LESSON 6

Theme: Allelic and non-allelic gene interactions

Mendelian inheritance patterns describes the traits controlled by a single gene but the inheritance patterns of many traits are a result of complex gene-gene interactions.

The patterns of single-gene inheritance refer to an interaction between alleles of a single gene so such pattern is known as *allelic genes interaction*. When interaction occurs between alleles of two or more genes it is *non-allelic genes interaction.*

Single-gene inheritance (Allelic Genes Interaction*)*

Complete dominance.

This term is commonly applied to the inheritance of alleles that obey Mendel's laws and follow a strict dominant/recessive relationship. In this case 50% of the protein, produced by a single copy of the dominant (functional) allele in the heterozygote, is sufficient to produce the dominant trait.

Example. The Rhesus factor.

The Rh System

The Rh system ranks with the ABO system in clinical importance because of its role in hemolytic disease of the newborn and in transfusion incompatibilities. The name Rh comes from Rhesus monkeys that were used in the experiments that led to the discovery of the system. In simplest terms, the population is separated into Rh-positive individuals, who express, on their red blood cells, the antigen Rh D, a polypeptide encoded by a gene (RHD) on chromosome 1, and Rh-negative individuals, who do not express this antigen. The Rh-negative phenotype usually originates from homozygosity (dd) for a nonfunctional allele of the RHD gene. The frequency of Rh-negative individuals varies enormously in different ethnic groups. For example, 17% of whites and 7% of African Americans are Rh-negative, whereas the frequency among Japanese is 0.5%.

Incomplete dominance.

This pattern occurs when the heterozygote has a phenotype that is intermediate between either corresponding homozygote. In this case 50% of the protein, produced by a

single copy of the functional allele in the heterozygote, is not sufficient to produce the same trait as the homozygote making 100%.

Example. The Sickle cell anemia (Sickle cell disease, SCD) is an inherited blood disorder that affects red blood cells. Normally, red blood cells are round and flexible so they can travel freely through the narrow blood vessels. People with sickle cell disease have red blood cells that contain mostly hemoglobin S, an abnormal type of hemoglobin. Sometimes these red blood cells become sickle-shaped (crescent shaped). These irregularly shaped cells get stuck in the blood vessels and are unable to transport oxygen effectively, causing damage to the organs. Organ damage and other complications often shorten patients live by about 30 years. Sickle cell disease is inherited as an autosomal recessive trait and has an incomplete dominance pattern of expression. Homozygous recessive persons (ss) for the sickle cell trait have red blood cells that all have abnormal hemoglobin. Such cells don't live as long as healthy red blood cells. So people with this disorder often have low red blood cell counts (anemia), which is why this disease is commonly referred to as sickle cell anemia. Homozygous dominant persons (SS) have normal red blood cells. Heterozygous persons (Ss) - carriers of recessive allele, have some abnormal cells and some normal cells. Both the dominant and recessive alleles are expressed due to an incomplete dominance pattern of expression, so the result is a phenotype that is a combination of the recessive and dominant traits.

Codominance. This pattern occurs when the heterozygote expresses both alleles simultaneously. The codominant alleles encode proteins that function slightly differently from each other, and the function of each protein in the heterozygote affects the phenotype uniquely.

Example. In blood typing, an individual carrying the *A* and *B* alleles will have an AB blood type.

Many genes exist as three or more different alleles. This phenomenon is called ***multiple alleles***. Alleles of the ABO blood group can be dominant, recessive, or codominant.

The plasma membranes of red blood cells have groups of interconnected sugars - oligosaccharides - that act as surface antigens. Antigens are molecular structures that are recognized by antibodies produced by the immune system. On red blood cells, two different types of surface antigens, known as A and B, may be found. The synthesis of these surface

antigens is controlled by two alleles, designated I^A and I^B, respectively. The i allele is recessive to both I^A and I^B. A person who is homozygous ii will have type O blood and does not produce either antigen. A homozygous I^AI^A or heterozygous I^Ai individual will have type A blood. The red blood cells of this individual will contain the surface antigen known as A. Similarly, a homozygous I^BI^B or heterozygous I^Bi individual will produce surface antigen B. A person who is I^AI^B will have the blood type AB and express both surface antigens A and B. The phenomenon in which two alleles are both expressed in the heterozygous individual is called *codominance.* In this case, the I^A and I^B alleles are codominant to each other (fig.1).

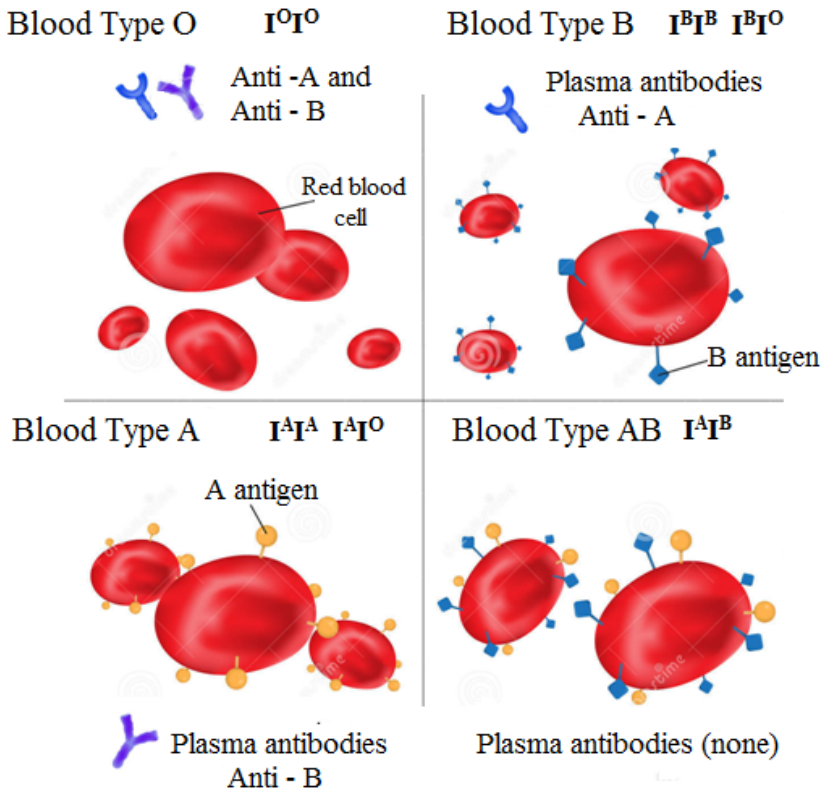


Fig. 1. ABO blood types

Overdominance (*Heterozygote advantage*). This pattern occurs when the heterozygote may display characteristics that are more beneficial for their survival in a particular environment. Such heterozygotes may be more likely to survive and reproduce. For example, a heterozygote may be larger, disease-resistant, or better able to withstand harsh environmental conditions.

Example. The Sickle cell anemia. Heterozygous individuals have a fitness advantage; they are resistant to severe malaria.

In spite of the harmful consequences to homozygotes, the sickle cell allele has been found at a fairly high frequency among human populations that are exposed to malaria. The protozoan genus that causes malaria, Plasmodium, spends part of its life cycle within the Anopheles mosquito and another part within the red blood cells of humans who have been bitten by an infected mosquito. However, red blood cells of heterozygotes are likely to rupture when infected by this parasite, thereby preventing the parasite from propagating. People who are heterozygous have better resistance to malaria than do homozygotes, while not incurring the ill effects of sickle cell disease.

Multifactorial inheritance (Non-Allelic Gene Interaction)

Complementation

Complementation is a kind of gene interaction when the manifestation of a character is determined by presence of both dominant alleles of non-allelic genes simultaneously.

The first case of two different genes interacting to affect a single trait was discovered by William Bateson and Reginald Punnett in 1906 while they were investigating the inheritance of comb morphology in chickens. Several common varieties of chicken possess combs with different morphologies, as illustrated in Figure 2A.

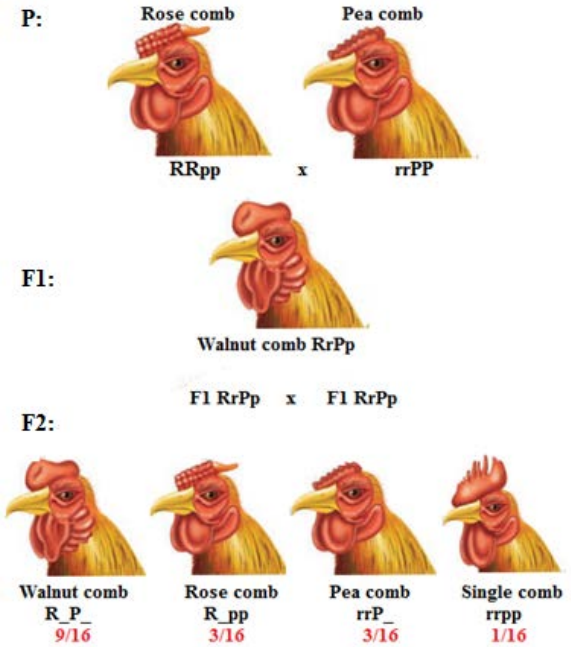


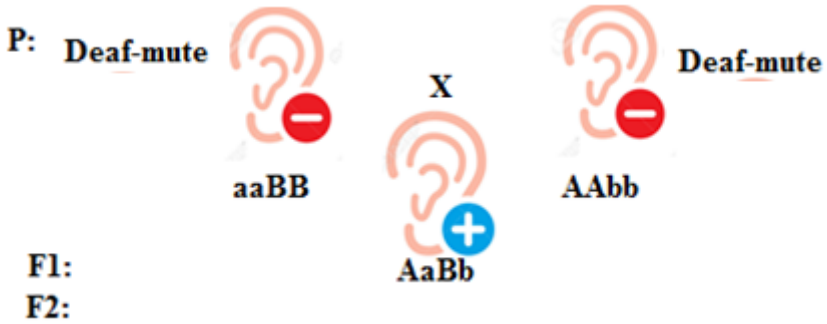
Fig.2 (A). Inheritance of comb morphology in chickens.

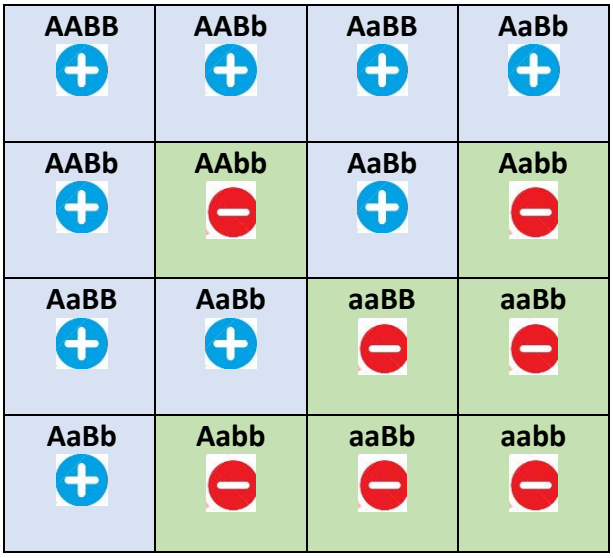
In their studies, Bateson and Punnett crossed a chicken having a rose comb to a chicken having a pea comb. All F1 offspring had a walnut comb. When these F1 offspring were mated to each other, the F2 generation consisted of chickens with four types of combs in the following phenotypic ratio: 9 walnut: 3 rose : 3 pea : 1 single comb (fig.2B). Such ratio is obtained in the F2 generation when the F1 generation is heterozygous for two different genes and these genes assort independently. However, an important difference here is that we have four distinct categories of a single trait. Based on the 9:3:3:1 ratio, Bateson and Punnett reasoned that a single trait (comb morphology) was determined by two different genes.

RRPP Walnut	**RRPp Walnut**	**RrPP Walnut**	**RrPp Walnut**
RRPp Walnut	**RRpp Rose**	**RrPp Walnut**	**Rrpp Rose**
RrPP Walnut	**RrPp Walnut**	**rrrPP Pea**	**rrPp Pea**
RrPp Walnut	**Rrpp Rose**	**rrPp Pea**	**rrpp Single**

Fig. 2(B). Inheritance of comb morphology in chickens.

Example . The Deaf-mutism in human (fig.3).





Ratio: 9/16:7/16

Fig.3. Inheritance of Deaf-mutism in human

In human the deaf-mutism is an example of complementary genes. The normal hearing and speech develops as a result of interaction between gene *A* and *B*. Whenever a person is homozygous for either of the two recessive alleles i. e. either *AAbb* or *aaBB*, he is deaf-mute.

There are also other variants of ratio: 9:6:1; 9:3:4.

Epistasis

Epistasis is a gene interaction in which two pairs of non-allelic genes interact in such a way when one gene suppresses or masks the expression of the other gene. The gene that masks the effect is *epistatic* gene and the gene that fails to produce its effect is *hypostatic* gene.

Epistasis may be dominant and recessive.

When epistasis is due to the dominant allele it is termed as *dominant epistasis.*

Example. The fruit color in summer squash (fig.4).

The expression of color in summer squash is due to the interaction of two dominant non-allelic genes *W* and *Y*. When *W* is present in a dominant form it suppresses the expression of *Y*, thus *W* is epistatic gene while *Y* is hypostatic gene. *Y* expresses only when *W* is present in a recessive form.

WWYY White	WWYy White	WwYY White	WwYy White
WWYy White	WWyy White	WwYy White	Wwyy White
WwYY White	WwYy White	wwYY Yellow	wwYy Yellow
WwYy White	Wwyy White	wwYy Yellow	wwyy Green

Ratio: 9/16:3/16:1/16

Fig.4. Inheritance of fruit color in summer squash

The expression of color in summer squash is due to the interaction of two dominant non-allelic genes *W* and *Y*. When *W* is present in dominant form it suppresses the expression of *Y*, thus *W* is epistatic gene while *Y* is hypostatic gene. *Y* expresses only when *W* is present in recessive form.

When epistasis is due to the dominant allele it is known as *recessive epistasis.*

Example. Bombay phenomenon.

Bombay blood type first discovered among three unrelated individuals in Bombay (now Mumbai) India in 1952 by Dr. Bhende and his colleagues. The major characteristic of the red blood cells of the Bombay blood group is the absence of the H antigen. The H antigen is located on the surface of red blood cells and is the precursor of A and B antigens. A person of the Bombay blood group inherited the recessive form (h) of the allele for the H antigen from each of his parents. He carries the homozygous recessive (hh) genotype instead of the

homozygous dominant (HH) or heterozygous (Hh) genotypes of the ABO blood group. As a result, the H antigen is not expressed in the red blood cell surfaces; consequently, the A and B antigens are not formed. The h allele is a recessive epistatic gene.

Polygenic or quantitative inheritance

The term polygenic inheritance refers to the transmission of a trait governed by two or more different genes. Such traits are viewed as *quantitative traits* because they can be described numerically. The location on a chromosome that harbors one or more genes that affect the outcome of a quantitative trait is called a quantitative trait locus (QTL). QTL is large chromosomal region, and it may contain a single gene or two or more closely linked genes that affect a quantitative trait. Each of these gene has one potential *additive allele* that contributes approximately equally to the phenotypic effect and one potential *nonadditive allele* that fails the effect. The greater the number of additive alleles in the genotype, the more intense the trait in the phenotype, because each of these allele has equal contribution and cumulative the total effect.

Quantitative traits can be categorized as anatomical, physiological, and behavioral. In addition, many human diseases exhibit characteristics and inheritance patterns analogous to those of quantitative traits.

Examles in human: height, weight, skin color, IQ, metabolic traits, atherosclerosis, hypertension, cancer, diabetes and so on.