

Lecture: Variability. Different types of variability in Biology and Medicine. Cytological essentials of heritable diseases

Plan of the lecture

1. **Notion of variability. Different types of variability.**
2. **Kinds of inheritable variation.**
3. **Classification of mutations.**
4. **Significance of mutations for Biology and Medicine.**

The goals of this lecture are to review the inheritable and noninheritable forms of variability and its significance for biology and medicine.

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 difficult to determine what contribution is made by heredity and what is due to the environment, especially 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 noninheritable.**

Noninheritable variation is acquired by an individual during its own life and is lost with its death. It is, therefore, also called the **phenotypic variation.**

Such form of variation is produced by three types of factors:

- environment,
- use and disuse of organs, and
- conscious efforts.

Environment includes all the factors that affect the organisms, such as habitat, light, temperature, food, air, pressure, humidity, etc. For example, increase of skin pigmentation in humans as a result of sunlight influence.

Use and disuse of organs is illustrated by the following example. A player who uses his muscles in daily exercise acquires a stronger and more muscular body than the one who does not take exercise.

Variation, introduced by human **conscious efforts**, includes *castration* in animals, i.e., damaging the testes; *bored pinnae* in women to wear ornaments; *small feet* acquired by wearing tight shoes in Chinese women and other examples.

Inheritable or genotypical variation is received by the individual from the parents and is transmitted to the next generation.

Genotypical variation includes **recombinations** of genes during meiosis and fertilization (combinative variability) and **mutations**.

Combinative variability can arise by two mechanisms: independent assortment and crossing over leading to recombination. Random fertilization during sexual reproduction further increases the potential for genetic variation.

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 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, behavioral, silent.

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

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 structural 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.

Spontaneous and induced mutations

The appearance of a new mutation is a rare event. Most mutations that were originally studied occurred spontaneously. This class of mutation is termed **spontaneous mutations**.

The frequency with which one allele mutates to another is known as the **mutation rate**. The spontaneous mutation rate varies for different loci, the limits of the observed range being between one in 10,000 and one in 1,000,000 per locus per gamete. The spontaneous mutation rate is essential for providing new variation necessary for survival in a changing environment; in other words it provides the raw material for evolutionary change.

Factors influencing spontaneous mutation rates are **parental age** and **sex**: Most mutations involving numerical aberrations of chromosomes are caused by **non-disjunction** during the first or second meiotic divisions. Non-disjunction is more common in female than in male germ cells; about 65% of all trisomies are due to **female non-disjunction**. Moreover, the **risk of non-disjunction** increases with increasing maternal age, especially for women above 35. A certain increase for older men is also observed. This has been demonstrated for fathers of children with **new dominant mutations**. Fathers of new-mutant achondroplastic dwarfs are on an average a few years older than other fathers in the population.

Mutagens

Mutations can be induced by *mutagens*. 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*.

Physical mutagens include ionizing radiation, UV radiation, and temperature. Visible light and other forms of radiation are all types of electromagnetic radiation (consists of electric and magnetic waves).

Radiation was the first mutagenic agent known; its effects on genes were first reported in the 1920's. X-rays discovered by Roentgen in 1895 cause multiple mutations and DNA rearrangements (insertions, translocations). UV radiation causes the formation of thymine dimers.

Examples of **chemical mutagens** include nitrous acid, hydrocarbons from cigarette smoke, 5-bromouracil. Nitrous acid acts directly on nucleic acids, and alters the genetic code by converting one base into another. For example, cytosine is converted into uracil, which bonds to adenine instead of guanine. Some commonly prescribed drugs are thought to be teratogens. There are androgens, streptomycin, tetracycline, and vitamin A in this group.

Biological mutagens include viruses, bacterial and fungous toxins.

Action of mutagens can be classified into two main types:

1. ***endogenous damage*** such as attack by reactive oxygen radicals produced from normal metabolic byproducts (spontaneous mutation);
2. ***exogenous damage*** caused by external agents such as ultraviolet [UV 200-300 nm] radiation from the sun, X-rays and gamma rays, toxins, cancer chemotherapy and radiotherapy.

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 pyrimidine is converted 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.

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

Sickle-cell anemia as an example of a missense mutation. Sickle-cell anemia was identified in 1957 as being caused by a missense mutation resulting in a single amino acid substitution in the beta-globulin subunit of the hemoglobin tetramer (2 alpha + 2 beta subunits). A transversion causes the codon GAG to be changed to GUG (GTG in the DNA). This replaces a glutamic acid with a valine as the sixth amino acid (counting from the N-terminus) in the mature beta-globulin molecule. That substitution causes the hemoglobin to precipitate into fibrous aggregates that distort the shapes of red blood cells under low-oxygen conditions, resulting both in blockage of capillary circulation and breakage of the red blood cells.

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.

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 chromosomal 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. The common example of deletion in humans is the *cri du chat* syndrome, in which part of the short arm of chromosome 5 is deleted.

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**.

In man, Turner's syndrome is an XO condition resulting from the deletion of a whole chromosome. This is the most evident and the most frequent chromosomal deficiency in man, compatible with life and related to the X chromosome.

Some mutations are extremely serious and can result in death before birth, when an individual is still in the embryonic or early fetal stages of development. Such type of mutations is called **lethal mutations**.

Somatic and germinal mutations

Eukaryotic organisms have two primary cell types . germ and somatic. Mutations can occur in either cell type. If a gene is altered in a germ cell, the mutation is termed a **germinal mutation**. Because germ cells give rise to gametes, some gametes will carry the mutation and it will be passed on to the next generation when the individual successfully mates.

Somatic cells give rise to all non-germline tissues. Mutations in somatic cells are called **somatic mutations**. Because they do not occur in cells that give rise to gametes, the mutation is not passed along to the next generation by sexual means. To maintain this mutation, the individual containing the mutation must be cloned.

Cancer tumors are an unique class of somatic mutations. The tumor arises when a gene involved in cell division, a protooncogene, is mutated. All of the daughter cells contain this mutation. The phenotype of all cells containing the mutation is uncontrolled cell division. It results in a tumor that is a collection of undifferentiated cells called tumor cells.

Molecular basis for dominance and recessiveness:

Recessive mutations usually result from partial or complete loss of a wild type function. **Amorphic** alleles are those that have completely lost the function. An example would be a mutation in which production of pigment is completely lost in the homozygous state, causing albinism. **Hypomorphic** alleles are those in which function is reduced, but not completely lost. An example would be a mutation that causes a partial loss of pigmentation, giving a lighter color when homozygous.

Dominance can be caused in a wider variety of ways. There are three classes of so called gain-of-function alleles:

1. **hypermorphic** alleles are those that cause excess product to be produced;
2. **antimorphic** alleles are those that produce an altered gene product that "poisons" or disrupts the function of the normal gene product;
3. **neomorphic** alleles cause the gene product to be expressed in the wrong types of cells, and can have drastic effects, such as that of the antennapedia gene that converts the antennae of flies into legs.