Mutations

Mutations: gene, chromosomal, genomic. Hereditary diseases. The value of mutations for the evolution of living nature.

1. Explain what a mutation is and its importance for evolution of life.
2. Classify and characterize the main types of mutations.
3. Define the terms: deletion, insertion, inversion, duplication, translocation, and explain what type of mutation each term belongs to and why.
4. Give specific examples of hereditary diseases

All organisms differ from each other in a varying degree. These small differences constitute variation, which may be the result of genetic changes taking place during the formation of the gametes, or of the influence of the environment, or a combination of both. In some cases it is dif- ficult to determine what contribution is made by heredity and what is due to the environment, es- pecially if the differences are very small. In humans, factors such as colour of the skin, hair colour, weight, shape of head and facial features all show variation and we know that many of these are inherited characteristics. Some of these factors, for example weight, can be affected by the level of nutrition or exercise, which are both environmental influences.

From viewpoint of genetics we recognize two forms of variation: **inheritable and non-inheritable.**

During the process of replication, DNA is normally copied exactly so that the-genetic material remains the same from generation to generation. However, very occasionally, changes can occur so that an organism may inherit altered genetic material. Such inherited changes are known as **mutations**. Mutations give rise to all variation, but their survival in the genome is influenced by many factors including effects on reproductive fitness, human population history, chromosomal location and recombination rates.

Mutations are the *source* of variation, but the *process* of mutation does not itself drive evolution. The rate of change in gene frequency from the mutation process is very low because spontaneous mutation rates are low. The mutation rate is defined as the probability that a copy of an allele changes to some other allelic form in one generation. Suppose that a population were completely homozygous *A* and mutations to *a* occurred at the rate of 1/100,000 Then, in the next generation, the frequency of *a* 0.00001 and the frequency of = 1/100,000 × alleles would be only 1.0 *A* alleles would be 0.99999. After yet another generation of mutation, the frequency of *a* 0.00009 to a new frequency of 0.000019, whereas the original allele would be reduced in frequency to 0.999981. It is obvious that the rate of increase of the new allele is extremely slow and that = 1/100,000 × would be increased by 0.99999 *it gets slower every generation* because there are fewer copies of the old allele still left to mutate.

Genetic variation is generated continuously by the mutational process, but its persistence in the genome is determined by different historical and genomic factors. Some of these factors leave an imprint on sequence variation across the whole genome, others only influence local patterns of variation.

Most new mutations that affect gene function have deleterious effects on reproductive fitness. But because genes represent only a small fraction of the human genome, most mutations are thought to have no effect on reproductive fitness and are effectively invisible to natural selection – a category referred to as ‘selectively neutral’. Most deoxyribonucleic acid (DNA) variants in the human genome are thought to be selectively neutral for three main reasons. First, the main portion of the genome, estimated as about 97%, neither codes for a functional product, such as protein or ribonucleic acid (RNA), nor indirectly affects gene function, by regulating expression or replication. Second, if a new variant does occur in the 1.5% of the genome that encodes a functional product (coding regions), it may not result in a change of amino acid (i.e. it may be a

'synonymous' substitution). Third, variants that do affect regulatory regions or coding regions and do change an amino acid (nonsynonymous substitutions) may have no effect on reproductive fitness.

Mutations may be subdivided according to:

A. Cause of mutation:

(1) spontaneous

(2) induced by exogenous and endogenous agents

B. Type of change brought about by a mutation:

(1) genome mutations (numerical chromosomal aberrations)

(2) chromosome mutations (structural chromosomal aberrations)

(3) gene or point mutation (alteration in the DNA at the molecular level)

C. Place (cells) where a mutation occurs:

(1) somatic mutations (occurring in body cells)

(2) germ cell mutations (occurring in germ cells—gametes).

D. Phenotypic properties: morphological (shape, size, quantity, coloration), biochemical, lethal, be-havioral, silent.

E. Regulatory: increased or decreased expression, altered message processing, stability, or rate oftranslation.

The mutant genes can be divided into *dominant, recessive, autosomal, sex-linked*. It has been suggested that the polypeptide products of the genes involved in dominant conditions make up struc- tural proteins, whereas those concerned in recessive conditions make up enzymes. The sex-linked conditions are determined by mutant genes located on the X- or Y-chromosomes.

Mutagens

Mutations can be induced by *mutagens*, substances that cause a much higher rate of mutation.A mutagen is a natural or human-made agent which can greatly increase the mutation rate.

Mutagens can be subdivided into three groups: *physical, chemical* and *biological*.

Point, chromosomal and genomic mutations

Point mutations involve only one base pair of DNA and include both ***substitutions*** (*transitions* and *transversions*), and a **insertions** or a **deletion** of a single base pair..

Transitions occur when a purine is converted to a purine (A to G or G to A) or a pyrimide is con- verted to a pyrimidine (T to C or C to T). A *transversion* results when a purine is converted to a pyrimidine or a pyrimidine is converted to a purine. Substitution of one nucleotide for another is a result of tautomeric shift, a rare process by which the hydrogen atoms of a deoxyribonucleotide base move in a way that changes the properties of its hydrogen bonding.

Other common forms of genetic variation include insertions, deletions and inversions of one or more bases.

Insertion

An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.

Deletion

A deletion changes the number of DNA bases by removing a piece of DNA. Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA may alter the function of the resulting protein(s).

Duplication

A duplication consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein.

Repeat expansion

Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a

tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that the short DNA sequence is repeated. This type of mutation can cause the resulting protein to function improperly.

Addition or deletion mutations are actually of nucleotide pairs; nevertheless, the convention is to call them base-pair additions or deletions. The simplest of these mutations are single-base-pair additions or single-base-pair deletions. There are examples in which mutations arise through simultaneous addition or deletion of multiple base pairs at once. Mechanisms that selectively produce certain kinds of multiple-base-pair additions or deletions are the cause of certain human genetic diseases.

A point mutation can result in **missense** (amino acid substitution), **nonsense** (insertion of a stop codon), or **frameshift** as result of insertions and deletions.

Base substitutions can have different consequences at the protein level. Some base substitutions are "silent," meaning that they result in a new codon that codes for the same amino acid as the wild type codon at that position or a codon that codes for a different amino acid that happens to have the same properties as those in the wild type. Substitutions that result in a functionally different amino acid are called "missense" mutations; these can lead to alteration or loss of protein function. A more severe type of base substitution, called a "nonsense" mutation, results in a stop codon in a position where there was not one before, which causes the premature termination of protein synthesis and, more than likely, a complete loss of function in the finished protein.

There are the **silent mutations** that don't alter the phenotype.Silent because either:

1) Mutation occurs in non-coding or non-regulatory region
2) Mutation occurs in an intron
3) Mutation changes a codon such that it codes for the same amino acid.

A mutation involving deletion of a few base pairs generally affects the function of a single gene. So **Gene mutations** are defined as those that occur entirely within one gene (and its upstream regulatory sequences) and may be either point mutations or other small disruptions of normal chro- mosomal structure that occur entirely within one gene

Chromosomal mutations are defined as those that involve deletion, inversion, duplication, or other changes of a chromosomal region that is large enough so the change can be detected cytologically. Many types of chromosomal abnormalities exist, but they can be categorized as either numerical or structural. Numerical abnormalities are whole chromosomes either missing from or extra to the normal pair. Structural abnormalities are when part of an individual chromosome is missing, extra, switched to another chromosome, or turned upside down.

Chromosomal abnormalities can occur as an accident when the egg or the sperm is formed or during the early developmental stages of the fetus. The age of the mother and certain environmental factors may play a role in the occurrence of genetic errors. Prenatal screening and testing can be performed to examine the chromosomes of the fetus and detect some, but not all, types of chromosomal abnormalities.

Genomic mutations are defined as those that involve loss or gain of whole chromosomes, translocation from one chromosome to another or other gross chromosomal rearrangements. Note that both chromosomal and genomic mutations can cause **aneuploidy**.

Literature:

1. Alberts et al., pp. 485-491;
2. Watson, pp. 313-340;
3. Norris Armstrong. Decoding the Flu (case study) / Biology Department, University of Georgia. (https://sciencecases.lib.buffalo.edu/collection/detail.html?case_id=597&id=597)