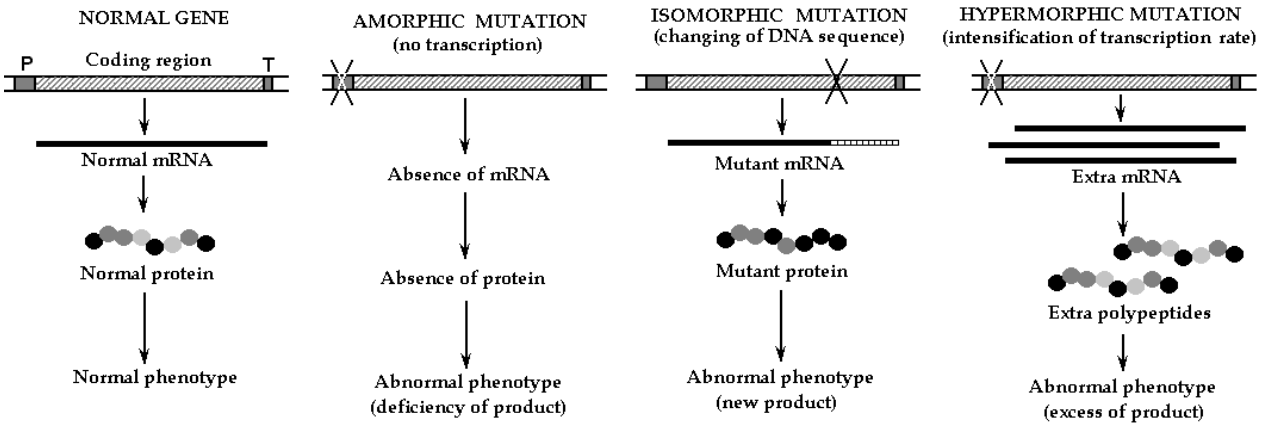
GENE'S INTERACTIONS

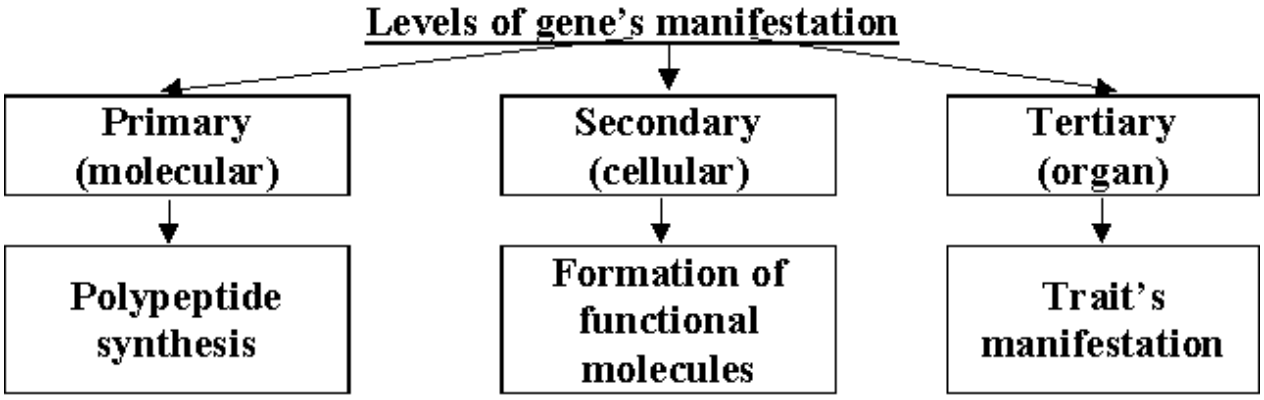
Human traits are determined by particulate elements called **genes.** A gene has different forms, called **alleles.** In human organism the genes are presented in pairs, one member of each pair having been transmitted from the paternal parent and the other member from the maternal parent. The specific alleles present in an individual constitute its **genotype;** the set of observable characteristics (physical or biochemical) of the individual is termed its **phenotype.**

Genotype may also refer to the nature of the genes (alleles) at a particular locus on a pair of chromosomes. If the two alleles of a pair are the same (for example, **AA** or **aa**), the organism is **homozygous** with respect to that gene; if the alleles are different (**Aa**), it is **heterozygous**.

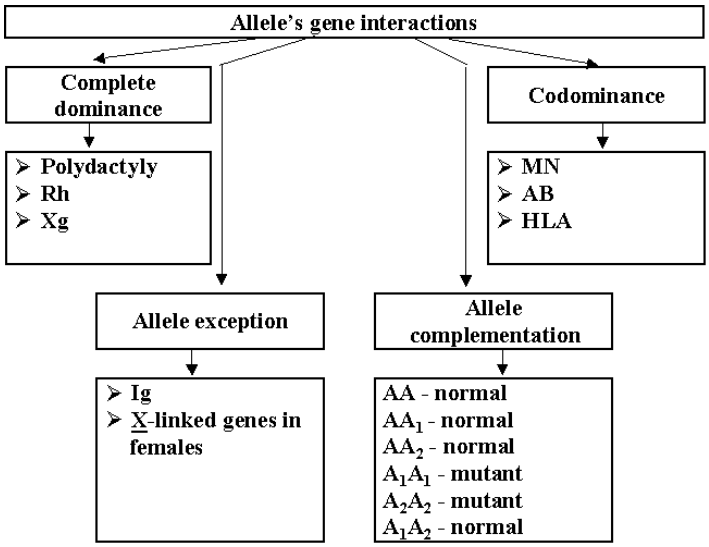
Different alleles of a particular gene appear as result of mutations at the level of nucleotide sequence of gene or regulatory regions (enhancers, silencers, promoters etc.). As result may be some types of alleles:

- **Amorphic allele**. The error occurs in promoter region or the signal of initiation of translation is corrupted. The mutant allele has no gene activity.
- **Isomorphic (neomorphic) allele**. Due to the changes in the structure of coding region a polypeptide with new proprieties is synthesized. The mutant allele is active, but the phenotype differs from original.
- **Hypermorphic allele.** Because of modifications in regulatory regions the quantity of mRNA and, as result, of protein increase. Alternatively, as result of errors in coding region, may be synthesized a protein with higher activity.
- **Hypomorphic allele**. Is opposite to hypermorphic allele. May be determined by errors in regulatory regions structure (decreasing of product's quantity), or errors in coding region (the product is less active).





Allelic interactions

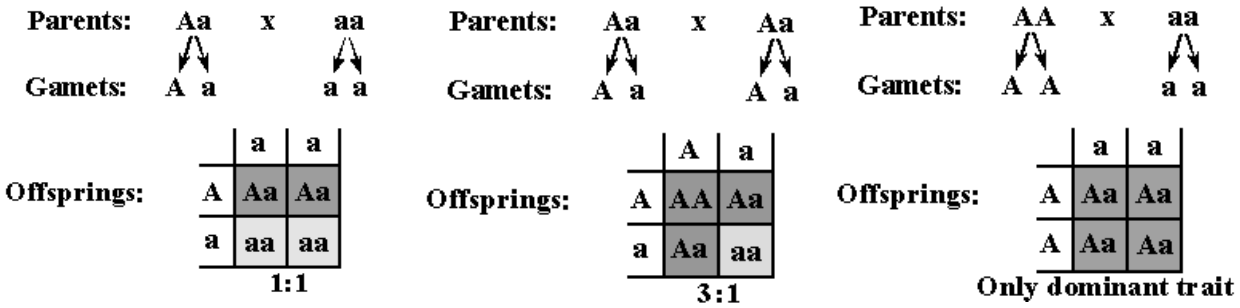


The alleles from the same pair may interact between them according to the nature of their activity.

Dominant-recessive patterns (complete dominance)

Alleles may be in two forms: dominant and recessive. When the phenotype of a heterozygote is the same as that of the homozygous combination, the expressed allele is said to be **dominant** over the other, and the hidden allele is termed **recessive** (recessive alleles results from amorphic mutations). For example, the Rh+ phenotype is brought about by the genotypes **DD** and **Dd**; whereas the Rh- phenotype is only brought about the genotype **dd.** The convention is to use a capital letter for a dominant trait and a small case letter for a recessive trait.

During the formation of gametes the paired alleles separate and segregate randomly such that each gamete receives one or other element (***principle of segregation***).

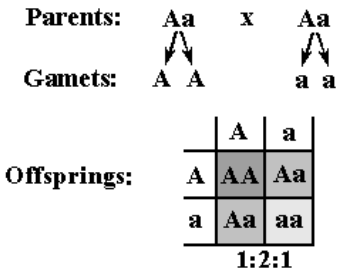


Aa - heterozygous; **AA** – homozygous dominant; **aa** – homozygous recessive.

Presence of at least one dominant allele determines the dominant trait, while homozygous recessive organisms have recessive trait (**AA**, **Aa** – dominant trait; **aa** – recessive trait).

The segregation by phenotype is different from segregation by genotype. For example, in hybridization **Aa** x **Aa** the segregation by phenotype is 3:1, while the segregation by genotype is 1:2:1.

In Mendel's experiments all traits had clear dominant-recessive patterns. However, lack of strict dominance is widespread in nature. Some examples will illustrate variations on dominance and phenotypic differences between heterozygous and homozygous dominant individuals.



In **incomplete dominance (no dominance)** the phenotype of a heterozygote is intermediate between the homozygous dominant or recessive types. Usually, in this case one of the allele is defective and the normal one produces only a half of required product. The segregation ratio by phenotype and genotype is the same (e.g. in hybridization **Aa** x **Aa** segregation by both phenotype and genotype will be 1:2:1).

In **co-dominance**, neither allele dominates expression on other in heterozygotes. Two different alleles in a heterozygote are both fully expressed, resulting in a phenotype that is qualitatively different from those of homozygotes (the alleles result from isomorphic mutations). The three MN blood groups found in human populations provide an example. Blood groups are

determined by the presence of antigen on the surface of the red blood cells. The three blood groups, M, N and MN correspond to the genotypes $\mathbf{L^ML^M}$, $\mathbf{L^NL^N}$ and $\mathbf{L^ML^N}$, respectively. As specified by their genotype, people have either antigen M (from $\mathbf{L^ML^M}$), or antigen N (from $\mathbf{L^NL^N}$), or they have both of them (from $\mathbf{L^ML^N}$). Because the heterozygote has both phenotypes, the two alleles are said to be **co-dominant**.

The human disease sickle-cell anemia gives interesting insight into dominance. The three genotypes have different phenotypes, as follows:

Hb(A)Hb(A): normal; red blood cells never sickle.

Hb(S)Hb(S): sever, often fatal anemia; abnormal hemoglobin causes red blood cells to have sickle shape.

Hb(A)Hb(S): No anemia; red blood cells sickle only under low oxygen concentration.

In regard to anemia, the **Hb(A)** allele is obviously dominant. In regard to blood cell shape, however, there is incomplete dominance. Finally, as we shall now see, in regard to hemoglobin itself there is codominance. The alleles **Hb(A)** and **Hb(S)** actually code for two different forms of hemoglobin and both these forms are present in the heterozygote, showing that the alleles are co-dominant. Sickle-cell anemia illustrates that the terms incomplete dominance and co-dominance are somewhat arbitrary. The type of dominance depend on the phenotypic level at which the observation are being made - organismal, cellular, or molecular.

Multiple alleles. Many genes have more the two alleles. Although a diploid organism can have only two alleles of a gene, in a population the total number of different alleles is often quite large. This situation is called multiple allelism, and the set of alleles itself is called an allelic series. Multiple alleles result from different mutations of the same gene.

Human AB0 blood types are determined by alleles A, B, and 0. A and B are co-dominant which are both dominant over 0. The only possible genotype for a type 0 person is $\mathbf{L^0L^0}$. Type A people have either $\mathbf{L^AL^A}$ or $\mathbf{L^AL^0}$ genotypes. Type B people have either $\mathbf{L^BL^B}$ or $\mathbf{L^BL^0}$ genotypes. Type AB people have only $\mathbf{L^AL^B}$ (heterozygous) genotype.

In **allelic exclusion**, one allele is active in some cells and another allele - in others. For example, genes for immunoglobulins (Ig), those determine a great antigenic diversity in human organism.

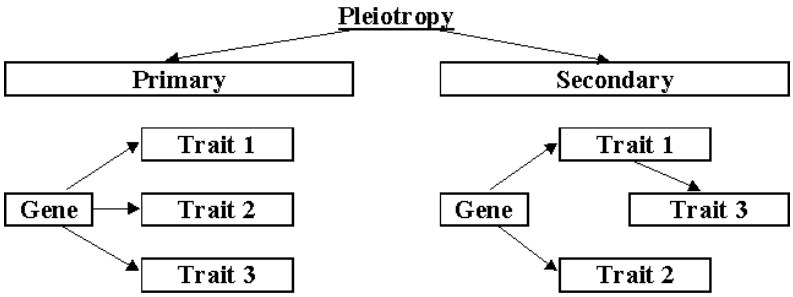
Imprinting. Recent evidence indicates that there may be differences in the expression of genes depending on their pattern of origin. This implies that an allele inherited from the mother may have an expression pattern different from those of the corresponding allele inherited from the father. Three groups of such genes were discovered in chromosomes 7 (7q32), 11 (11p15), 15 (15q11.2q13).

Allele complementation (allele complementarity). This type of interaction is possible when multiple alleles are present in population. [e.g.: A (ancestral, normal allele), A_1, A_2 (mutant alleles). The organisms containing normal allele have a normal phenotype, while the homozygotes by mutant alleles are defective. As the same time the heterozygous A_1A_2 are normal too, because of complementary activity of encoded polypeptides].

The phenotypic expression of some genes is the same in all individuals having the same genotype. However, the phenotypes determined by most genes are more variable. Such genes are said to have variable **expressivity**, meaning that they vary in expression in different individuals. The different degrees of expression often form a continuous series from full expression to no expression of phenotypic characteristics. [e.g. in polydactyly: some persons presents complete abnormality (six finger in both hands; six toes in both foots) but other, with the same genotype, may have six fingers only in one hand]. A second form of variation in the expression of a gene is variable penetrance. **Penetrance** is defined as the proportion of individuals whose phenotype matches their genotype for a given character. A genotype that is always expressed has a penetrance of 100 percent. Examples of this phenomenon include cases of identical human twins in which a genetically determined character occurs in one twin but not in the other. [e.g. in

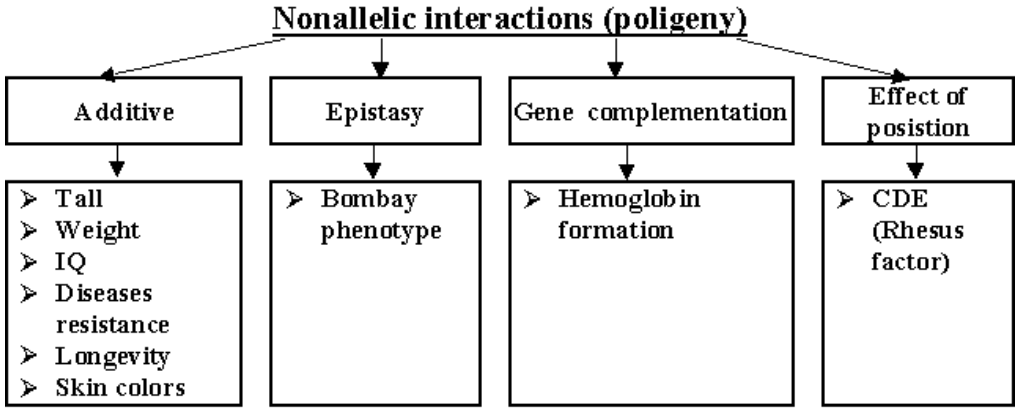
epilepsy: all people **AA** are defective, but only a part of heterozygous **Aa** have the disorder, depending on environmental conditions).

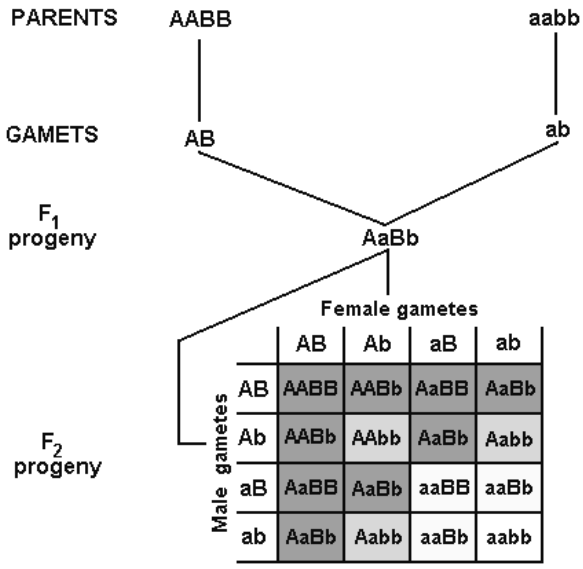
Pleiotropy refers to the multiple effects of a gene in different tissues or organs. In this case a single mutant gene affects two or more distinct and seemingly unrelated traits. For example, the diagnosis of Marfan syndrome is made based a triad of cardiovascular (aortic aneurysm, aortic insufficiency), skeletal (long limbs, fingers and toes, loose-jointedness), and eye structure (dislocated lens). Although several organ systems are involved, the basic defect is an abnormality in the fibrillin protein, which is found in connective tissue.



There are two levels of pleiotropy. In **primary pleiotropy** mutations in a single gene affect some traits if their formation requireds the same product. [e.g. in sickle anemia allele HbS produces defective hemoglobin, the shape of erythrocytes is defective and may be interfered the process of oxygen transporting]. In **secondary pleiotropy** the phenotype is changed as result of action of another abnormal trait. [e.g. in sickle anemia in low oxygen environment may be affected brain, kidney, liver, hart because erythrocytes cannot provide enough quantity of oxygen].

Nonalellic gene interactions





Human organism is a highly complex system in which all functions interact to a greater or lesser degree. At the level of genetic determination, the genes likewise can be regarded as cooperating. Therefore, a gene does not act in isolation; its effects depend not only on its own functions but also on the functions of other genes as well as on the environment. One gene pair can influence other gene pairs, with their combined activities producing some effect on phenotype.

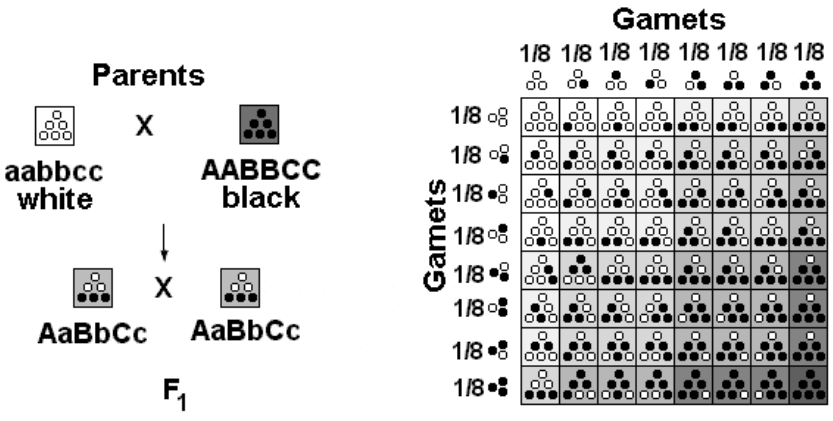
Segregation of the members of a pair of alleles is independent of the segregation of other pairs during the processes leading to formation of the reproductive cells (**principle of independent assortment**).

Usually polygenic traits are distinguished by:

* Traits are usually quantified by measurement rather than counting.
* Two or more gene pairs contribute to the phenotype.
* Phenotypic expression of polygenic traits varies over a wide range.

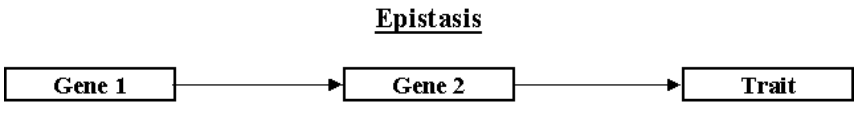
Based on this reasons are distinguished some types of interactions between genes located in non-homologous loci in the same chromosome or even in different chromosomes.

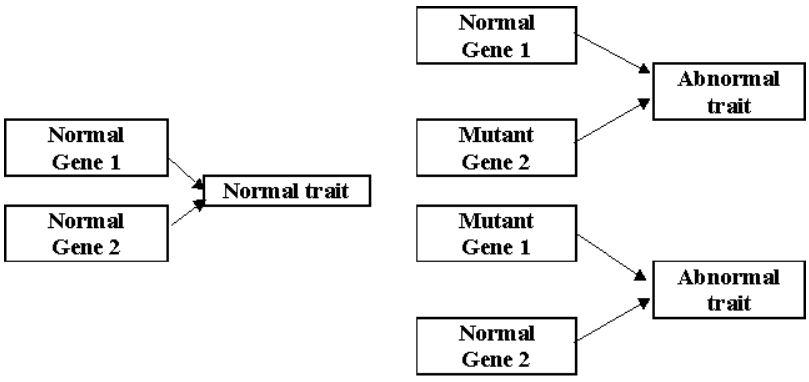
Polygenic inheritance is a pattern responsible for many features that seem simple on the surface. Many traits such as height, shape, weight, skin color, many forms of behavior and metabolic rate are governed by the cumulative effects of many genes. Polygenic traits are not expressed as absolute or discrete characters. Instead, polygenic traits are recognizable by their expression as a gradation of small differences (a **continuous variation**). Traits showing continuous variation are usually controlled by the **additive effects** of two or more separate gene pairs. The inheritance of each gene follows Mendelian rules. In inheritance of skin color are implied at least six genes (in picture are represented only tree). Each dominant allele assures synthesis of a quantity of pigment. More dominant alleles provide more pigment quantity, and, as result, more dark color. Other genes, with non-additive effect, are also implied in control of pigmentation: gene which controls the distribution of pigment in the cell, gene which control the skin thickness et al.



Inheritance of skin color

In **epistasis (epistasy)**, one gene blocks the expression of another and some expected phenotypes do not appear at all. Many phenotypes appear as a result of a chain of different reactions. In this case the final product of one gene serves as substrate for activity of another gene. For example: in ABO blood groups alleles **A** or **B** required a normal gene **H**. This gene (**H**) assures synthesis of a precursor, which will be modified by enzymes encoded by **A** or **B**. If there areno normal **H** allele (genotype **hh**) genes **A** or **B** cannot work properly and the person will present the **Bombay phenotype** (identical with phenotype O group). [See attached page].





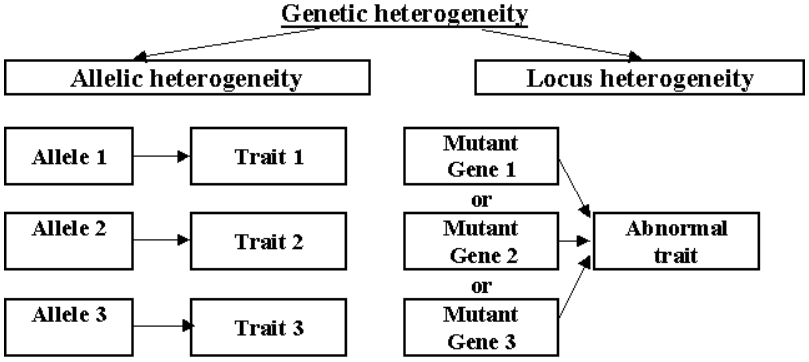
Gene complementation (complementary gene interaction) is observed when two (or more) non-allelic genes are required for formation of one normal trait. If the both alleles of one such gene are defective, the trait will be abnormal. For example: each hemoglobin

molecule consists of 2 α and 2 β chains. At least one normal allele of gene α and β are required for formation of normal molecule. If both alleles are defective (which encodes for α or β) abnormal hemoglobin will be synthesized.

Position effect. A group of very close linked genes are designed as a **haplotype**. Some times the activity of one gene may be interfered by the nature of nearby allele. In Rh phenotype **D** gene is the most important, but the closed located genes **C** and **E** also influence the quantity of antigens on the cell's surface. In fact the effect **CDE** sequence is different from **cDE** or **CDe**.

Genetic heterogeneity

Genetic heterogeneity means different relationships between genotypes and phenotypes.



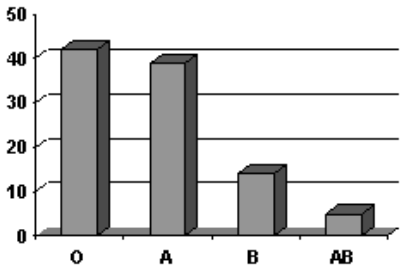
There are two kinds of genetic heterogeneity.

In **allelic heterogeneity** different alleles of one gene form diverse phenotypes.

In **gene heterogeneity** mutations in different, non-homologous genes have similar effects. Some times such genes are cold **genocopies.**

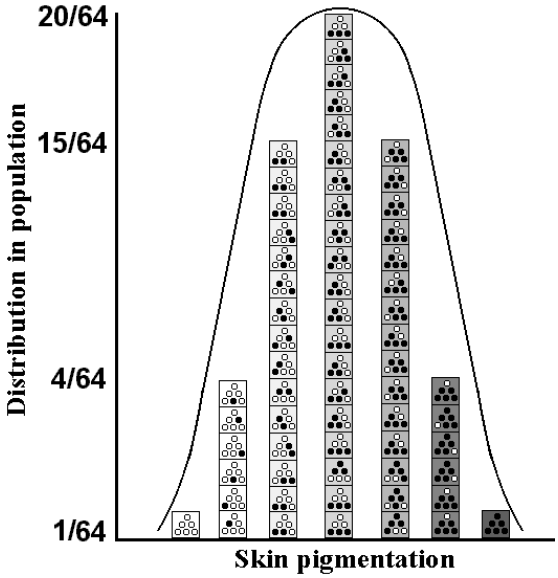
Distribution of genetic traits in populations

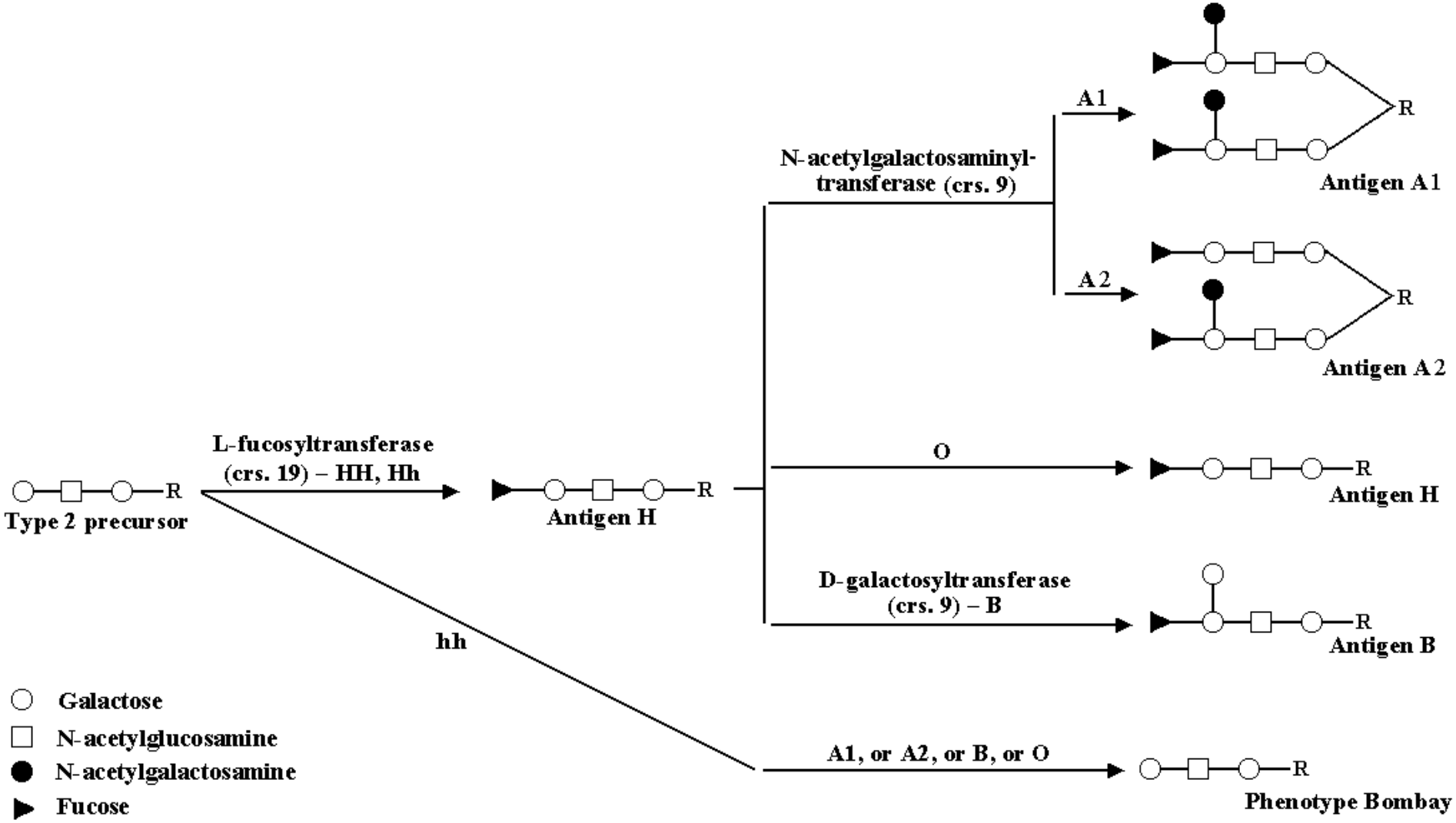
The distribution of a trait in population is a description of the population in terms of proportion of individuals that have each possible phenotype. There are two kinds of distribution of characters in populations.



Straightforward (bimodal) distribution. In this case there are few distinct phenotypes. Bimodal distribution is characteristic for single-gene traits, which are determined bay a pair of alleles. Such traits are less influenced by environment. As example may be: ABO groups (42% - O; 39% - A; 14% - B; 5% - AB) or Rh (85% - Rh+; 15% - Rh-).

Continuous (normal, Gaussian) distribution. Variation between individuals in a population, in which differences are quantitative rather than qualitative and produce a continuous spectrum of variation over the whole population. Continuously variable traits (e.g. height, skin color in humans) in which some hereditary component is present, are presumed to be due to the actions of many different genes and also usually to be subject to considerable environmental influence. The results form a bell shaped curve, with a mean value and extremes in either direction.




Type 2 precursor
R
L-fucosyltransferase
(crs. 19) – HH, Hh
Antigen H
N-acetylgalactosaminyl-
transferase (crs. 9)
A1
A2
Antigen A1
Antigen A2
O
Antigen H
D-galactosyltransferase
(crs. 9) – B
Antigen B
hh
A1, or A2, or B, or O
Phenotype Bombay
Galactose
N-acetylglucosamine
N-acetylgalactosamine
Fucose