription and subsequent translation into the primary protein construct. In terms of mutations with an effect on DNA sequences the following types can be distinguished:

Substitution, inversion, insertion and deletion.

Substitution represents the substitution of one or more bases. Within substitution, we distinguish between transversion, which consists of the replacement of a purine base by a purine base or a pyrimidine base by a pyrimidine base, and transversion, which consists of the replacement of a purine base by a pyrimidine base and vice versa. For clarification, the term purine base refers to adenine or guanine and the term pyrimidine base describes the presence of cytosine or thymine.A mutation, like an inversion, represents a change in the order of the bases. An insertion is the incorporation of one or more redundant bases, and a deletion is a type of mutation where one or more bases are lost.

The following picture describes the types of gene mutations with an effect on the DNA sequence. Transition or transversion-type substitutions, in which one nucleotide is replaced by another nucleotide, can lead to a change in the amino acid sequence during translation, and consequently alter or switch off the function of the protein. In the case of an inversion, the order of the entire stretch of DNA is changed by inverting it. A small inversion involves only a few

bases in a gene, while a longer inversion involves large regions of the chromosome containing several genes. The insertion involves the addition of one or more nucleotides to a DNA sequence. Insertions are usually caused by transposable elements or errors in DNA replication. An insertion into the coding region of a gene causes a shift in the reading of the gene sequence, which can significantly alter the gene product. In the case of deletion, one or more nucleotides are removed from the DNA sequence. Like insertion, deletion can also change the reading frame of a gene.

Mutations localized in the coding regions of genes, abbreviated as exons, cause a change in the amino acid sequence. According to their effect, the following types of mutations can be distinguished:

- Missense mutations that encode a different amino acid compared to the original amino acid before the mutation,
- neutral mutations that result in the inclusion of a different amino acid but chemically similar to the original amino acid,
- silent mutations the degeneration of the genetic code results in the inclusion of the same amino acid despite a change in the codon sequence.

The following picture describes the types of gene mutations with an effect on the amino acid sequence. A missense mutation is a change in DNA sequence that results in the incorporation of a different amino acid into a protein. This change in the DNA sequence leads to a change in the codon sequence and thus the inclusion of a different amino acid, during protein synthesis on the ribosome. Changes in the amino acid sequence can significantly affect the function of the protein. A neutral mutation is a change in the DNA sequence, that is neither beneficial nor detrimental to the viability of the organism. This type of mutation causes one amino acid to be replaced, by another amino acid, but with similar properties, so that the change is less pronounced. A silent mutation is a DNA mutation that does not observable effect on the phenotype of the organism. It is a change in the DNA sequence encoding amino acid in a protein sequence but does not change the encoded amino acid. It is essentially a specific type of neutral mutation that encodes the same amino acid.

A reading frame is the way nucleotide sequences are interpreted into amino acid sequences. Mutations that affect the reading codons on mRNA are large-scale changes almost always leading to the synthesis of a non-functional protein. These are the following types of mutations:

- nonsense mutations, which cause the inclusion of a STOP codon, thereby terminating protein synthesis,
- frameshift mutations are a special type of mutation that involves the insertion or deletion of several nucleotides that are not a multiple of three, resulting in a shift in the reading of codons on the ribosome. This results in a completely different order of amino acids arising from the site of mutation.

The next picture describes the types of gene mutations with an effect on the reading frame:

- Nonsense mutation is a change in the DNA sequence that results in the inclusion of a premature stop codon in the transcribed mRNA, resulting in a truncated, incomplete, and usually non-functional protein product.
- Frameshift mutations involve the addition or deletion of a nucleotide in which the number of base pairs removed is not divisible by three.

Each group of three bases corresponds to one of the 20 different amino acids used to form the protein. If the mutation disrupts this reading frame, then the entire DNA sequence following the missense mutation will be misread.

Many of these mutations can only be recognised if they affect the phenotype of the individual. Mutations affecting protein function may behave differently. Based on the effect of the mutation on protein function, we divide mutations into gain-of-function mutations, loss-of-function mutations, and dominant-negative mutations.

A gain-of-function mutation causes the gene product to change so that it acquires a new and abnormal function. These mutations usually have dominant phenotypes. It is also often called a neomorphic mutation.

A loss-of-function mutation causes the gene product to have reduced or no function. With complete loss of function, this mutation is referred to as an amorphous mutation. The phenotypes associated with such mutations are most often recessive. Exceptions are cases where the organism is haploid or where the reduced dose of the normal gene product is not sufficient to produce a normal phenotype.

The dominant negative mutation causes the synthesis of an altered gene product that acts antagonistic to the original form of the protein without the mutation. These mutations usually lead to an altered molecular function and are characterised by dominant phenotype.

Thanks for your attention!