Lecture: **ñGene interactions. Realization of genetic information on the organism levelò**

Plan of the lecture:

1. Mechanism of gene interactions
2. Interactions of allelic genes. Multiple alleles
3. Lethal action of genes
4. Interactions of non-allelic genes
5. Genotype-environment interaction
6. Penetrance, expressivity
7. Pleiotropy
8. Modifier genes

The contributions of genes to phenotypic traits are modified by interactions with other genes and the environment.

The **goal of this lecture** is to review the importance of gene-gene and gene-environment interactions in the expression of the phenotype. Gene-gene interactions include interactions between different alleles of a gene (intra-allelic gene interactions), and between different genes (inter-allelic gene interactions).

In the 20th century, the geneticists have extended Mendelian principles not only to diverse organisms, but also to patterns of inheritance more complex than Mendel actually described.

But relationship between genotype and phenotype is rarely so simple.

By now, geneticists found out a lot of other patterns of inheritance. These patterns are referred to the **non-Mendelian Genetics** because many facts can not be clarified using Mendelôs Laws. But some of them can be clarified by ***gene interaction***, i.e., by simultaneous influence of different genes on different characters.

1. *Mechanism of gene interaction*

Now we know that genes are segments of the DNA that code for a particular polypeptide in the form of a specific sequence of its base pair. The polypeptide chain may act as a structural protein and form cellular organelle or form proteinaceous biochemical such as hemoglobin, insulin, or serve as an enzyme and catalyze some chemical reaction. In other words, a polypeptide may contribute to a morphological or a functional trait (phenotype) of an organism.

Proteins are the endproducts of gene expression, and so gene interactions are interactions between proteins that are controlled by these genes (Genes do not interact directly [*with the exception of such cases as synapsis and crossing-over in meiosis*] !).

Hereby, gene interaction has biochemical basis.

Types of Gene Interactions

Gene interactions can be classified as:

- interaction of allelic genes
- interaction of non-allelic genes

[A reminder:

- *allelic* genes are genes located in the identical loci of homologous chromosomes;
- *non-allelic* genes are genes located in the different loci of homologous chromosomes or in the non-homologous chromosomes **]**

INTRA-ALLELIC GENE INTERACTIONS

2. *Interactions of allelic genes*

Alleles can interact with each other in complex ways: **complete dominance, incomplete dominance, codominance, and superdominance (overdominance).**

Complete dominance

Mendelís laws describe a relatively simple pattern of inheritance: each character is determined by one gene, for which there are only two alleles, one completely dominant to the other. This type of gene interaction is called complete dominance.

In ***complete dominance*** both heterozygotes (*Aa*) and dominant homozygotes (*AA*) have the same phenotype. In complete dominance, the dominant allele must produce enough of its protein product so, that a single copy of the dominant allele (as in a heterozygote) gives the maximum phenotypic response.

Inheritance patterns of some human traits also obey Mendelian laws and correspond to complete dominance. An English physician *Archibald Garrod* (1857-1936) was the first to connect a human disorder with Mendel's laws of inheritance. He also proposed the idea that diseases came about through a metabolic route leading to the molecular basis of inheritance.

In 1903, Garrod demonstrated that human diseases were transmitted according to Mendelís laws, and in particular, a disease *alkaptonuria* (black urine disease). A.Garrod collected family history information (as well as urine) from his patients and revealed the ratio of 3:1 (dominant/recessive relationship, autosomal recessive disease) in affected families that corresponded to Mendelian principles of inheritance. He noted that affected individuals excrete homogentisic acid in their urine as a result of the breakdown of dietary proteins. Garrod postulated that the disease was due to a defect in an enzymatic pathway - *ñinborn error in metabolismò* It was also the first suggestion that genes can code for enzymes.

Typical examples of dominant human traits are *dark color of hair and eyes, thick lips, big nose, long and wide ears* and also some *deformities and diseases, for instance, extra finger (polydactyly), elliptocytosis, achondroplasia, congenital dislocation of the hip*.

Incomplete dominance

Works on problems of heredity have shown that the dominance is not of universal occurrence and there are many examples of incomplete dominance in which the genes of an allelomorphic pair express themselves partially when present together in the hybrid. As a result the heterozygotes (*Aa)* are phenotypically intermediate between two homozygous types (*AA* × *aa*).

For instance, when red snapdragon plants are crossed with white snapdragon plants, all the F_1 hybrids have pink flowers. This third phenotype results from the heterozygote flowers having less red pigment than the red homozygotes. The breeding of the F_1 hybrids produces F_2 offspring with a phenotypic ratio of 1 red to 2 pink to 1 white. In incomplete dominance we can distinguish the heterozygotes from the two homozygous varieties, and the genotypic and phenotypic ratios for the F_2 generation are the same, 1 : 2 : 1. The segregation of the red and white alleles in the gametes produced by the pink-flowered plants confirms that the genes for flower color are heritable factors that maintain their identify in the hybrids; that is, inheritance is particulate.

It is ***incomplete dominance*** ï the kind of inheritance of allelic genes where a cross between organisms with two different phenotypes (*AA* × *aa*) produces offspring with a third phenotype that is a blending (*Aa*) of the parental traits. Incomplete dominance is manifested when the interacting enzymes are slightly different in their activity.

In humans, traits with incomplete dominant inheritance are *size of nose, salience of lips, size of mouth and eyes, distance between eyes,* hair types (straight, wavy) and such hereditary disorders as Friedreichõs ataxia, cystinuria are inherited according to principle of incomplete dominance. For any character, the dominant/recessive relationship we observe **depends on the level** at which we examine phenotype; e.g., consider a fatal recessive *Tay-Sachs disease*, inherited disorder of lipid metabolism when crucial enzyme *hexosaminidase* does not work properly. Brain cells of Tay-Sachs babies lack a crucial lipid-metabolizing enzyme. Thus, lipids accumulate in the brain, causing the disease symptoms and ultimately leading to death.

At the *organism level* of normal versus Tay-Sachs phenotype, the Tay-Sachs allele qualifies as a recessive (*aa*).

At the *biochemical level*, however, we observe intermediate phenotype characteristic of incomplete dominance. The *hexosaminidase* enzyme deficiency can be detected in heterozygotes who have an activity level of the lipid-metabolizing enzyme that is intermediate between individuals homozygous for the normal allele and individuals with Tay-Sachs disease. Heterozygous individuals are genetically programmed to produce only 40-60% of the normal amount of an enzyme that prevents the disease.

Codominance

Codominance is a kind of gene interaction, in which the heterozygotes express both dominant phenotypes. In human, an example is AB type of ABO blood system. The heterozygote fully expresses both alleles. Blood type AB individuals produce both A and B antigens. Since neither A nor B is dominant over the other and they are both dominant over O they are said to be codominant.

Multiple alleles

In some cases a gene for a character may exist in many alternative alleles.

For example, gene responsible for the color of eyes in *Drosophila* fruit fly exists in 20 alternative alleles. These forms of a gene are due to mutation of a single wild type. When more than two allelic forms of wild type are located on the same locus in a given pair of chromosomes, they are known as ***the series of multiple alleles***.

Now, if there are *4* or more possible phenotypes for a particular trait, then more than 2 alleles for that trait must exist in the population.

Another example of multiple alleles is the inheritance of coat-color in domestic rabbits. In rabbits coat color is determined by 4 alleles. The dominant allele *C* causes full color of coat. Recessive homozygotes (*cc*) have white (albino) color of coat. However, there are still some alleles of this gene, having own phenotype in homozygous condition - chinchilla ($c^{ch}c^{ch}$), Himalayan ($c^{h}c^{h}$). The allele c^{ch} is dominant to the alleles c^{h} and *c*, and at the same time is recessive to the allele *C*. The same as allele c^{ch}, allele c^{h} is dominant to the allele *c* and is recessive to the allele c^{ch}. In that way, dominance is relative property of genes.

In human population, one of examples of multiple allelism is inheritance of ABO blood types involving three alleles (*i, I^A, I^B*). Some traits are controlled by far more alleles. The human HLA system (*histocompatibility gene complex*), which is responsible for identifying and rejecting foreign tissue in our bodies, can have at least 30,000,000 different genotypes. The histocompatibility gene complex consists of at least four genes located upon the chromosomes of sixth pair, and each gene has up to about 100 alleles.It is the HLA system which causes the rejection of organ transplant. Unless identical twins tissue transplantation is generally unsuccessful. The host immune system reacts to produce antibodies which destroy the transplant.

The phenomenon of multiple allelism results in phenotypical heterogeneity of human populations. Now, if there are *4* or more possible phenotypes for a particular trait, then more than 2 alleles for that trait must exist in the population.

Overdominance is a kind of gene interaction, in which the phenotypic expression of the heterozygous condition exceeds the phenotype of the homozygous dominant condition. The example of overdominance is the phenomenon of ***heterosis*** resulting from the total effect of similar action of heterogeneous genetic processes.

3. ***Lethal action of genes***

Genes which become a cause for death of individuals carrying them are called as ***lethal genes***. Lethal alleles can be dominant and recessive. In crossing of heterozygous carriers, expected ratio comes equal to 2:1, because the presence of a lethal gene in homozygous condition often leads to the embryonic death during the early stages of development.

In humans examples of lethal genes are brachidactyly (dominant trait), thalassemia and sickle-cell anaemia (recessive traits, these diseases are also called *haemoglobinopathies*).

Thalassemia is hereditary disorder of haemoglobin synthesis.

Haemoglobin is protein, located in erythrocytes. It carries out the transport of oxygen. Haemoglobin molecule has two components, the "haeme" part, containing the iron atom and globin portion, formed by four polypeptide chains. In HbA (haemoglobin in adult) these are two Ŭ chains and two ß chains. The Ŭ-chain has 141 amino acids and ß-chain has 146 amino acid. The Ŭ-chain is coded by Ŭ gene on chromosome 16. The ß-chain is coded by ß gene on chromosome 11. Since they are located on different chromosomes, mutation may involve either Ŭ-chain or ß-chain.

The disease leads to the *decreased production* and *increased destruction* of RBCs.

Thalassemia is originated in the Mediterranean region, so its name is derived from a Greek word ***ñ****halassa***ò** meaning ñthe seaò It is also called Mediterranean anaemia according to its distribution.

In talassemia the structure of haemoglobin is not defective however the rate of synthesis of any one of polypeptide chains is lowered. This synthesis rate reduction of one chain leads to excess of other having normal synthesis rate, and creates problems with maturation and survival of erythrocytes.

There are two groups of the disease: Ŭ-talassemia, which is characterized by a lowered rate of synthesis or an absence of synthesis of Ŭ chains and ß-talassemia (defect in ß chain synthesis). ß -talassemia occurs more frequently and is caused by mutation or deletion of ß gene on chromosome 11. Homozygotes for this gene perish in 90-95% of cases. Living homozygotes have severe anaemia, which is called talassemia major or Cooleyôs anaemia. The most striking diagnostic character of talassemia is appearance in great number of target-like erythrocytes.

Symptoms: severe anemia, and the oxygen depletion in the body becomes apparent within the first 6 months of life. If left untreated, death usually results within a few years.

INTER-ALLELIC GENE INTERACTIONS

The genes of an individual do not operate isolated from one another, but obviously are functioning in a common cellular environment. Thus, it is expected interactions between genes would occur. It means that a trait can be controlled by numerous genes, perhaps up to 100 or more.

4. ***Mechanism of inter-allelic gene interaction***

Most cell processes are the culmination of a set of reactions linked together into a pathway. Each of the reactions is controlled by a different enzyme, and each enzyme is the product of a separate gene.

Enzyme **1** Enzyme **2**
Molecule A Ÿ Molecule B Ÿ Molecule C

In the hypothetical pathway above, *molecule A* is converted into *molecule B* by *enzyme 1* and *molecule B* is then processed to become *molecule C* by *enzyme 2*. If either *enzyme 1* or *enzyme 2* is defective, *molecule C* cannot be manufactured, producing a mutant phenotype. Defects in *enzyme 1* or *2* may show up as one or two mutant phenotypes. The result of defects in such pathways leads to modified Mendelian phenotypic ratios for crosses. The simplest cases of gene interaction to consider are those in which only two genes are interacting to produce a single phenotype, normally.

There are various ways in which genes at different loci can interact with each other.

Non-allelic genes can interact with each other in complex ways: **complementation, epistasis, polygenic inheritance**

Complementation: 9:7 Ratio. **Example:** Flower color in sweet pea.

Complementation is a kind of gene interaction where the manifestation of a character is determined by presence of two dominant genes of different allelomorphic pairs simultaneously (A_B_).

If two genes are involved in a specific pathway and functional products from both are required for expression, then one recessive allelic pair at either allelic pair would result in the mutant phenotype. This is graphically shown in the following diagram.

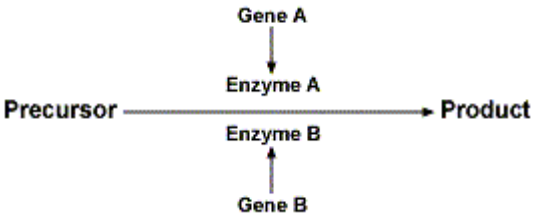
If a pure line pea plant with colored flowers (genotype = *CCPP*) is crossed to pure line, homozygous recessive plant (= *ccpp*) with white flowers, the F_1 plant will have colored flowers and a *CcPp* genotype. The normal ratio from selfing dihybrid is 9:3:3:1, but interactions of the *C* and *P* genes will give a modified 9:7 ratio. The following table describes the interactions for each genotype and how the ratio occurs.

Genotype	Flower Color	Enzyme Activities
9 *C_P_*	Flowers **colored**; anthocyanin produced	Functional enzymes from both genes
3 *C_pp*	Flowers **white**; no anthocyanin produced	***p*** enzyme non-functional
3 *ccP_*	Flowers **white**; no anthocyanin produced	***c*** enzyme non-functional
1 *ccpp*	Flowers **white**; no anthocyanin produced	***c*** and ***p*** enzymes non-functional

Because both genes are required for the correct phenotype, such interaction is called ***complementary gene action (complementation)***.

Duplicate gene action: 15:1 Ratio. **Example:** Kernel Color in Wheat.

For this type of pathway a functional enzyme *A* or *B* can produce a product from a common precursor. The product gives color to the wheat kernel. Therefore, only one dominant allele at either of the two loci is required to generate the product. Thus, if a pure line wheat plant with a colored kernel (genotype = *AABB*) is crossed to plant with white kernels (genotype = *aabb*) and the resulting F_1 plants are selfed, a modification of the dihybrid 9:3:3:1 ratio will be produced. The following table provides a biochemical explanation for the 15:1 ratio.



Genotype	Kernel Phenotype	Enzyme Activities
9 *A_B_*	colored kernels	functional enzymes from **both genes**
3 *A_bb*	colored kernels	functional enzyme from the ***A*** gene pair
3 *aaB_*	colored kernels	functional enzyme from the ***B*** gene pair
1 *aabb*	colorless kernels	non-functional enzymes produced at both genes

If we sum the three different genotypes that will produce a colored kernel we can achieve a 15:1 ratio. Because either of the genes can provide the wild type phenotype, this interaction is called ***duplicate gene action***.

Epistasis

Sometimes the effect of gene interaction is that one gene masks (hides) the effect of another gene at a different locus, a phenomenon known as **epistasis.** Epistasis was first defined by the English geneticist William Bateson in 1907.

Epistasis is the interaction of two or more genes to control a single phenotype.

Epistasis should not be confused with dominance, which refers to the interaction of genes at the same locus (allelic genes). The cause might be that both genes produce enzymes which act in the same biochemical pathway. In epistasis,

- the gene that does the masking is called the **epistatic gene**
- the gene whose effect is masked is a **hypostatic gene**

Epistatic genes may be recessive or dominant in their effects.

Example 1: 12:3:1 Ratio. **Phenotype:** Fruit Color in Squash

With this interaction, fruit color in squash is recessive to no color at one allelic pair. This recessive allele must be expressed before the specific color allele at a second locus is expressed. At the first gene white colored squash is dominant to colored squash, and the gene symbols are *W*=white and *w*=colored. At the second gene yellow is dominant to green, and the symbols used are *G*=yellow, *g*=green. If the dihybrid is selfed, three phenotypes are produced in a 12:3:1 ratio. The following table explains how this ratio is obtained.

Genotype	Fruit Color	Gene Actions
9 *W_G_*	White	Dominant white allele negates effect of ***G*** allele
3 *W_gg*	White	Dominant white allele negates effect of ***G*** allele
3 *wwG_*	Yellow	Recessive color allele allows yellow allele expression
1 wwgg	Green	Recessive color allele allows green allele expression

Because the presence of the dominant *W* allele masks the effects of either the *G* or *g* allele, this type of interaction is called **dominant epistasis**.

Example 2: 13:3 ratio. **Phenotype:** Malvidin production in *Primula*

Certain genes have the ability to suppress the expression of a gene at a second locus. The production of the chemical malvidin in the plant *Primula* is an example. Both the synthesis of the chemical (controlled by the *K* gene) and the suppression of synthesis at the *K* gene (controlled by the *D* gene) are dominant traits. The F_1 plant with the genotype *KkDd* will not produce malvidin because of the presence of the dominant *D* allele. What will be the distribution of the F_2 phenotypes after the F_1 was crossed?

Genotype	Phenotype and genetic explanation
9 *K_D_*	no malvidin because dominant *D* allele is present
3 *K_dd*	malvidin productions because dominant *K* allele present
3 *kkD_*	no malvidin because recessive *k* and dominant D alleles present
1 *kkdd*	no malvidin because recessive *k* allele present

The ratio from the above table is 13 no malvidin production to 3 malvidin production. Because the action of the dominant *D* allele masks the genes at the *K* locus, this interaction is termed **dominant suppression epistasis**.

Suppressor - a genetic factor that prevents the expression of alleles at a second locus; this is an example of epistatic interaction

Recessive epistasis

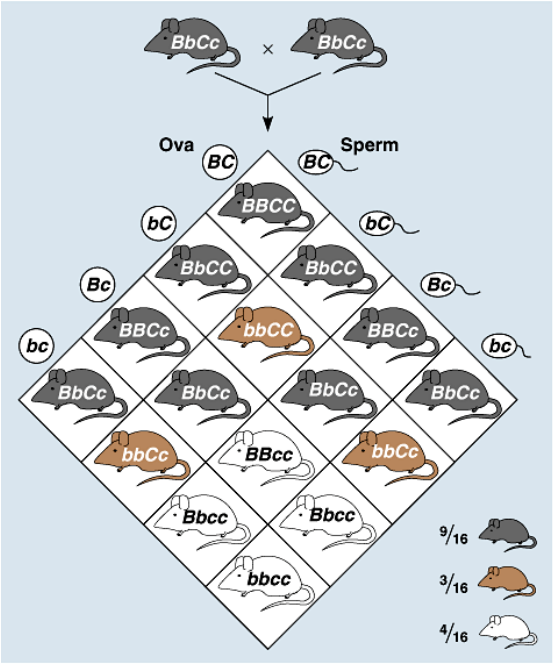
The presence of recessive alleles at one locus makes useless the presence of dominant alleles at another locus. This happens if two enzymes are needed in series; "the chain breaks" if either link fails.

Examples: coat color of labrador retriever dogs, color coat in mice, Bombay phenomenon in human.

Example 1: 9: 3 : 4 (9:7) Ratio. **Example:** coat color of mice.

In the example of epistasis, two of the genes responsible for coat color are:

- *Gene B* - determining whether hair has bands:
  - dominant allele (*B*) - results in hair with bands and **agouti** coat (brown),
  - recessive allele (*b*) - homozygotes have no bands and their coat is **black**.
- *Gene C* - affecting early steps of production of an enzyme responsible for pigment production:
  - dominant allele (*C*) - **normal** pigment production,
  - recessive allele (*c*) - homozygotes block all of the pigment production and are **albino**.



A Black mouse *BBCC* is crossed with an Albino mouse *bbcc*. All F_1 offspring will be black mice *BbCc* .

Then if we cross mice from the F1 generation (*BbCc* × *BbCc*), the gametes each mouse could produce would be (*BC, Bc, bC*, and *bc*).

The F_2 would be = 9 black : 3 brown : 4 albino

In epistasis involving coat colour in mice, alleles at the gene *C* alter the phenotypic effect of alleles at the gene *B* - *cc* mice will all be albinos irrespective of their genotype at gene *B*! So, genotype *cc* at gene *C* is **epistatic** to gene *B*.

Example 2: ***Bombay phenomenon in human***

There are many examples of epistasis. Epistatic interactions in human are associated with the genes taking part in the regulation of ontogenesis and immune system. One of the first to be described in humans is the *Bombay phenotype*, involving the ABO blood group system. Individuals with this phenotype lack a protein called the H **antigen** (genotype ***hh***), which is used to form A and B antigens. Even though such individuals may have A or B genes, they appear to be blood group O because they lack the H antigen.

Epistatic interactions make it difficult to identify loci conferring risk for complex disorders.

To locate interacting loci involved in the genetic origins of complex diseases requires collecting DNA samples from a large number of families where two or more individuals have the disorder. Such large-scale studies are usually difficult to conduct.

5. *Genotype-environment interaction*

The expression of a gene can be altered not only by other genes, but also by the environment. Such environmental variables as light, temperature, and nutrition can sharply affect the translation of a genotype into a phenotype.

For example, Siamese house cats have light color except on their ears, nose, tail, and paws. The expression of gene responsible for this hair color pattern is temperature-sensitive. The enzyme that catalyzes the production of dark pigment in these cats is unable to work at the normal body temperature. In lowering of temperature the enzyme is activated and can produce pigment that darkens the ears, paws and tail. Thus, the phenotype of an organism is a function of the interactions of genotype and environment.
Temperature also affects *primrose flower color* and *fur of Himalayan rabbits*.

In buttercup plant (*Ranunculus peltatus*), leaves below water-level are finely divided and those above water-level are broad, floating, photosynthetic leaf-like leaves.

6. *Penetrance, expressivity*

The degree of gene expression is called **expressivity**. The environment influence on the expressivity of the genotype may lead to problems in correct diagnosis and interpretation of pedigree, especially in an autosomal dominant inheritance. Clinically, variable expressivity of the genotype is exhibited by mild, moderate or severe form of the disease. Examples of dominant genes expressivity are different degrees of *cleft lip and cleft palate, bifurcation of pendulous palate, different depth of cotiloid cavity, different degree of polydactyly*.

One and the same trait may show in some organisms and be absent in others, having the same gene. The proportion of individuals with a given genotype that actually show the expected phenotype is

called the **penetrance** of the genotype for a given population. For example, in humans blood groups inheritance in system ABO has 100 % of penetrance, inheritance of epilepsy - 67% , diabetes mellitus - 65% , congenital dislocation of the hip - 25%.

It is necessary to remember, that genes responsible for pathologic traits can have different penetrance and expressivity. Changing the environment conditions one can influence on the development of a trait. For example, in an autosomal recessive disorder called phenylketonuria (PKU), an enzyme phenylalanine hydroxylase is deficient. This enzyme deficiency leads to accumulation of phenylalanine in the blood (0,5-0,6 g/l instead of 0,003-0,04 g/l in the norm) and its transformation into phenylpyruvic acid and other toxic metabolites. It causes severe mental retardation, phenylketonuria (passing phenyl kitones in urine), hypopigmentation, etc. Prescription of phenylalanine-free diet prevents the development of mental retardation in children with PKU.

Polygenic Inheritance

Polygenic inheritance is a pattern responsible for many traits which are governed by the cumulative effects of many genes. Polygenic traits are not expressed as absolute or discrete characters. Polygenic traits are recognizable by their expression as a gradation of small differences (a continuous variation). Human polygenic traits include height, weight, eye color, intelligence, skin color, many forms of behavior.

The biological role of polygeny is to increase of trait stability.

7. ***Pleiotropy***

Pleiotropy is the effect of a single gene on more than one characteristic. There are two kind of pleiotropy: ***primary*** and ***secondary***. In primary pleiotropy the gene shows own multiple actions *simultaneously*. Examples of such conditions are *osteogenesis imperfecta, Marfanõs syndrome, Hartnup disease.*

In osteogenesis imperfecta, the basic defect is in collagen synthesis. This accounts for multiple secondary effects like brittle bones, osteosclerosis, blue sclerae, etc. In another condition called Marfanõs syndrom primary defect lies in synthesis of elastic fibres. This exhibits in pleiotropic manifestations such as skeletal, ocular and cardiovascular anomalies. Marfanõs syndrom is recognized clinically in patients who have spindly digits, a high-arched palate and in whom there is a tendency to lens dislocation. The main cardiac complications are aortic dilatation and aortic valve regurgitation.

In Hartnup disease, mutation of gene causes disorder of tryptophan absorption in intestine and tryptophan reabsorption in canaliculi of kidneys. The membranes of epythelial cells in intestine and in canaliculi of kidneys are striked simultaneously.

In secondary pleiotropy, a primary phenotypic effect of gene leads to multiple secondary effects *developed one for other*. Examples of such conditions are *sickle-cell anaemia, phenylketonuria, galactosemia*.

The sickle cell anaemia is caused by gene (HbS), which is lethal in homozygous condition. It was found that the ß globin chain of HbS is different from HbA. Valine replaces glutamic acid in the sixth position of ß chain in HbS molecule. In heterozygotes under anoxic conditions, sickle haemoglobin forms long, needle-like tactoids, which deform the red cell into the characteristic sickle shape. The presence of large number of sickled cells in small blood vessels impairs blood flow to the tissues causing hypoxia and local acidosis with further sickling of red cells. This leads to anaemia, splenomegaly and weakness. The red cells tend

to cluster, that in one's turn causes thrombosis, infarction and ischaemia. Sickle-celled individuals suffer from a number of problems, all of which are pleiotropic effects of the sickle-cell allele.

9. *Modifier Genes*

Instead of masking the effects of another gene, a gene can modify the expression of a second gene.

Modifier genes are those that have small quantitative effects on the level of expression of another gene.

In mice, coat color is controlled by the *B* gene. The *B* allele conditions black coat color and is dominant to the *b* allele that produces a brown coat. The intensity of the color, either black or brown is controlled by another gene, the *D* gene. At this gene, the dominant *D* allele controls full color whereas the recessive d allele conditions a dilute or faded expression of the color expression at the *B* gene. Therefore, if a cross is made among mice that are BdDd, the following phenotypic distribution will be seen:

- 9 *B_D_* (black)
- 3 *B_dd* (dilute black)
- 3 *bbD_* (brown)
- 1 *bbdd* (dilute brown)

The *D* gene does not mask the effect of the *B* gene, rather it modifies its expression.