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GENETICS

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This book is especially designed to serve the needs of the 1st grade students of specialties 31.05.01 General Medicine, 31.05.02 Pediatrics, 31.05.03 Dentistry, 33.06.01 Pharmacy, 32.05.01 Preventive Medicine of medical universities to study one of the sections within the biology course in English.

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Introduction

An important task of any doctor is the ability to recognize correctly the causes of various diseases, identify hereditary diseases, and determine the prognosis for future offspring.

In this course of medical genetics, the basic concepts of genetics, types of inheritance of traits and the main methods the diagnosis of genetic diseases in humans are studied. This course is the basis for further, deeper study of genetics in senior courses.

The book includes fundamental concepts of the topics in general and molecular genetics. The content includes a theoretical material for each section, examples of problem solving, situational problems with reference standards. The language of book is quite easy and understandable based on scientific approach. The book helps students to prepare classes in the “Teach Yourself” style. Many illustrations helps to visualized and understand difficult topics.

Chapter 1

Genetics is a branch of biology that concerned with the study of heredity and variations.

The term «genetics» was introduced into Biology by William Bateson in 1906.

Heredity and variations are controlled by genes. Gene is a sequence of nucleotides in DNA that codes for a molecule of protein that has a particular function. Each protein provides for the formation of the phenotypic trait.

Each organism transmits its genes to offspring during reproduction. That's why a gene is the basic physical and functional unit of heredity.

A sequence of nucleotides in DNA also may change, that's why genes provide variation.

1.1 Historical overview on the gene discovery.

The concept of gene has been changing with progress in research in genetics and molecular biology. Mendel was the first to visualize a gene as unit of inheritance in 1865. He called it a factor. He postulated that the gametes brought from the parents distinct particulate factors which made their respective characters appear in the offspring.

The world "gene" was introduced by Johanson in 1909 for a single unit of heredity occupying a specific position (locus) in a chromosome.

In 1926 Morgan in article "Gene Theory" determined the Chromosome Theory. In which, the genes lay in a linear order in the chromosomes and were carried along with them to daughter cells in cell division. Behavior of chromosomes and genes was found to be parallel.

It later has been found that DNA is the hereditary material composed of a linear series of deoxyribonucleotide pairs. A gene is a segment of DNA having a limited number of nucleotide pairs in a unique sequence. Different genes have different sequence of nucleotide pairs. The specific sequence of bases in a gene forms the code that directs the cell to manufacture a particular protein. A gene undergo crossing over and can mutate also.

In 1948 Beadle and Tatum proposed their famous one gene-one enzyme (protein)hypothesis, and considered gene as a unit of hereditary material which codes for the formation of a single protein (enzyme). Gradually it was found that all proteins do not act as enzyme, some proteins have structural role in cells and some function as membrane receptors. Moreover, certain proteins are composed if more than one polypeptide chains. As a result of these findings, the Beadle and Tatum hypothesis has been replaced by one gene -one polypeptide chain principle.

In 1960-s, genes were found to code for r-RNA and t-RNA. Regulatory genes, such as the operators of prokaryotic DNA, were also discovered. These genes are never transcribed. Besides these, some viruses have overlapping genes which code for more than one polypeptide. Certain viruses and higher organisms have genes which code for long polyproteins. A eukaryotic gene may have noncoding introns between coding exons. These researches have led to the concept that a gene is a segment of DNA molecule that codes for a unit of function. The function may be to code for a polypeptide, a polyprotein, ribosomal and transfer RNA, or to regulate the activity of other functional units within the DNA.

1.2 THE MAIN TERMS OF GENETICS.

Gene is a sequence of nucleotides in DNA that codes for one molecule of protein. Each gene is responsible for one trait.

Alleles are the different forms of one gene. They are responsible for different variants of one trait.

Allelic gene are located in the same locus of homologous chromosomes.

A **locus** is the location of gene in the chromosome.

A **phenotypic trait** is a distinct variant of a phenotypic characteristic of an organism.

- **Simple traits** are controlled by in single genes. So, one protein with it's particular function is a simple trait. *For example, phenilalaninhydroxilase*
- **Complex traits** are those that are influenced by more than one factor. The factors can be genetic (several genes are responsible for that trait) or environmental. For example, dementia that is resulted of phenylketonuria.

Alternative (or contrasting) traits are different variants of one trait that are encoded by different alleles of one gene.

Dominant allele is a louder allele that is always expressed independently of the second allele. It produces the same phenotype whether its paired allele is identical or different.

Recessive allele produces its characteristic phenotype only when its paired allele is identical. This allele is not expressed if a dominant allele is present.

Homozygous means that an individual has the same allele for a gene. If both alleles are dominant the individual is a homozygous dominant (AA). If both alleles are recessive the individual is a homozygous recessive (aa). Homozygous organism forms only 1 type of gametes.

Heterozygous mean that an individual has different alleles for a gene (Aa). Heterozygous organism produces 2 types of gametes.

Hemizygous organism has only a single copy of a gene instead of two.

Hybridization is crossing of individuals differing on genotype and phenotype, followed by further analysis of individuals obtained in filial generations (hybrids).

Monogenic inheritance refers to the kind of inheritance whereby a trait is determined by the expression of a single gene or allele

Polygenic inheritance - a trait is determined by the expression of several genes

Monohybrid cross is a mating between two organisms with different variations at one gene.

Dihybrid cross is a cross between two different organisms that differ in two genes (two observed traits).

Genotype is a complex of all genes of diploid cell (diploid organism)

Phenotype is a complex of all traits of organism that are resulted of gene expression and depended of environment.

Heredity is the ability of living organism to transmit characteristics and properties to next generation during reproduction

Inheritance is the way in which characteristics are passed from one generation to the next

Variability - the ability of organisms to acquire new features and properties during the life

Chapter 2. The basis of Molecular Genetics

2.1 Chemical composition of DNA molecule.

Chemical structure of DNA was explained by P.A.Levene (1869 — 1940). DNA is a polymer (a molecule containing repeating units). The basic subunit of DNA molecule is the deoxyribonucleotide (deoxyribotide, nucleotide). Each deoxyribonucleotide unit consists of three molecules:

- deoxyribose sugar (2'-deoxyribose);

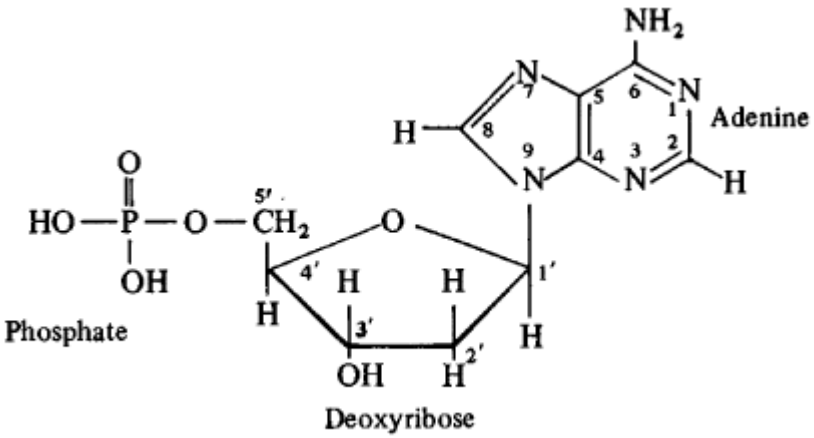
- phosphoric acid (H_3PO_4);

- nitrogen-containing base (purine or pyrimidine).

The deoxyribose sugar of DNA has 5 carbons. The carbon atoms are numbered 1', 2', 3', 4', 5'.

The nitrogenous base molecules are joined to the sugar molecules by glycosidic bonds. The glycosidic bond develops between the 1' carbon of the sugar and the nitrogen at the position 1 in case of pyrimidine base and at the position 9 in case of purine base.

The phosphate is joined to the 5' carbon atom of deoxyribose by ester bond.



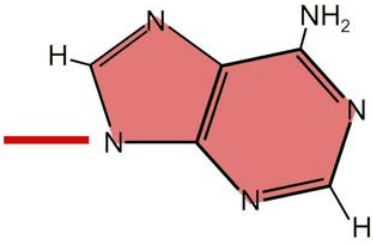
Four different bases are present in the DNA molecule:

- the *purines*: adenine (A) and guanine (G);

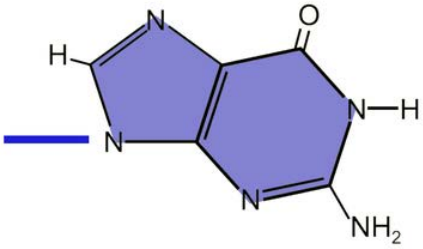
- the *pyrimidines*, cytosine (C) and thymine (T).

Purines are heterocyclic organic compounds containing a six-membered ring with two nitrogen atoms, which is fused to an imidazole ring.

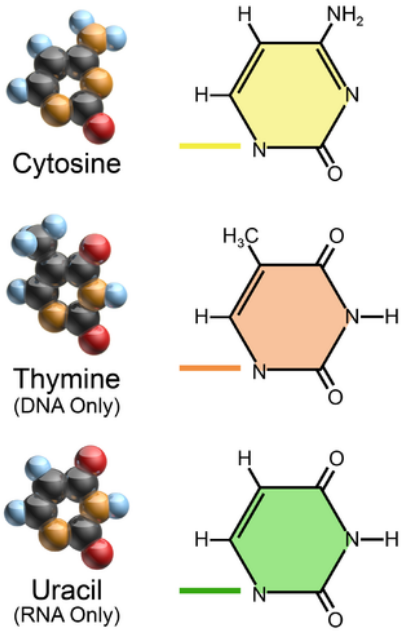
Adenine



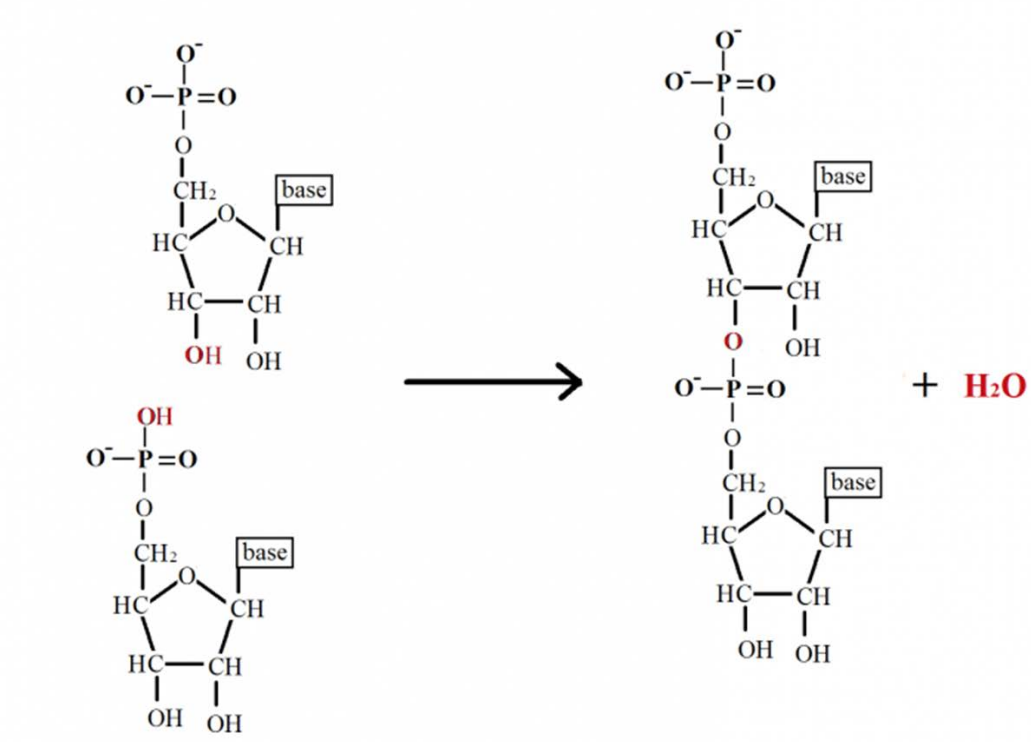
Guanine



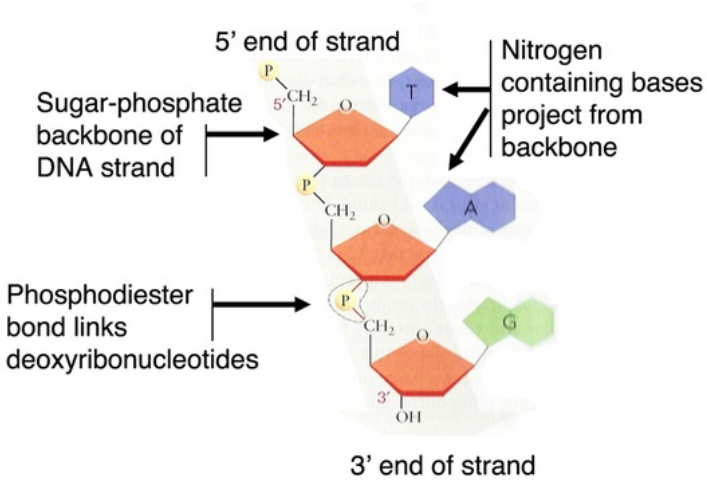
Pyrimidines are heterocyclic organic compounds, containing a six-membered ring with two nitrogen atoms. In pyrimidine, nitrogen atoms are found in the positions, 1 and 3 in the heterocyclic ring. Cytosine and thymine are the two nucleobases found in DNA. Uracil is found in RNA. While forming the double-stranded structure of nucleic acids, pyrimidines form hydrogen bonds with complementary purines in the process called complementary base pairing. Cytosine forms three hydrogen bonds with guanine and thymine forms two hydrogen bonds with adenine in DNA. In RNA, uracil forms two hydrogen bonds with adenine instead of thymine.



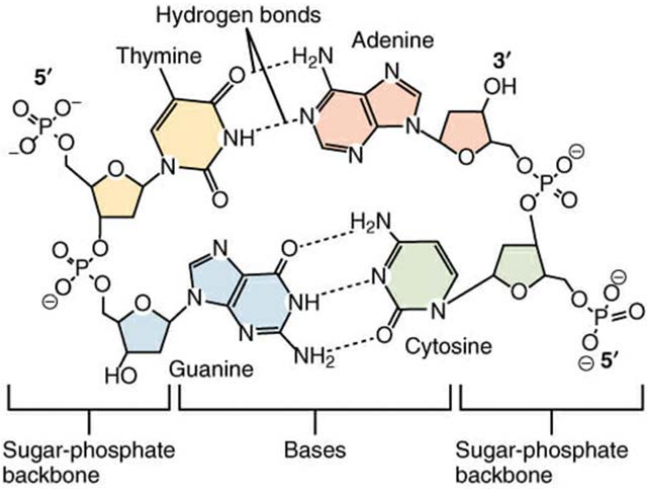
The backbone of the polymer is formed by linking the phosphate of one nucleotide to the deoxyribose of the adjacent nucleotide. The phosphate component carried by the 5'carbon atom of one nucleotide unit is joined by phosphodiester bond to the hydroxyl component of the 3' carbon atom of the sugar in the next nucleotide unit. These 3', 5' phosphodiester bonds provide a considerable stiffness to the polynucleotide.



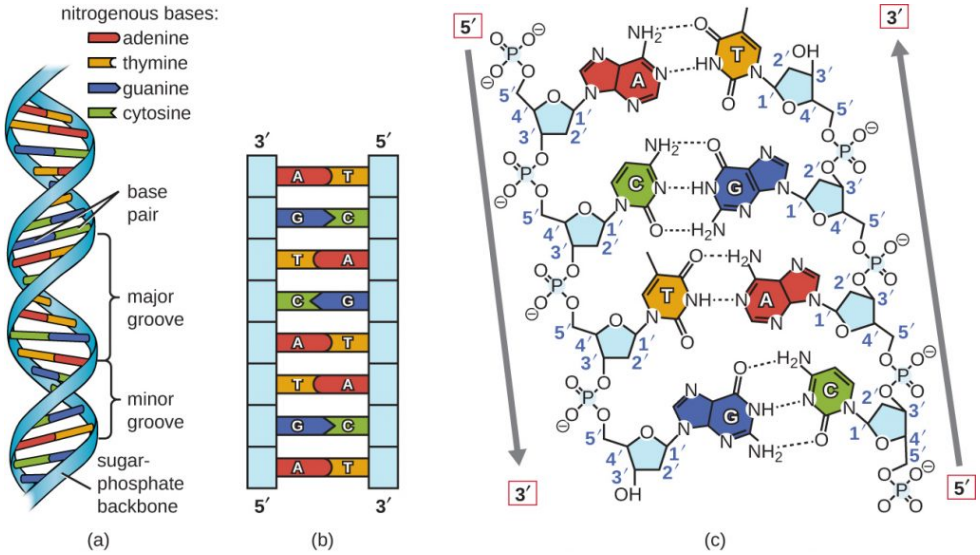
The resulting strand of nucleic acid has a free phosphate group at the 5′ carbon end and a free hydroxyl group at the 3′ carbon end. That ends are called 5’ end and 3’ end.



DNA usually exists as a double-stranded structure with two complementary strands. Two deoxyribonucleotide chains are held together by *hydrogen bonds.* Adenine of one chain is always joined to thymine of the other chain by two hydrogen bonds and cytosine of one chain is always linked to guanine of the other chain by three hydrogen bonds.



The two DNA strands are antiparallel, such that the 3′ end of one strand faces the 5′ end of the other. The resultant structure is exceeding stable, and the nucleotide sequence functions as the genetic template for the proteins of the cell.



Watson and Crick proposed the double helix model for DNA. (a) The sugar-phosphate backbones are on the outside of the double helix and purines and pyrimidines form the "rungs" of the DNA helix ladder. (b) The two DNA strands are antiparallel to each other. (c) The direction of each strand is identified by numbering the carbons (1 through 5) in each sugar molecule. The 5′ end is the one where 5' carbon is not bound to another nucleotide (there is free phosphate group); the 3′ end is the one where 3' carbon is not bound to another nucleotide (there is free OH-group).

2.1.1. The characters of DNA double helix.

Watson and Crick proposed that DNA is made up of two strands that are twisted around each other to form a right-handed helix.

1. The distance between the two successive nucleotides is 0.34 nm (3.4 A).
2. Each turn of the double helix covers a distance of 3.4 nm (34A).
3. Each nucleotide in turned 36^0 from the preceding one so that a complete turn of 360^0 involves ten (10) base pairs.
4. The diameter of the double helix is approximately 2.0 - 2.2 nm (20—22 A) and this is possible only if the pairing takes place between a purine and a pyrimidine.

2.1.2. Chargaff's rules.

1. The concentration of purine bases equals that of the pyrimidine bases; that is: [total purines]=[A]+[G]=[total pyrimidine]=[T]+[C].

2. The concentration of adenine and thymine are equal, as are the concentration of guanine and cytosine; that is [A]=[T] and [G]=[C]

3. The base ratio (A+G)/(T+C) = 1 may vary from one species to another, but is constant for a species. This ratio can be used to identify the source of DNA, and can help in classification.

4. The deoxyribose sugar and phosphate components occur in equal proportions.

2.1.3. DNA polymorphism.

DNA polymorphism is an ability of DNA molecule to form different configurations. Now, there are six DNA-forms.

B-form was described by G.Watson and F.Crick and has standard structure.

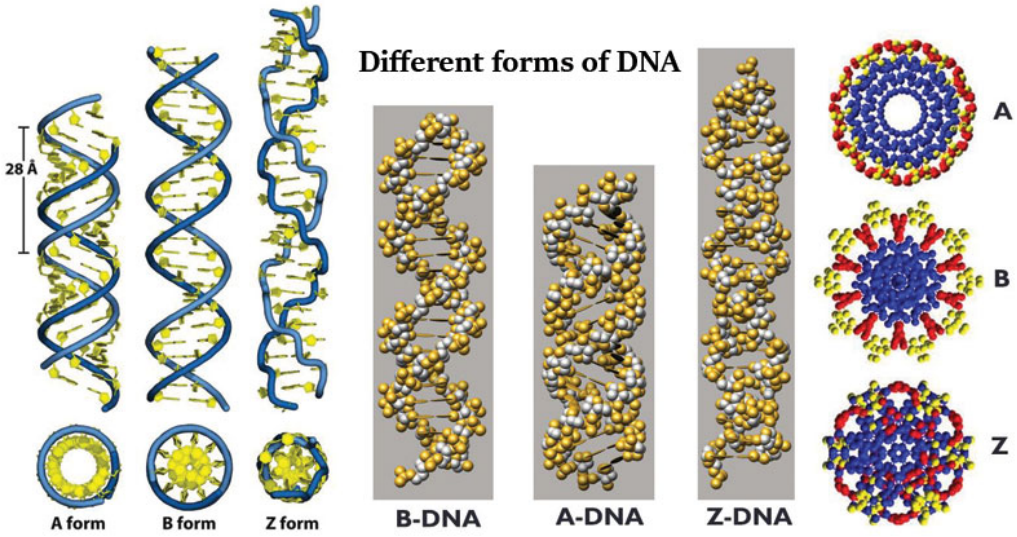
A-form was found in environment, where the concentration of K^+ and Na^+ ions was high.

C-form is the same with B-form, but the number of base pairs in one turn in C-form less than in B-form.

D- and E-forms are extreme variants of one form, have few base pairs in one turn. These forms were found in DNA molecule, which don't contain guanine.

Z-form is formed only when purines and pyrimidines are present alternately in the chain. This form may be left-handed or right-handed and was discovered several years ago by Rich of the Massachusetts Institute of Technology (MIT). In this DNA the backbone of the strands follows a zigzag course. The Z-conformation is stabilized only in a solution with a high salt concentration or when the DNA is brominated or methylated. Z-form plays a role in the regulation of the activity. It is known, that when certain control sites in the genes are stabilized in the Z-configuration by methylation, a regulatory protein binds to the sites and keeps the gene turned off. Demethylation

might switch the site to the B-conformation, causing the regulatory molecule to let go, and the gene is turned on. Thus, Z-configuration presumable has the regulatory function.



Comparison geometries of the most common DNA forms

Geometry attribute:	A-form	B-form	Z-form
Helix sense	right-handed	right-handed	left-handed
Repeating unit	1 bp	1 bp	2 bp
Rotation/base pair (bp)	32.7°	34.3°	60°/2
Mean bp/turn	11	10	12
Inclination of bp to axis	+19°	−1.2°	−9°
Rise/bp along axis	2.6 Å (0.26 nm)	3.4 Å (0.34 nm)	3.7 Å (0.37 nm)
Rise/turn of helix	28.6 Å (2.86 nm)	35.7 Å (3.57 nm)	45.6 Å (4.56 nm)
Mean propeller twist	+18°	+16°	0°

Nucleotide phosphate to phosphate distance	5.9 Å	7.0 Å	C: 5.7 Å, G: 6.1 Å
Diameter	23 Å (2.3 nm)	20 Å (2.0 nm)	18 Å (1.8 nm)

2.2 DNA Replication

Replication is a molecular mechanism of precise self–copying of a DNA molecule – the process of synthesizing of two molecules based on the complementary parent molecule. In the process of replication, the chains of the maternal DNA molecule diverge, and a new complementary chain is built on each of them. As a result, two molecules identical to the original are formed from one double helix. The biological meaning of DNA replication is to copy genetic information to transfer it to the next generation of cells. The process of DNA synthesis is accompanied by many events and is, as a rule, very accurate and consistent.

This becomes possible due to the structural features of the DNA molecule: double-stranded structure, complementarity and antiparallel properties.

After the discovery of the DNA structure, at least three replication models were proposed by the scientific community: conservative, dispersive and semi-conservative.

Semiconservative (most of prokaryotes and eukaryotes).

In this type of replication, DNA is replicated each daughter duplex contains one parental and one newly synthesized strand.

Conservative *(viruses)*

In this type of replication, the integrity of the whole parental double helix is conserved in the replication process. After one replication cycle, one of the daughter DNA molecules consists of two newly synthesized strands, while the other has both parental strands. Conservative replication would involve the duplication of only one of DNA strands which serves as the template. The newly formed strand then serves as a template for the synthesis of its own complementary strand.

Dispersive *(viruses)*

This type of DNA replication is possible if the two strands break down along their length into small pieces. Each piece would then replicate and the pieces (old and new) would randomly

join with another one to form the two DNA molecules, each having some old and some new pieces.

Later, it was the semi-conservative method of DNA replication that received experimental confirmation.

EXPERIMENTAL EVIDENCE FOR SEMICONSERVATIVE REPLICATION.

Meselson and Stahl in 1958 provided a strong experimental evidence which supported the semiconservative type of DNA replication. They grew E. Coli bacteria in a medium containing the heavy nitrogen isotope ^{15}N for many generations. This produced a population of bacterial cells that had uniformly ^{15}N-labelled DNA, and this DNA was heavier that the DNA obtained from E. Coli grown in ^{14}N-containing medium.

The bacterial cells with the heavier DNA were then transferred to a medium having the ordinary ^{14}N isotope. From the daughter cells of first generation, DNA was extracted, purified and centrifuged. It was that all the DNA molecules were hybrid ^{15}N-^{14}N , i. e. all were half heavy. This is what is expected in case of semiconservative mode of replication. Daughter cells were allowed to divide again. The second generation cells were found to have two types of DNA molecules, 50% half heavy with ^{14}N-^{15}N hybrid density and 50% light with ^{14}N-^{14}N density. This again conforms to the prediction based on semiconservative mode of DNA replication.

DETAILS OF SEMICONSERVATIVE DNA REPLICATION.

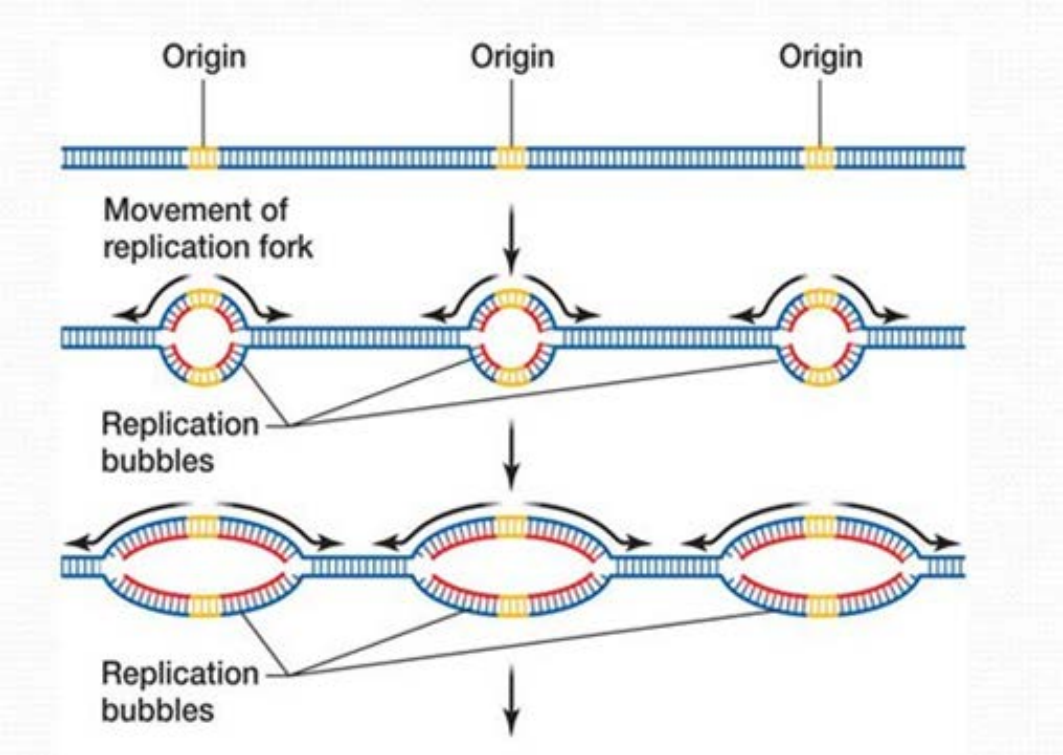
Activation of Deoxyribonucleotides

The deoxyribonucleoside monophosphates (AMP, GMP, CMP, TMP) found floating free in the nucleus serve as the raw materials in DNA synthesis. These nucleotides are synthesized from precursor molecules available from digestion and metabolism. For incorporation into DNA, nucleotides are activated by union with ATP. This reaction is called phosphorylation and is

catalyzed by an enzyme phosphorylase. It produces deoxyribonucleoside triphosphates, namely, ATP, GTP, CTP, and TTP.

Exposure of Parent DNA Bases

The replication begins from a fixed origin of replication but then proceeds bidirectionally (with moving forks at both ends of the replication piece). The DNA strands start to separate at this specific point. Viral and prokaryotic DNA generally forms a single point of replication. Eukaryotic chromosomal DNA begins the process at many origins of replication. Unzipping of the double stranded DNA forms a Y – shaped structure called replication fork.



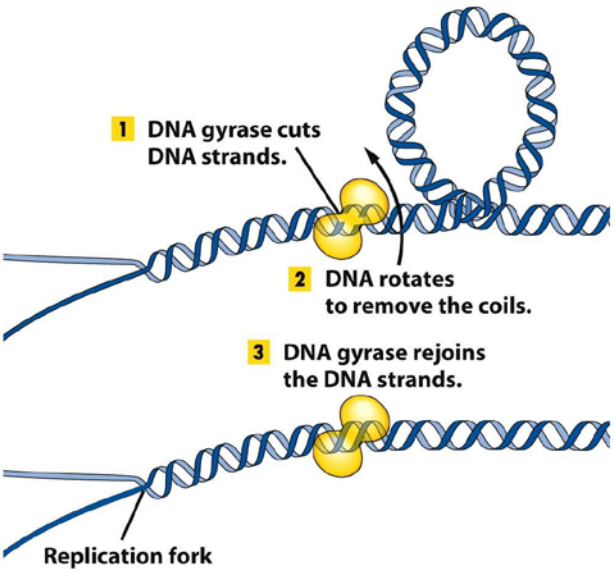
New DNA strands grow from and towards the fork. The DNA molecule is intricately coiled in its chromosome and its unwinding is not an easy job. The initiation of replication is began forming of supercoils in DNA molecule. The enzymes called topoisomerases help to convert rings (supercoils) of DNA from one topological form to another.

One topoisomerase, DNA gyrase (topoisomerases II) can induce twisting and coiling of the DNA, called supercoiling.

The supercoiled form may facilitate unwinding of the helix due to energy (ATP) of supercoiling.

Enzymes helicases help in unwinding the helix. Other enzymes named topoisomerases I may cut and rejoin one strand of DNA to facilitate uncoiling.

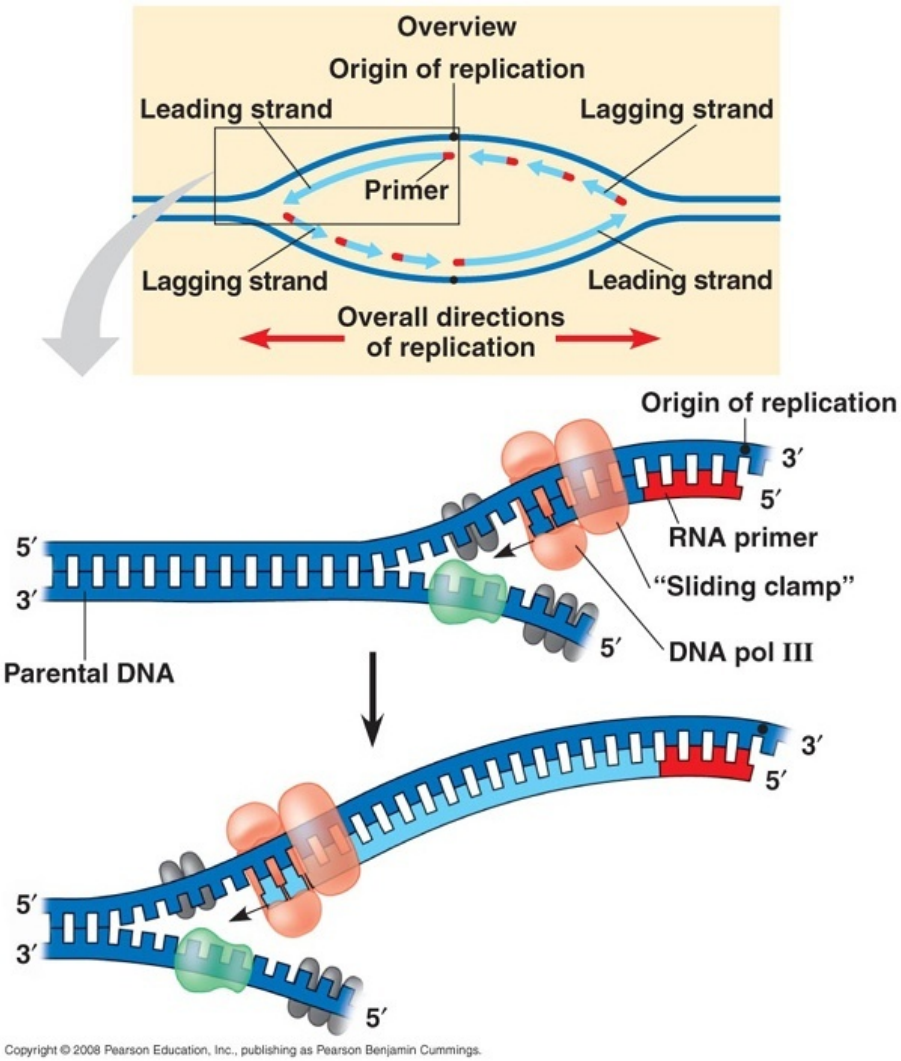
The free single-stranded region would be subject to degradation, but it is protected by another protein termed the single-stranded DNA-binding (SSB) protein.



Formation of RNA primer

DNA polymerases cannot initiate DNA synthesis - they can only add on to an existing strand of DNA or RNA. The existing strand is said to "prime" DNA synthesis. During DNA

replication, RNA primers (a short chain of RNA) are produced by RNA primase in order to provide a starting point for DNA polymerases to extend from. The primers are later removed and the gaps so left are filled with deoxyribonucleotides to make the DNA strand continuous.



Base Pairing

The deoxyribonucleoside triphosphates get joined by hydrogen bonds to the appropriate nitrogen bases pairing rule of Watson and Crick , A-T; T-A; C-G; G-C.

Conversion to Deoxyribonucleoside Monophosphates

The deoxyribonucleoside triphosphates joined to each single DNA chain break off their inner high energy bonds and set free pyrophosphate (P~P) molecules. This changes them to deoxyribonucleoside monophosphates that are the normal components of DNA. Pyrophosphate

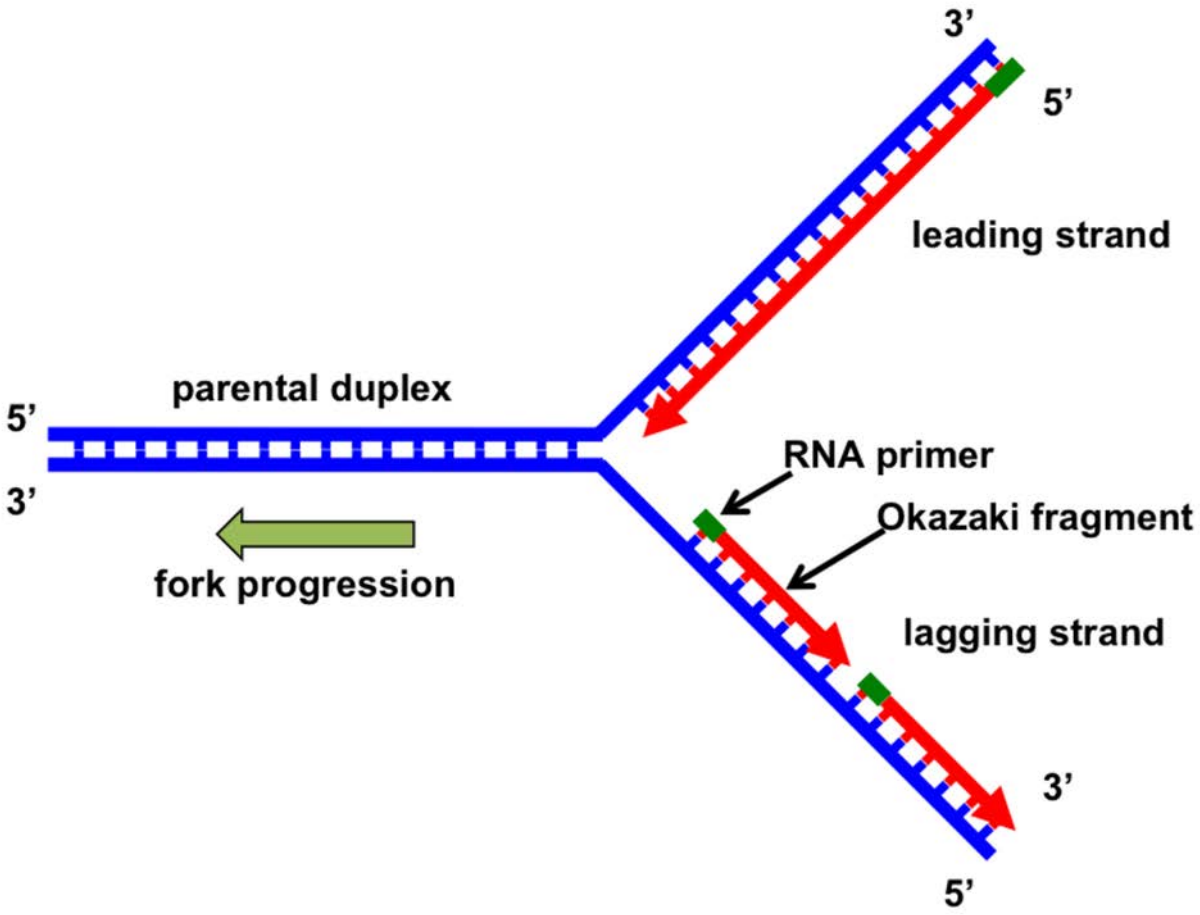
undergoes hydrolysis by an enzyme pyrophosphatase and release energy and set free inorganic phosphate groups.

Formation of New DNA Chains

With the energy so released, the adjacent deoxyribonucleoside monophosphates joined to each single DNA chain become linked together, forming a new DNA chain. The process is catalyzed by an enzyme DNA polymerase and aided by metal ions Mn^{2+} or Mg^{2+}.

There are three DNA polymerases (DNA-polymerase I, II, III). The enzyme first studied by Kornberg, now termed DNA polymerase I, is not the principal DNA replication enzyme, so here as enzyme termed DNA polymerase III probably is. All of the known DNA polymerases synthesize new chains only in the 5'- to 3'- direction, that is, from carbon 5'- end to carbon 3'- end of the sugar molecules in the DNA strands. Because the two DNA strands are anti parallel, the new strands must be formed on the old (parent) strands in opposite directions. One new strand is formed in a continuous stretch in the 5' – 3'- direction. This strand is called leading strand. On the other parent strand, short DNA segments are formed in the 5'- 3' – direction, starting from RNA primers. These DNA segments are known as Okazaki fragments (Japan scientist was the first, who saw these fragments).

They are later joined together, forming a continuous lagging strand. The Okazaki fragments are linked up by the enzyme DNA ligase (DNA synthetase) with polymerase I after replacing the RNA primers with deoxyribonucleotides. The Okazaki fragments have 100-200 b.p. in eukaryotes and 10-60 b.p. in prokaryotes. The process in which the Okazaki fragments are linked up is called maturation.



Editing (Proofreading) and DNA repairs.

The specificity of base pairing ensures accurate replication. However, sometimes wrong bases do get in. These are removed by DNA polymerase, which can go back for this purpose. The abnormal regions of DNA resulting from mutation are cleaved by enzymes termed nucleases. The DNA polymerase I resynthesizes the missing segments of DNA strand, using the intact DNA strand as the template. The DNA ligase joins the new and old segments of the strand under repair. This makes the damaged DNA strand normal.

Helix Formation

Each daughter double DNA molecule becomes spirally coiled to from a double helix.

2.3. GENETIC MATERIAL IN EUKARYOTIC CELLS

The DNA molecules in the mammalian chromosomes are exceedingly long, containing more than 10^8 bases with a linear length of almost 1 mm. The main genetic material of eukaryotic cell is found into eukaryotic nucleus, where the DNA is packed in several chromosomes and not in a single chromosome as in prokaryotes. This is a chromosomal heredity. Also, there is cytoplasmic genetic material. It is a DNA of mitochondria and plastids (in plant cells). This is a cytoplasmic (non-chromosomal) heredity.

The number of chromosomes varies in different species. All individuals of a species, however, have the same number of chromosomes in all body cells. The somatic or body cells have a double set of chromosomes, i.e. they have both the chromosomes of each homologous pair. This chromosome number is termed the diploid number or full number. It is indicated by the symbol 2n. There are the same genes in the same loci of homologous chromosomes. These genes are called allelic genes. That means that each gene in diploid organism consist of 2 alleles.

A gamete, sperm or egg, has a single set of chromosomes, i.e., it has one chromosome of each homologous pair. This chromosome number is called the haploid number or reduced number (1n). It is denoted by the results from the union of sperm and ovum in sexual reproduction. That means that each gamete carries only one allele for each gene.

Chapter 3. The Mendelian lows

3.1. MONOHYBRID CROSS. Mendelian Crosses

In the 1860's, an Austrian monk named Gregor Mendel introduced a new theory of inheritance based on his experimental work with pea plants.

Mendel's seminal work was accomplished using the garden pea, Pisum sativum, to study inheritance. This species naturally self-fertilizes, such that pollen encounters ova within individual flowers. The flower petals remain sealed tightly until after pollination, preventing pollination from other plants. The result is highly inbred, or "**true-breeding**," pea plants. These are plants that always produce offspring that look like the parent. By experimenting with true-breeding pea plants, Mendel avoided the appearance of unexpected traits in offspring that might occur if the plants were not true breeding. The garden pea also grows to maturity within one season, meaning that several generations could be evaluated over a relatively short time. Finally, large quantities of garden peas could be cultivated simultaneously, allowing Mendel to conclude that his results did not come about simply by chance.

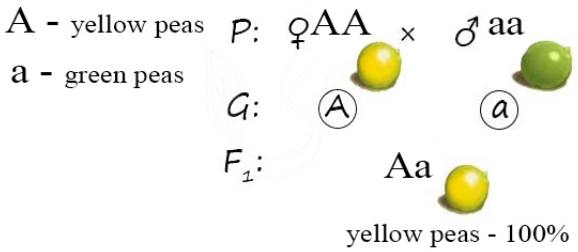
Mendel performed **hybridizations**, which involve mating two true-breeding individuals that have different traits. In the pea, which is naturally self-pollinating, this is done by manually transferring pollen from the anther of a mature pea plant of one variety to the stigma of a separate mature pea plant of the second variety. In plants, pollen carries the male gametes (sperm) to the stigma, a sticky organ that traps pollen and allows the sperm to move down the pistil to the female gametes (ova) below. To prevent the pea plant that was receiving pollen from self-fertilizing and confounding his results, Mendel painstakingly removed all of the anthers from the plant's flowers before they had a chance to mature.

Plants used in first-generation crosses were called **P**, or ***parental generation***. Mendel collected the seeds belonging to the P plants that resulted from each cross and grew them the following season. These offspring were called the **F1**, or the ***first filial*** (filial = offspring, daughter or son), generation. Once Mendel examined the characteristics in the F1 generation of plants, he allowed them to self-fertilize naturally. He then collected and grew the seeds from the F1 plants to produce the **F2**, or ***second filial***, generation. Mendel's experiments extended beyond the F2 generation to the F3 and F4 generations, and so on, but it was the ratio of characteristics in the P0−F1−F2 generations that were the most intriguing and became the basis for Mendel's laws.

3.1.1. Mendel's law of dominance

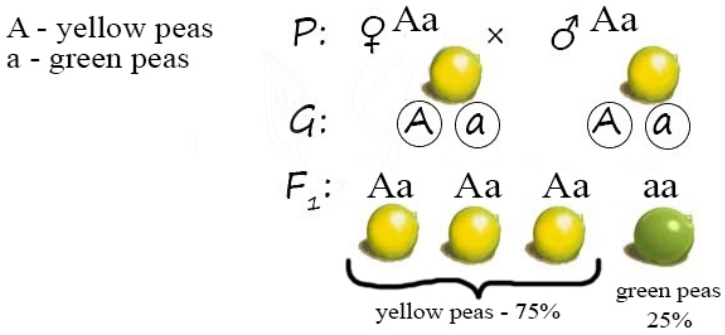
Mendel's law of dominance states that *in a cross of parents that are pure for contrasting traits, only one form of the trait will appear in the next generation. All offspring will have only the dominant trait in the phenotype, and recessive alleles will always be masked by dominant alleles.*

For example, he crossed plants with yellow and grean peas. All offspring had yellow peas. After a series of crosses he made a conclusion that was named principle (or law) of dominance.



3.1.2. Law of Segregation

Then Mendel crossed hybrids of F1. He got 2 phenotypes of an offspring: 3 parts with yellow peas and 1 part with green peas.



So he formulated **the Law of Segregation**:

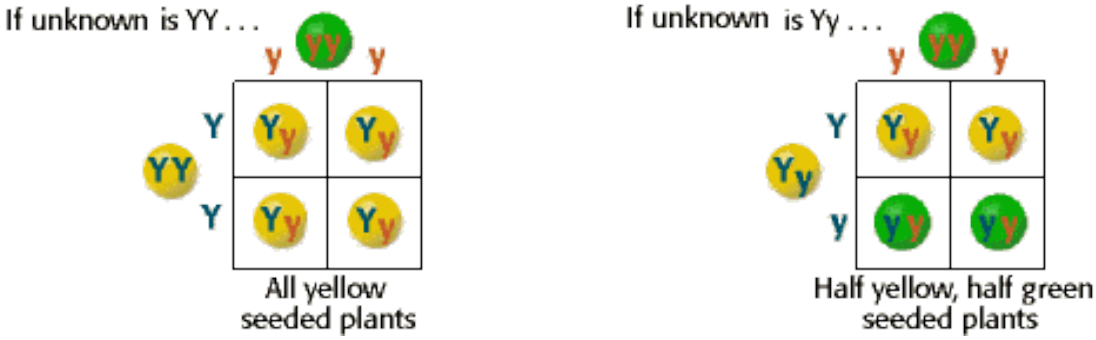
every individual diploid organism contains two alleles for each trait, and that these alleles segregate (or separate) during meiosis such that each gamete contains only one of the alleles.

If heterozygous individuals are crossed and analyzed by one pair of alternative characters, then segregations of characters ratios 3:1 for phenotype and 1:2:1 for genotype are observed. Phenotypic ratio: 3 groups of individuals having the dominant character and 1 group with the recessive character. Genotypic ratio: 1 group of individuals includes dominant homozygotes (AA), 2 groups are homozygotes (Aa), 1 group is composed of recessive homozygotes (aa)

3.1.3. Test cross (or analyzing cross).

Test cross is crossing of an individual having a dominant character and unknown genotype, with a recessive homozygote for determining its genotype.

If uniformity of hybrids is observed as the result of analyzing cross then the initial organism is homozygous; if segregation of characters occurs with 1:1 ratio, then the initial organism is heterozygous.



3.1.4. Backcrossing

Backcrossing is a crossing of a hybrid with one of its parents or an individual genetically similar to its parent, in order to achieve offspring with a genetic identity which is closer to that of the parent. It is used in horticulture, animal breeding.

Backcrossed hybrids are sometimes described with acronym "BC", for example, an F1 hybrid crossed with one of its parents (or a genetically similar individual) can be termed a BC1 hybrid,

and a further cross of the BC1 hybrid to the same parent (or a genetically similar individual) produces a BC2 hybrid.

Questions for self-control

1. Genetics as a science, studing of heredity and variability.

2. The subject-matter of genetics.

3. Give the definition to the following genetic terms: gene, alleles, genotype, phenotype, homozygousity, heterozygousity, hemizygousity, dominance and recessiveness.

4. Give the definition to "inheritance" and differentiate it to the "heredity".

5. Hybridological method and its features.

6. Mendel and his experiments with pea plants. Mendel's conclusions:

a) Principle of Dominance

b) Law of Segregation (law of purity of gametes)

8. Test cross for determine the zygosity of individual

Genetic problems

Problem 1. In human being the gene of brown colour of eyes dominates over gene of blue colour of eyes. Determine the phenotypes of children in the family, in which the father has blue colour of eyes and the mother has brown color of eyes (her father was blue-eyed and mother - brown-eyed).

Problem 2. In human being right hand-writing dominates over left hand-writing. In the family the both parents have right hand-writing and are heterozygotes for the gene of hand-writing. Determine the children phenotypes in this family.

Problem 3. Polydactyly is inherited as an autosome dominant character. Determine the probability of the birth of a child with extra fingers in the family, in which the mother has normal structure of hand and the father is heterozygous for the gene of polydactyly.

Problem 4. Phenylketonuria (PKU) is inherited as an autosome recessive disease. In the family, in which both parents were healthy there were born dizygotic twins - the girl with PKU and healthy boy. Determine the parental genotypes and the probability of the birth of the next healthy child in this family.

Problem 5. In human, the albinism is inherited as an autosome recessive character. In the family, in which both parents were healthy there was born albino son. Determine the probability of birth of the next child without anomaly.

Problem 6. The cataract in human is an autosome dominant disease. Woman, whose mother had cataract, got married to healthy man. Determine the probability of the birth of healthy children in this family, if it was known, that woman received anomaly from her mother.

Problem 7. The positive Rh-factor is an autosome dominant character. The woman with Rh-positive factor got married to the man with negative Rh-factor. There were born the boy with Rh-negative factor and the girl with Rh-positive factor. Determine the parental genotypes and the probability of the birth of the next children with Rh-positive factor.

Problem 8. Some forms of deafness and dumbness are inherited as autosome recessive characters. In the family, where both parents had good ear there was born the deaf-and-dumb child. Determine the parental genotypes and the probability of the birth of a child with good ear in this family.

Problem 9. Albinism is recessive to normal body pigmentation in man. It is an autosomal trait. If a homozygous normal man marries an albino girl, what would be the phenotypic and genotypic ratios in offspring of their daughter, if she'll marry man with same genotype?

Problem 10. Albinism, the total lack of pigment is due to a recessive gene. A man and woman plan to marry and wish to know the probability of their having an albino child. What advice would you give to them if…

(a) Both are normally pigmented, but each has one albino parent.

(b) The man is an albino, and woman is heterozygous.

(c) The man is an albino and woman's family includes no albino for at least three generations.

Problem 11. A brown eyed man marries a blue eyed woman and they have eight children, all brown eyed. What are the genotypes of all the individuals in the family?

Problem 12. A blue eyed man, whose both parents were brown eyed, marries a brown-eyed woman. They had one child, who is blue eyed. What are the genotypes of all the individuals in problem mentioned above?

Problem 13. A woman has a rare abnormality of the eyelids called ptosis, which makes it impossible for her to open her eyes completely. The condition has been found to depend on a single dominant gene. The woman's father had ptosis, but her mother had normal eyelids. Her father's mother had normal eyelids. What are the probable genotypes of the woman, her father and mother? What proportion of her children will be expected to have ptosis if she marries a man with normal eyelids?

Problem 14. A woman is Rh positive and both of her parents are Rh positive. She marries an Rh negative man. Is there any chance that they may have any Rh negative children? Explain.

Problem 15. A woman bears a child with erythroblastosis at her second delivery. She has never had a blood transfusion. On the basis of this data, classify the woman, her husband and both children as to Rh type.

Chapter 4. Sex-determination systems

A sex-determination system is a biological system that determines the development of sexual characteristics in an organism. Most organisms that create their offspring using sexual reproduction have two sexes: males and females.

There are two major types of sex-determining mechanisms:

- **genetic sex determination**, where sex is determined during fertilization and genetic differences are expected between the sexes;
- **epigenetic (or environmental) sex determination**, where there are no genetic differences between sexes and sex is determined after fertilization in response to an environmental signal. For example, in some species of reptiles, including alligators, some turtles, sex is determined by the temperature at which the egg is incubated during a temperature-sensitive period. Other examples: clown fish (the dominant individual in a group becomes female while the other ones are male), marine worm Bonellia viridis (larvae become males if they make physical contact with a female, and females if they end up on the bare sea floor) and so on.

In many species, sex determination is genetic. Males and females have different sex chromosomes that specify their sexual morphology.

Chromosomal sex determination systems:

The XX/XY sex-determination system is typical for humans and most other mammals, as well as some insects (for example, Drosophila fly). In this case, females have XX chromosomes and would be referred to as the homogametic sex, and males have XY and would be referred to as the heterogametic sex

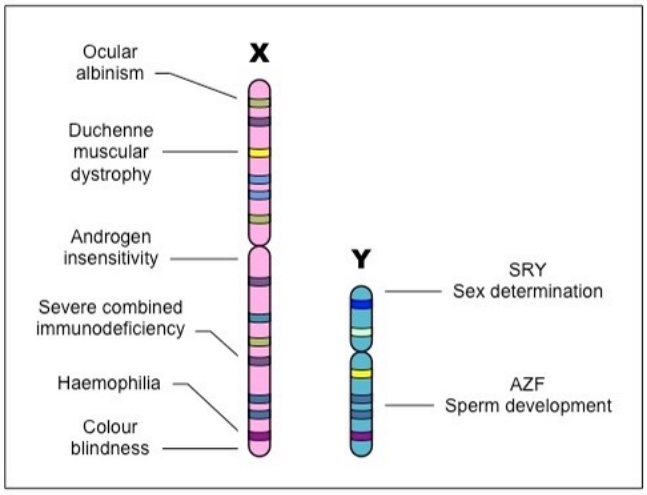
The ZW/ZZ sex-determination system is typical for birds. In this case, females have ZW chromosomes and would be referred to as the heterogametic sex, and males have ZZ and would be referred to as the homogametic sex

The XX/X0 system. In this case females have two copies of the sex chromosome (XX) but males have only one (X0). This system is observed in a number of insects.

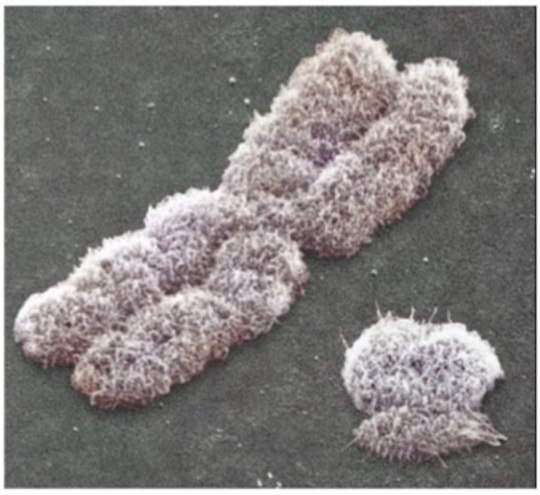
Haplodiploidy is found in insects, such as ants and bees. Unfertilized eggs develop into haploid individuals, which are the males. Diploid individuals are generally female.

4.1. Features of sex-linked inheritance

Sex linkage refers to when a gene controlling a characteristic is located on a sex chromosome (X or Y). The Y chromosome is much shorter than the X chromosome and contains only a few genes (50 million bp; 78 genes). The X chromosome is longer and contains many genes not present on the Y chromosomes (153 million bp ; ~ 2,000 genes).

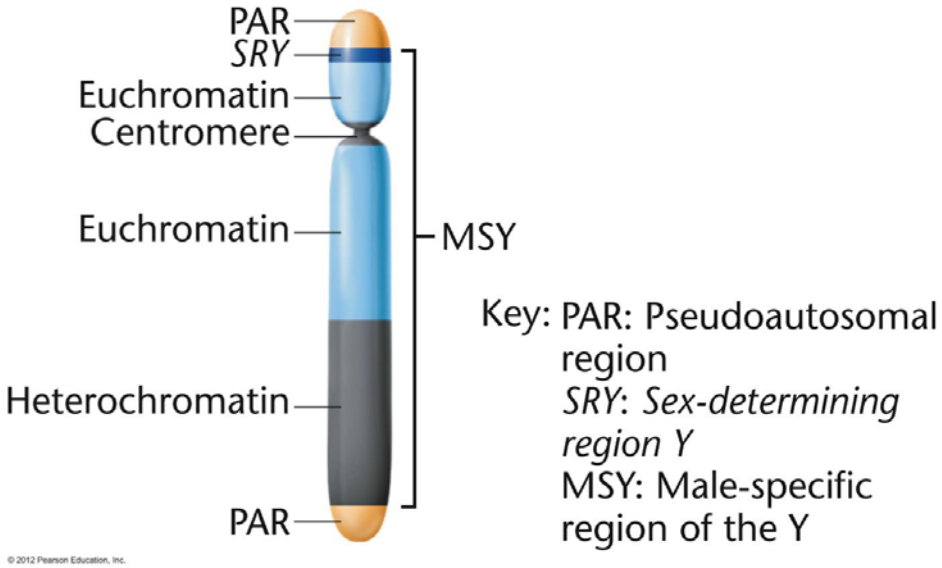


Genetic Comparison of X and Y Chromosomes



Micrograph of X and Y Chromosomes

Hence, sex-linked conditions are usually X-linked - as very few genes exist on the shorter Y chromosome.



Sex-linked inheritance patterns differ from autosomal patterns due to the fact that the chromosomes aren't paired in males (XY). This leads to the expression of sex-linked traits being predominantly associated with a particularly gender.

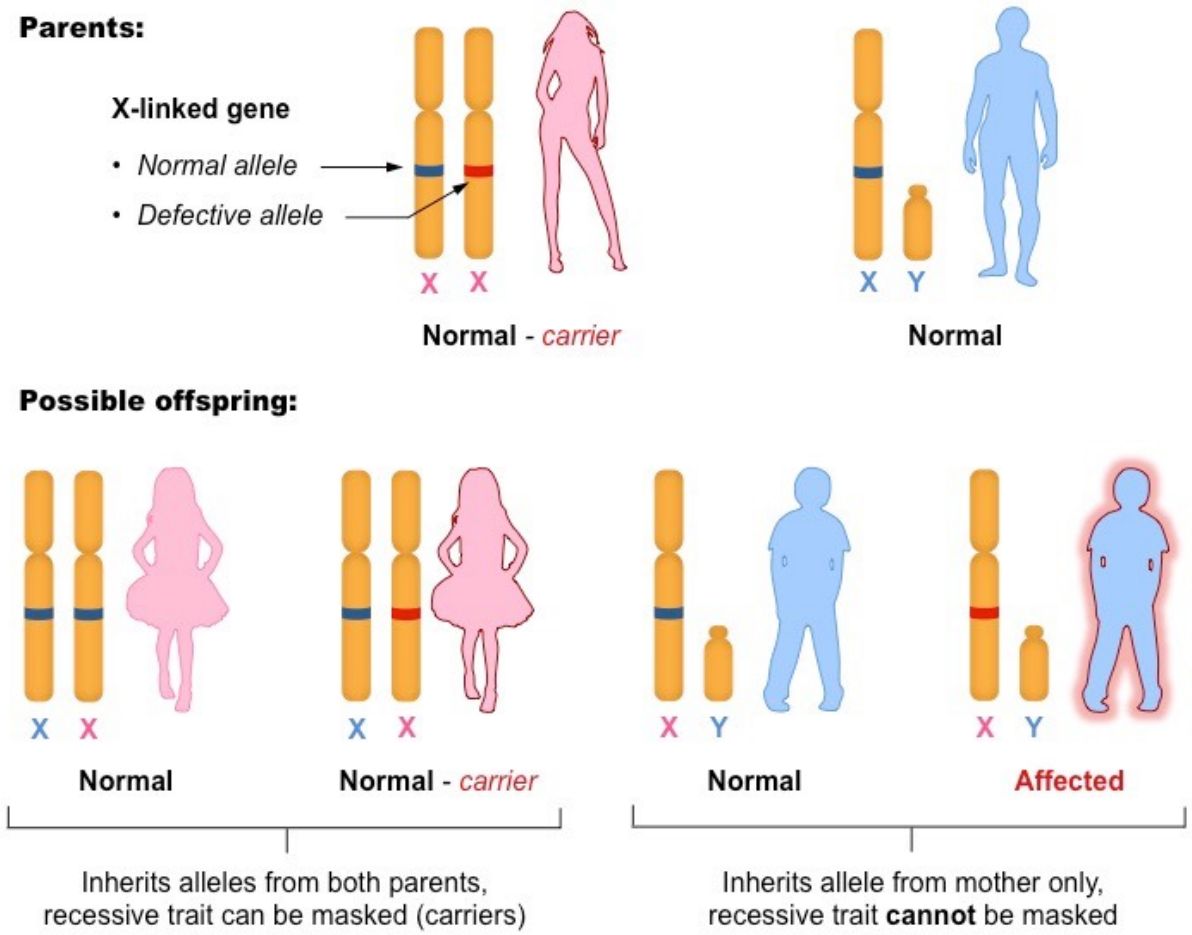
As human females have two X chromosomes (and therefore two alleles), they can be either homozygous (X^AX^A or X^aX^a) or heterozygous (X^AX^a).

Hence, X-linked dominant traits are more common in females (as either allele may be dominant and cause disease)

Human males have only one X chromosome (and therefore only one allele) and are hemizygous for X-linked traits (X^AY or X^aY). X-linked recessive traits are more common in males, as the condition cannot be masked by a second allele

The following trends always hold true for X-linked conditions:

- Only females can be carriers (a heterozygote for a recessive disease condition), males cannot be heterozygous carriers
- Males will always inherit an X-linked trait from their mother (they inherit a Y chromosome from their father)
- Females cannot inherit an X-linked recessive condition from an unaffected father (must receive his dominant allele)



Some of the more familiar sex-linked traits are:

- *hemophilia*
- *color blindness*
- *congenital night blindness*
- *some high blood pressure genes*
- *Duchenne muscular dystrophy*
- *Fragile X syndrome.*

Genes located in the non-homologous region of the Y-chromosome determine **holandric** characters; 6 of them are described (ichthyosis, membranes between toes, hypertrichosis pinnae auris (hairy ears) and etc.) they are inherited from males and are revealed only in men.

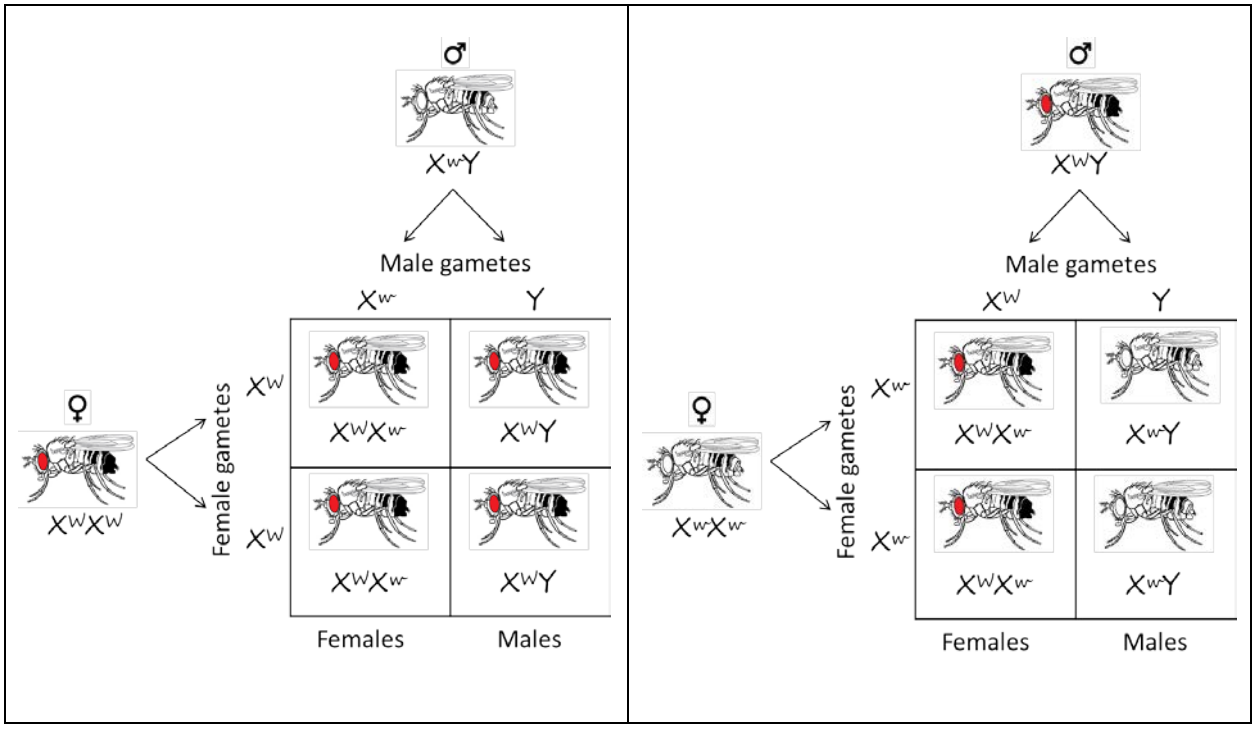
4.2. Reciprocal cross

Reciprocal cross is a cross, with the phenotype of each sex reversed as compared with the original cross, to test the role of parental sex on inheritance pattern.

Example:

In Drosophila, normal flies have red eyes. Red eye color is dominant. Morgan discovered a recessive mutation (allele) that caused white eyes. When Morgan mated a red eyed female to a white eyed male, all the progeny had red eyes. This result makes perfect sense with a dominant/recessive inheritance pattern.

But Morgan got a surprising result when he made the reciprocal cross, mating white eyed females to red eyed males. Instead of all red eyed progeny, he saw that all the females had red eyes and all the males had white eyes. This result seemed to violate Mendel's principle. The only way to explain these results was if the gene that caused eye color was located on (linked to) the X chromosome. Here is the Punnett square demonstrating this cross:



THE QUESTIONS FOR SELF-CONTROL.

1. *The chromosome determination of sex. Autosomes and sex chromosomes. Role of X and Y chromosomes in sex determination.*
2. *Homogametic and heterogametic sex.*
3. *Genetic determination of sex in the different biological species.*
4. *Chromosome and gene basis of sex determination in human.*
5. *Discovery of sex chromatin. Barr body.*
6. *Sex-linked inheritance. Examples in human being.*
7. *Holandric signs in man and peculiarities of their genetic determination.*
8. *Testcross, backcross and reciprocal cross.*

GENETIC PROBLEMS.

Problem 1. Hypoplasia of enamel is inherited as X-linked dominant character. In the family, in which both parents had disease there was born son with healthy teeth. What are the possible phenotypes of their second son?

Problem 2. Classical hemophilia is inherited as recessive X-linked disease. Man with hemophilia marries heterozygous healthy woman. In this family were born healthy children. What is the probability of the birth of the sick children in this family?

Problem 3. The gene of daltonism (color blindness) is located in X chromosome and is inherited as a recessive character. Woman with normal sight, whose father had daltonism, got married to healthy man, whose father had daltonism. Determine the phenotypes of children in this family.

Problem 4. A colour blind man marries a woman with normal vision. Her mother was colour blind. What kind of children would you expect from this marriage?

Problem 5. A woman with normal vision marries a man with normal vision and they have a colour blind son. Her husband dies and she marries a colour blind man. Show the type of children that might be expected from the second marriage and the proportions of each.

Problem 6. A man has hypertrichosis of the ears, a condition which is due to a gene on the non–homologous portion of the Y chromosome (hollandria). He marries a normal woman. Show the types of children they may expect.

Problem 7. Suppose a young lady comes to you for advice in your capacity as a marriage counselor. She tells you her brother has hemophilia, but both of her parents are normal. She wishes to marry a man who has no history of hemophilia in his family. She would like to know the probability of having hemophilic offspring. Explain.

Problem 8. Anhydrotic ectodermic dysplasia is inherited as a recessive X-linked disease. Healthy woman gets married to the sick man. In this family there were born sick daughter and healthy son. Determine the probability of the birth of the next child without disease.

Problem 9. When a baemophilic male is mated with a heterozygous baemophilic female, what baemophilic proportion will be resulted in each sex?

Problem 10. When a haemophilic male is mated with a homozygous non-baemophilic female—What will be the result?

Problem 11. Of what type will be the children with reference to colour blindness, when a woman is colour-blind and her husband is normal?

Problem 12. When both the parents are colour-blind, can they produce a normal daughter?

Problem 13. In a cross between a white-eyed female fruit fly and red-eyed male, what percent of the female offspring will have white eyes? (White eyes are X-linked, recessive)

Chapter 5. DIHYBRID CROSS.

5.1. INDEPENDENT INHERITANCE

Law of Independent Assortment (Mendel's law)

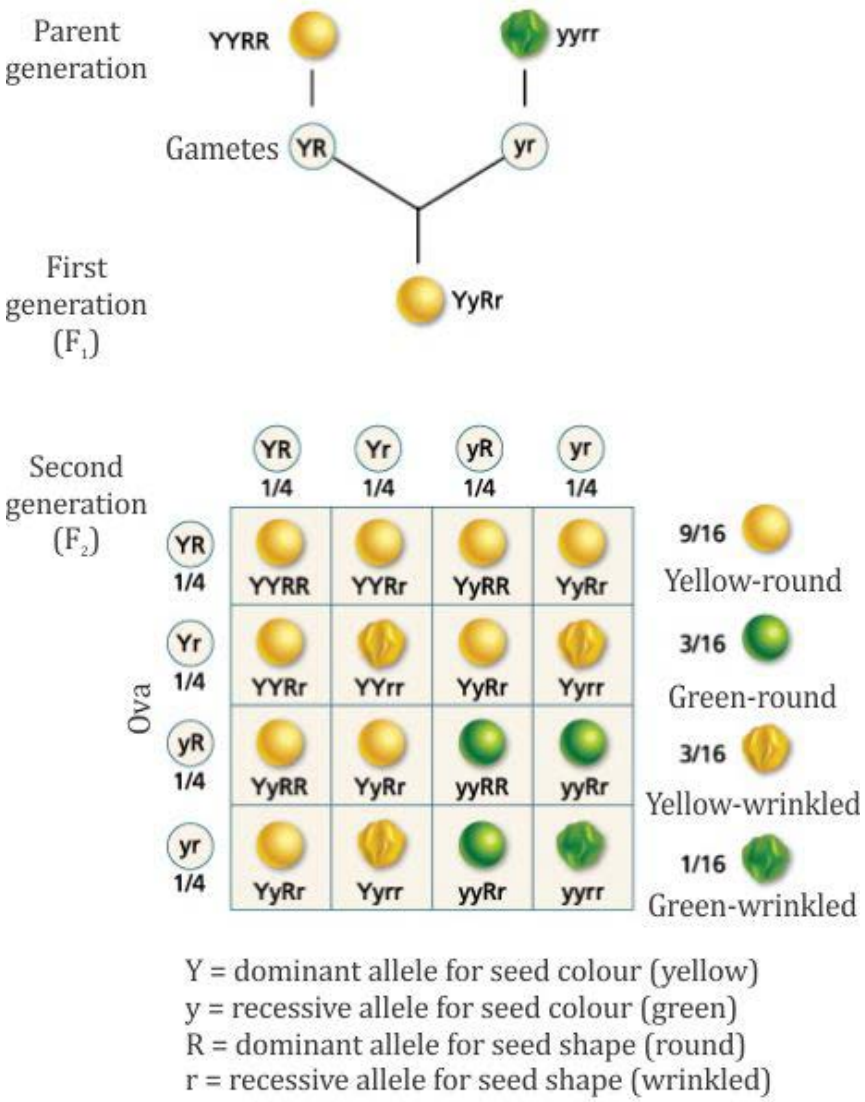
> *The Law of Independent Assortment states that alleles for separate traits are passed independently of one another. That is, the biological selection of an allele for one trait has nothing to do with the selection of an allele for any other trait.*
>
> *Mendel found support for this law in his dihybrid cross experiments. In his monohybrid crosses, an idealized 3:1 ratio between dominant and recessive phenotypes resulted. In dihybrid crosses, however, he found a 9:3:3:1 ratios. This shows that each of the two alleles is inherited independently from the other, with a 3:1 phenotypic ratio for each.*

Independent assortment occurs in eukaryotic organisms during meiotic metaphase I, and produces a gamete with a mixture of the organism's chromosomes. The physical basis of the independent assortment of chromosomes is the random orientation of each bivalent chromosome along the metaphase plate with respect to the other bivalent chromosomes.

The number of gametes formed by definite organism is decided by the number of heterozygous alleles present in its genotype.

Number of gametes = 2^n

where n=number of heterozygous alleles present in the genotype.



Conditions limiting the manifestation of Mendel's laws:

1. Different survival of individuals with different phenotypes (the presence of lethal and semi-lethal genes). Lethal genes cause organism's death at the moment of birth or before. Semi-lethal genes reduce life span of the organism.
2. Genetic linkage.
3. Cytoplasmic heredity
4. Gene interactions of (except complete dominance).
5. Penetrance of genes
6. Pleiotropy of the gene

Pleiotropy of the gene — one gene is responsible for development of several characters. An example is the syndrome of «blue sclera»: a gene causes a blue color of the sclera, breakable bones and congenital deafness.

Penetrance — frequency of gene manifestation: a ratio (per cents) of the number of individuals having the character to the number of individuals having the gene.

Expressiveness (Expressivity) — the degree of phenotypic manifestation of the gene. It depends on environmental factors and effect of other genes.

THE QUESTIONS FOR SELF-CONTROL.

1. Combinative variability. The main mechanisms of combinative variability.

2. Principle of independent assortment. Punnett square.

3. Give the characters to dihybrid crosses.

4. Characterize the conditions of Mendelian inheritance.

5. Statistics of di- and Polyhybrid crosses.

GENETIC PROBLEMS.

Problem 1. Polydactyly and myopia are inherited as autosome dominant characters. Determine the possible genotypes and phenotypes of the children in the family, in which the mother is healthy and the father has both anomalies and is diheterozygote.

Problem 2. Brown colour of eyes dominates over blue colour of eyes. Blue-eyed woman got married to the brown-eyed man. Their first child has blue colour of eyes and phenylketonuria. Phenylketonuria is autosome recessive disease. Determine the parental genotypes and the probability of the birth of healthy child in this family.

Problem 3 Polydactyly (extra fingers) is inherited as an autosome dominant character, fructosuria - as a recessive character. In the family, in which the man had polydactyly and the woman was healthy, there was born a child with normal structure of hand and fructosuria. Determine the parental genotypes and the probability of the birth of a healthy child in this family.

Problem 4. In man brown eyes (B) are dominant to blue (b) and dark hair (R) are dominant to red hair (r). A man with brown eyes and red hair marries a woman with blue eye and dark hair. They have two children, of whom one has brown eyes and red hair. Give the genotypes of the parents and children.

Problem 5. In Drosophila, vestigial wings and ebony colour are due to two separate recessive genes. The dominant alleles are normal (long) wings and normal (gray) body colour.

1) What type of offspring would you expect from a cross between a bomozygous vestigial ebony female and a normal double homozygous (long–winged, gray–bodied) male?

2) If the F1 are allowed to breed among themselves what types of offspring would you expect in the F2? Show complete genotype and phenotype of both generations.

3) If you made a test cross of the F1 males of the preceding problem what results would you expect to obtain?

Problem 6. About 75% of Americans get a bitter taste from a chemical called phenyl thiocarbamide (PTC); the others do not. A normally pigmented woman who is non–taster has a father who is an albino–taster. She marries an albino man who is a taster, but who has a mother who is non–taster. Show the types of children which this couple may have.

Problem 7. In tomatoes, yellow fruit and dwarfed vine are due to recessive alleles of genes which produce the more common red fruit and tall vine. If pollen from the pure–line dwarf plant bearing red fruit is placed on the pistil of a pure–line tall plant bearing yellow fruit, what type of plant and fruit would be expected in the F1 ? If these are crossed among themselves, what results would be expected in the F2 ?

Problem 8 Some dogs bark while trailing, others are silent. The barking trait is due to a dominant gene. Erect ears are dominant to drooping ears. What kind of pups would be expected from a double heterozygous erect–eared, barker mated to a drooped–eared, silent trailer?

Problem 9. In pigeons, the checkered pattern is dependent on a dominant gene A and plain on the recessive allele a. Red colour is controlled by a dominant gene B and brown by the recessive allele b. Diagram completely a cross between homozygous checkered, red and plain, brown birds. Summarize the expected F2 results.

Problem 10. A checkered–brown female mated with a plain–red male produced 2 checkered–red, 2 plain–red, and 1 checkered–brown offspring. Give the probable genotypes of the parents.

5.2. LINKED INHERITANCE. CHROMOSOME THEORY OF INHERITANCE

Experiments of Thomas Morgan. Complete and partial genetic linkage.

In Experiments on Drosophila were performed in Morgan's laboratories in 1911–1912. That fly is convenient for genetic investigations because of:

– it has few chromosomes (4 pairs);

– early sex maturation, fast alternation of generations;

– a great number of offspring

- it is easy to make similar conditions for Drosophila flies.

Two pairs of alternative characters were analyzed on crossing Drosophila.

B — grey body

b — black body

V — normal wings

v — vestigial wings

The 1st cross of flies was done according to Mendel's scheme:

P: ♀ BBVV x ♂ bbvv

G: BV bv

F1 BbVv —

grey with normal wings

100 %

To clear out the genotype of hybrids an analyzing cross of a male of the 1st generation was performed. It is crossing of an individual that have dominant characters with a recessive homozygote.

According to 3rd Mendel's law, Morgan expected to get equal number of hybrids for each phenotype — per 25 %. But he got just two phenotypes (per 50 %) with characters of parents. Morgan proposed that genes of the body color and wings length was located in one chromosome and was inherited together, i. e. linked. Genetic linkage is a joint transmission of genes located in one chromosome pair.

A male Drosophila has a **complete genetic linkage**. One chromosome of a pair contains 2 dominant genes (BV), and the other — 2 recessive (bv). During the meiosis one chromosome (with genes BV) gets into one gamete and the other (with genes bv) in the other gamete. Thus, there form not 4 but 2 types of gametes in a diheterozygous organism. Hybrids also have same characters as their parents.

P: ♀ bbvv x ♂ BbVv

G: bv BV bv

F1 BbVv bbvv

grey with normal wings *black body vestigial wings*

50 % *50%*

In the 3rd experiment T. Morgan crossed a hybrid female Drosophila with a recessive male. He got 4 types of hybrids: 2 types (83 %) with parental characters and 2 types (17 %) with a new combination of characters. Per 8.5 % of individuals were formed in the process of crossing over and they are called **crossover individuals**. So female Drosophila has an **incomplete genetic linkage** The total number of crossover individuals is 17 %, that corresponds to the distance between genes of the body color and wing length — 17 centimorgans.

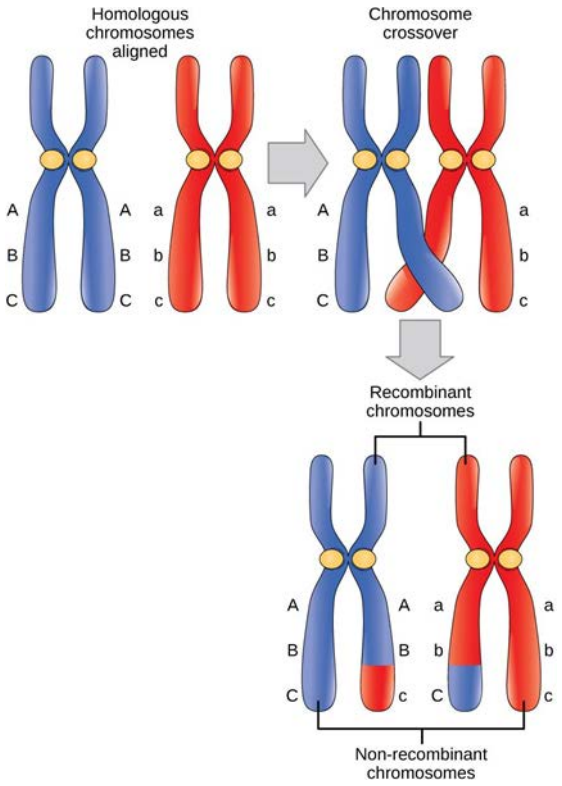
P: ♀ BbVv x ♂ bbvv

G:	BV	bv	Bv	bV	bv
F1	BbVv	bbvv	Bbvv	bbVv	
	41,5%	41,5%	8,5%	8,5%	

Centimorgan (cM) is the typical unit of genetic linkage. A distance of 1 cM between two genes is equal to a 1% chance that a gene at one genetic locus will be separated from a gene at another locus due to crossing over in a single generation.

Crossing-over, crossover and non-crossover gametes.

Linkage Genetic linkage is broken by a biological phenomenon — crossing over, which occurs in the prophase of meiosis I. Crossing over is formation of a cross and following exchange of identical chromatid regions of homologous chromosomes in a bivalent. It does not occur in a male Drosophila and a female silkworm. Crossover gametes are gametes containing chromatids that have undergone crossing over. Non-crossover gametes have not changed chromatids.



<u>The number of crossover individuals is usually less than the number of noncrossover ones because crossing-over occurs not always</u>.

The linkage force between genes (frequency of crossing-over) depends on the distance between

them: ***the more the distance, the less the linkage forces and the more frequently crossing-over.***

Chromosome theory of inheritance

Boveri and Sutton's chromosome theory of inheritance states that genes are found at specific locations on chromosomes, and that the behavior of chromosomes during meiosis can explain Mendel's laws of inheritance.

Thomas Hunt Morgan, who studied fruit flies, provided the first strong confirmation of the chromosome theory.

Main statements:

1. Genes are arranged in chromosomes in a linear order in definite loci.
1. Allelic genes are in identical loci of homologous chromosomes.
2. All genes of one chromosome compose a linkage group and are inherited together. The number of linkage groups is equal to the number of pairs of homologous chromosomes.
3. Crossing-over (exchange of allelic genes) is possible between homologous chromosomes.
4. The percentage of crossing-over depends on the distance between genes in the chromosome. 1% of crossing-over is equal to 1 centimorgan — a unit of the distance between genes called to honor T. Morgan.

QUESTIONS FOR SELF-CONTROL.

1. *How are the genes localized in the chromosomes?*
2. *Phenomenon of gene linkage. Complete and incomplete linkage.*
3. *Characterize the main types of correlative inheritance (independent, complete linked, incomplete linked).*
4. *Crossing over, its biological role in genetic variation.*

5. *Centimorgan. Its definition.*
6. *The main states of chromosome theory and show its biological essence.*
7. *What is cytoplasmic heredity?*

GENETIC PROBLEMS.

Problem 1. Cataract and polydactily in human are autosome dominant characters. The genes are in the same chromosome and show the complete linkage (there is no cross-over). Woman received the cataract from her mother and polydactily – from her father. Her husband is healthy for both diseases. Determine the probability of the birth of healthy children in this family.

Problem 2. The genes determining Rh-factor and erythrocytes shape are in the same chromosome and the distance between them is 3 morganids. Woman received both dominant genes: Rh+ and oblong erythrocyte shape from her father and both recessive genes (Rh- and normal erythrocyte) - from her mother. Her husband had Rh- gene and the gene of normal shape of erythrocytes. Determine the probability of the birth of a child with oblong shape of erythrocyte and Rh- negative factor.

Problem 3. You cross a true-breeding yellow-bodied, smooth-winged female fly with a true-breeding red-bodied, crinkle-winged male. The red body phenotype is dominant to the yellow body phenotype and smooth wings are dominant to crinkled wings. You perform a dihybrid test cross between the F1 flies with a true-breeding yellow-bodied, crinkle-winged fly. The following F2 results are detected: red body and smooth wings - 102; yellow body and smooth wings - 404; red body and crinkled wings - 396; yellow body and crinkled wings - 98. Determine the recombination frequency (%) between the body color and wing surface genes.

Problem 4. One of autosome gene controls wing length in flies. This gene has two alleles, "L or l" where long wings are dominant to short wings. The other autosome gene controls body colour. Red body phenotype is dominant to the yellow body phenotype. Red-bodied, short wing male with yellow-bodied, long wing female. All F1 are red-bodied, long wing. After test cross between the F1 flies above with yellow-bodied, short-winged flies, you get the following F2 results: red body

and long wings – 45; red body and short wings – 460; yellow body and long wings - 440; yellow body and short wings – 55. What is the recombination frequency (%) between the genes for body color and wing length?

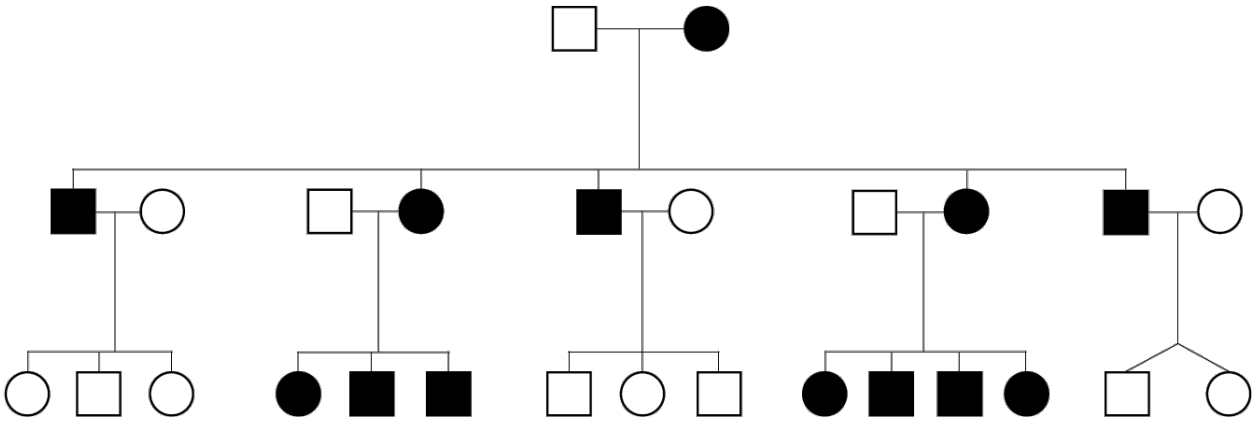
Problem 5. Myasthenia and Protanopia are inherited as recessive X-linked diseases. The distance between genes is the 10 centimorgans. Healthy woman (her father had myasthenia and her mother had protanopia) gets married to the healthy man. What are the phenotypes of their children?

Chapter 6. Cytoplasmic inheritance (or extranuclear inheritance, somal inheritance and maternal inheritance)

Cytoplasmic inheritance is the transmission of genes that occur outside the nucleus. It is found in most eukaryotes and is commonly known to occur in cytoplasmic organelles such as mitochondria and chloroplasts or from cellular parasites like viruses or bacteria.

Extra nuclear inheritance has several distinct features:

- It is more or less maternal inheritance i.e., only female contribute towards inheritance and therefore.
- If the mother is affected, all offspring will be affected. If the father is affected, he does not pass it on to his offspring.
- The result of reciprocal crosses are not the same. In these features, extra-nuclear inheritance contrasts sharply from nuclear inheritance.



Examples of cytoplasmic inheritance in human include LHON (Lebers Hereditary Optic Neuropathy). The condition involves a gradual to rapid loss of central vision, often starting around age 30 but patients from 1 to 70 have been reported. The condition has been traced to defects in ATP synthesis Complex I in mitochondria.

Another example of human "cytoplasmic inheritance" is MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) which most often is caused by an A to G transition in a mitochondrial leu-tRNA.

Chapter 7. GENOTYPE AS INTEGRATIVE GENETIC SYSTEM

Gene interactions

Mendelian genetics does not explain all kinds of inheritance, because his laws are correct only for complete dominance interaction (for example, allele A, which is responsible for yellow seed, suppresses of the allele a, and Aa has yellow phenotype).

But genes can interact in several different ways and lead to markedly different phenotypic effects in different gene combinations.

Main types of gene interactions:

- **Allelic gene interactions** - Interactions between the alleles of one gene.
- **Non-allelic interactions** – in this case the development of single character is due to two or more genes affecting the expression of each other in various ways.

7.1. Allelic gene interactions

1. **Complete dominance** – the dominant allele completely suppresses the recessive allele expression. In this case, the Mendelian ratios apply. Examples: color of peas, brown and blue eyes or straight and curly hair in humans and other characters. They are called mendelizing — segregation obeys Mendel's laws

2. Incomplete (partial) dominance – in this situation the phenotype of a heterozygote is intermediate between the two homozygotes. *For example, A is responsible for red color of strawberry fruit, a – white color, but Aa will be rose (monohybrid cross show ratio 1:2:1 in F2 both for genotype and phenotype).* At the molecular level, incomplete dominance is generally caused by a quantitative effect of the number of "doses" of allele; two doses produces most

functional transcript and therefore most functional protein product; one dose produces less transcript and product, whereas zero dose has no functional transcript or product.

3. Overdominance (or Super-dominance) can be described as heterozygote advantage, wherein heterozygous individuals have a higher fitness than homozygous individuals. It may occurs due to lethal alleles, which cause death in homozygous condition.

For example, normal wild-type mice have coats with a rather dark overall pigmentation. Mutant allele A is pleiotropic (it is responsible for 2 traits - coat color and survival). But the allele A for yellow color is dominant to the wild-type allele a. But A acts as a recessive lethal allele. Thus, a mouse with the homozygous genotype AA dies before birth and is not observed among the progeny. Heterozygous organisms are survive. A cross between two heterozygotes show a 2:1 ratio.

4. Codominance - Heterozygotes for codominant alleles fully express both alleles. Phenotypes of both the parents appear in F1 hybrid rather than the intermediate phenotype. An example is in human ABO blood types, the heterozygote I^AI^B manufactures antigenes to both A and B types.

5. Multiple alleles – is a case of occurance of more than 2 alleles in single locus. It is a result of multiple mutations of one gene. But only two of them present in a diploid organism. Thus the realization of trait is due to present of particular alleles in genotype of organism.

For example, in rabbits allele C determines black fur. c^{ch} - chinchilla, c^h – Himalayan, c – albino.

Human ABO blood group system is also the example of multiple alleles.

Inheritance of blood groups.

Inheritance of blood groups in the human on the AB0 system occurs due to the gene I. Alleles of gene I are: I^0, I^A, and I^B.

Presence of the gene I^0 does not cause synthesis of anti-genes in erythrocytes (group I).

Genes I^A and I^B are dominant to gene I^0.

Being in the genotype in homozygous (I^AI^A) or heterozygous (I^AI^0) states allele I^A causes synthesis of anti-gene A in erythrocytes: A(II) — blood group.

Allele I^B is responsible for synthesis of anti-gene B (B(III) - blood group) being in homozygous (I^BI^B) or heterozygous (I^BI^0) states also.

If they both are in the genotype, then 2 types of anti-genes are synthesized in erythrocytes: A and B — blood group IV(AB).

7.2. Non-allelic interactions

Some of the heritable characters in plants and animals depend upon the combined effect of two or more pairs of different non-allelic genes.

There are several main types of non-allelic interaction.

7.2.1. Complementary inheritance. In this case two or more genes (mainly dominant alleles) when present together produce effects qualitatively distinct from the separate effect of any one of them.

For example, A determines normal formation of cochlea, a – abnormality of cochlea. B – normal formation of auditory nerve, b – abnormality of nerve.

In sweet peas the flower color is of two types – purple and white. The development of the purple color is dependent on the presence of two independent dominant genes C and P. Gene C controls the synthesis of colorless pigment, and gene P determines the enzyme synthesis. This enzyme catalyzes the formation of colorless pigment to anthocyanin, which is responsible for purple color of flower (**9:7**).

P White flowers CCpp × White flowers ccPP

Gametes Cp cP

Purple flowers CcPp

Gametes : CP.Cp, cP, cp Gametes

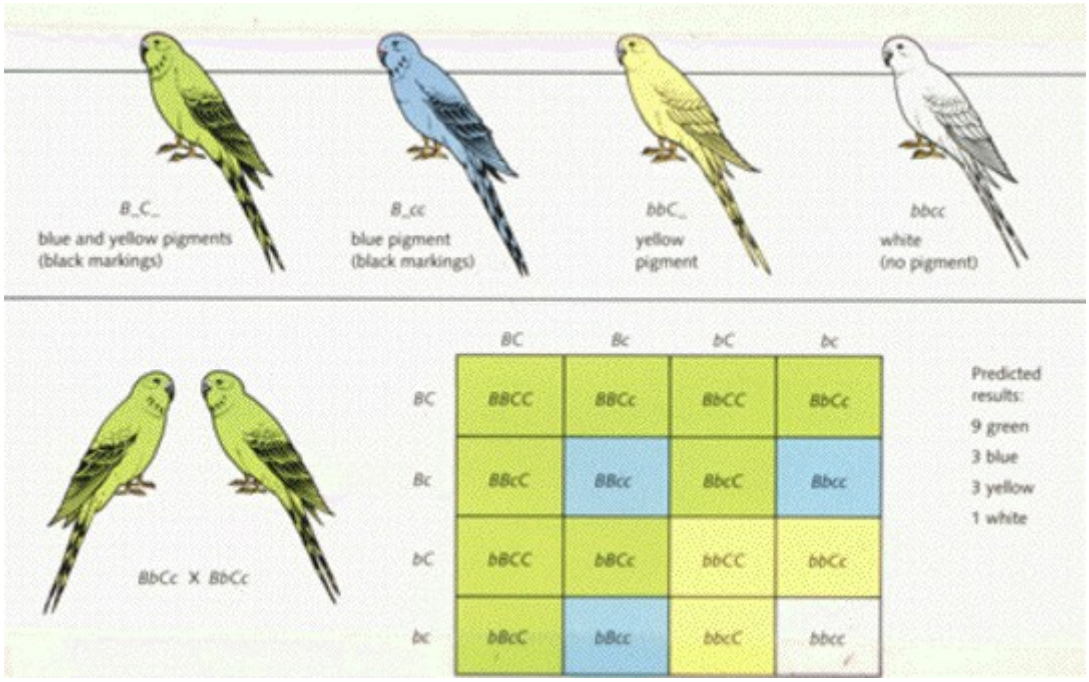
♀ \ ♂	CP	Cp	cP	cp
CP	CCPP Purple	CCPp Purple	CcPP Purple	CcPp Purple
Cp	CCPp Purple	CCpp White	CcPp Purple	Ccpp White
cP	CcPP Purple	CcPp Purple	ccPP White	ccPp White
cp	CcPp Purple	Ccpp Whie	ccPp White	ccpp White

Gametes

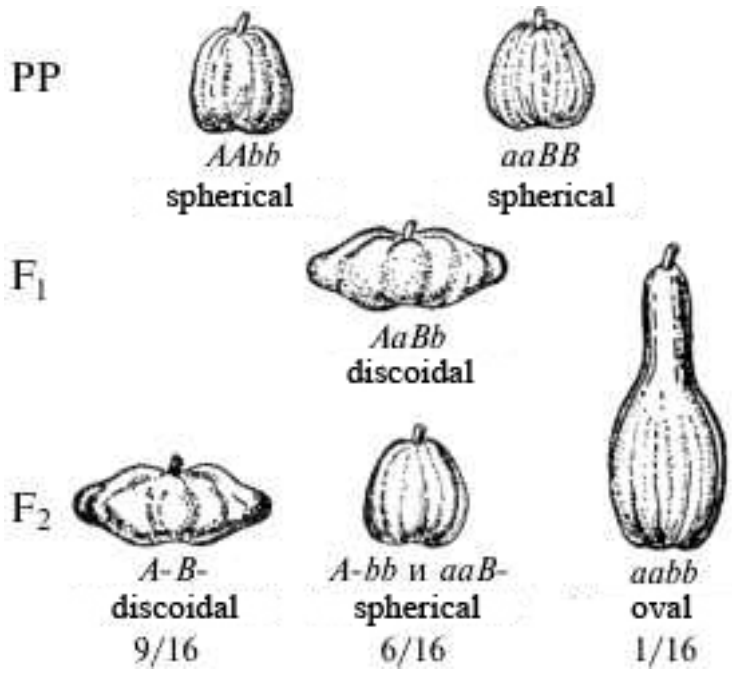
Phenotypic ratio : 9 Purple : 7 White

(Representing a Cross between two varieties of sweet pea)

9:3:3:1 - blur, yellow, green and white color of budgerigar



9 : 6 : 1 – discoidal, spherical and oval form of squash



7.2.2. Epistasis is the phenomenon where the effect of one gene (hypostatic) is dependent on the presence of another gene (epistatic). Epistatic gene suppresses the expression of hypostatic gene

There are 2 types of epistasis:

Dominant epistasis happens when the dominant allele of one gene masks the expression of all alleles of another gene. (12: 3: 1)

In s squash Yellow (AA, Aa) is dominant over green (aa). Gene B shows epistasis, and colorless.

13:3 – A – coloured leg horn, a – non coloured leg horn, B – epistatic

13/16 = White
3/16 = coloured
White leg horn × White plymouth Rock
AABB ↓ aabb
AaBb × AaBb
White White
AB = 9 white
Ab = 3 coloured
aB = 3 white
ab = 1 white
13 : 3
White : Coloured

	AB	Ab	aB	ab
AB	AABB White	AABb White	AaBB White	AaBb White
Ab	AABb White	AAbb* Coloured	AaBb White	Aabb* Coloured
aB	AaBB White	AaBb White	aaBB White	aaBb White
ab	AaBb White	Aabb* Coloured	aaBb White	aabb White

Recessive epistasis - Recessive alleles at one gene mask the phenotypic expression of other gene. The phenotypic ratio is 9: 3: 4.

In onion A – red color of bulb, a – yellow color. Allele b shows epistasis on both A and a alleles.

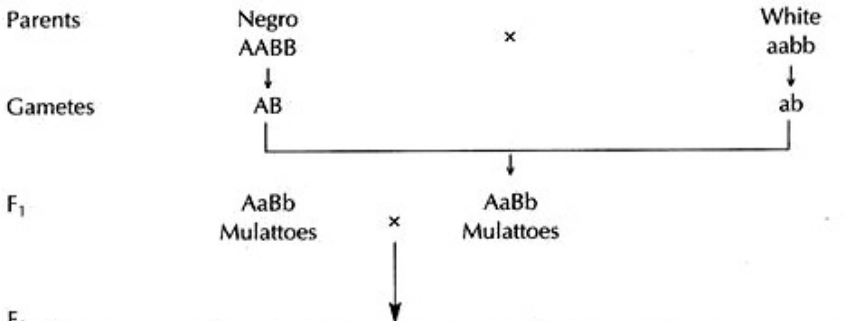
7.2.3. Polygenic Inheritance (Polymeric gene action)

The term polygenic inheritance is applied when two or more independent pairs of genes affect the same character in the same way and in additive fashion. In such cases, the net effect on the trait depends upon the combined action of several genes, each of which has a small effect on the same trait.

Human polygenic traits include

- Height
- Weight Eye Color

- Intelligence
- Skin Color
- Many forms of behavior



No. of dominant gene	4	3	2	1	0
Phenotype	Negro	Intermediate between Mulattoes and Negro	Mulattoes	Intermediate between Mulattoes and White	White
Ratio	1	4	6	4	1

Fig. 7.18: Inheritance of skin colour in human

7.3. Interaction of Heredity and Environment

All traits depend both on genetic and environmental factors. Heredity and environment interact to produce their effects. This means that the way genes act depends on the environment in which they act. In the same way, the effects of environment depend on the genes with which they work.

For example, people vary in height. Although height is highly heritable, environmental variables can have a large impact. For example, Japanese-Americans are on the average taller and heavier than their second cousins who grew up in Japan, reflecting the effect of environmental variables, especially dietary differences.

Phenylketonuria (PKU) is an excellent example of environmental modification of a genetically controlled effect. PKU is a form of mental retardation that results from toxic (~damaging) effects

of abnormal breakdown of the essential amino acid, phenylalanine, which is found in all protein. The enzyme that breaks down phenylalanine is defective, so it accumulates and breaks down abnormally. So in PKU, a single gene can dramatically affect behavior: it is clearly a genetically influenced process.

But the effect of that defective gene expression depends on the environment in which it occurs. When this abnormal metabolism of phenylalanine was discovered, an effective treatment became available: a diet low in phenylalanine. The abnormal gene is still there, but because little phenylalanine is present in the diet, little toxic effects result. This defective gene was no longer expressed in mental retardation, because the environment was different: phenylalanine was greatly reduced in the food the child with the defective gene ate.

The treatment for PKU illustrates the principle that the way a gene is expressed depends on the environment in which it is expressed. This principle is called interaction of heredity and environment.

QUESTIONS FOR SELF-CONTROL.

1. The definition of the terms of "allelic" and "non-allelic" genes.

2. Biological essence of complete dominance; the examples.

3. The interaction of allelic genes in the incomplete dominance; the examples.

4. The peculiarities of phenotype formation in codominance; the examples.

5. The inheritance of blood groups of ABO system in human.

6. Epistatic and hypostatic genes, their role in the phenotype formation; the examples of epistatic interaction of genes.

7. Biological essence of the complementary interaction of genes and its influence to phenotype formation; the examples.

8. Pleiotropy and its role in phenotype formation; the examples.

9. Polymeric gene action as the base of genetic determination of quantitative signs. Additive effect of polymeric genes.

10. The role of heredity and environmental factors in the formation of phenotype.

11. The examples of phenotype expression depending on environment.

GENETIC PROBLEMS.

Problem 1. Acatalasia is inherited as autosome incomplete recessive character. The heterozygotes have the reduced activity of catalyze. In the family, both parents and their son have the reduced activity of enzyme. Determine the probability of the birth of next child without anomaly. Determine the probable children phenotypes in the family, in which one parent has disease and the other has the reduced activity of catalyze.

Problem 2. In shorthorn cattle, the gene R for red coat colour is not dominant over white r. The heterozygous combination Rr produces roan. A breeder has white, red and roan cows and bulls. What phenotypes might be expected from the following matings and in what proportions:

1. red x red
2. red x roan
3. red x white
4. roan x roan
5. roan x white
6. white x white

Problem 3. In snapdragons, flower colour shows intermediate inheritance rather than dominance. Homozygous plants, RR, are red, heterozygous Rr are pink, and homozygous rr are white. Diagram a cross between a red–flowered and a white–flowered plant and summarize the F results under the headings of phenotypes, genotypes, genotypic frequency, and phenotypic ratio.

Problem 4. Sickle cell anemia (S-anemia) is inherited as autosome incomplete dominant character. Homozygotes die before puberty, the heterozygotes have subclinic anemia. The plasmodium can not use the S-hemoglobin and human with S-anemia has no malaria. What is the probability of the birth of children stable to malaria, in family in which one parent is heterozygous for S-anemia and the other is healthy? What is the probability of the birth of children not stable to malaria, in family, in which both parents are stable to malaria?

Problem 5. The human blood groups of ABO system are determined by three allelic genes: I^A, I^B, i^0 . The combination of alleles i^0 i^0 determine the I(O) blood group, I^A I^A or I^A i^0 - II (A); I^B I^B or I^B i^0 - III (B); I^A I^B - IV (AB). In the family, in which mother has II blood group and heterozygote, father - IV blood group. Determine the blood groups of their children.

Problem 6. In the family, in which brown-eyed parents, one of them had I blood group and another one - III blood group there was born blue-eyed child with first blood group. Determine the parental genotypes.

Problem 7. Can a child having blood type A be born to parents having types AB and B respectively? Explain.

Problem 8. A man has blood type A and his wife has type B. A physician types the blood of their four children and is amazed to find one of each of the four blood types among them. He is not familiar with genetics and calls upon you for an explanation. Provide one.

Problem 9. In the family, in which the wife had the II blood group and her husband had the III blood group, there was born the son with colour blindness and the I blood group. Both parents differed colours in norm. Determine the probability of the birth of the healthy son and his possible variants of blood groups. It is known that colour blindness is X-linked recessive disorder.

Problem 10. The pea plant flowers may have white and red colour. This sign is controlled by two pairs of alleles. The red colour of flowers is a result of complementary interaction of genes. In the cross of two pure lines with white colour of flowers, all F_1 progeny have red colour of flowers. There is cross of F_1 hybrid and homozygous recessive for both genes pea plant. Determine the F_2 genotypes and ratio.

Problem 11. Bombay phenomenon: in the family, in which the father had I blood group and mother – II blood group there was born the daughter with I blood group. She got married to the man with II blood group. They had two daughters with the following blood groups – IV and I, correspondently. The appearance of the girl with the IV blood group is impossible, according the principles of inheritance of blood groups. Geneticists proved that there is recessive epistatic gene, which may inhibit the appearance of genes, determining the blood groups. Determine the probable genotypes of all generations in Bombay phenomenon.

Chapter 8. Variability

Variability is the ability of organisms to acquire new features and properties during the life.

Types of variation

- Phenotypic (non-hereditary, definite, group) – Modification variation
- Genotypic (hereditary, individual, indefinite)
    - Combinative
    - Mutative

8.1. Phenotypic variation.

A phenotypic or modification variation is modification of the phenotype without changing the structure of the genotype. That is why it is non-hereditary.

Modifications occur under the action of environmental factors, changes can be predicted for a whole group of individuals. As a rule, modifications have an adaptive character (enhancing of skin pigmentation (suntan) under ultra-violet rays).

Properties of modifications:

- Not inherited, because genotype is intact
- Have a group character
- Predictable
- Not matter for natural selection
- Reversible
- Adaptive for the organism

Reaction norm determines the limits of modification variation. It is controlled by the genotype and is inherited. If the character has a narrow reaction norm, it changes insignificantly (fat content of milk). The character with a wide reaction norm changes in wide limits (body mass).

The main factors capable of providing variation of signs within the reaction norm are:

1) polygenic determination of the trait and reaction of the organism;

2) pleiotropy of the gene action;

3) dependence of mutation manifestation on environmental conditions;

4) heterozygosity of the organism;

5) interaction of genes at the level of gene products (subunits of protein molecules);

6) alternative ways of development in the body system and the implementation of biosynthesis in the cell (blocking of one pathway is compensated by another).

The reaction norm controlled by the genotype is the result of an evolutionary process. For example, the limits of changes in blood pressure in humans are determined by the genome of the species and the genotypes of definite people. However, the average values of blood pressure vary depending on the geographical location of places of residence, ethnic group, as well as with age.

The basis for the existence of modifications is that the phenotype is the result of the interaction of the genotype and environmental conditions. Therefore, changes in environment can cause changes in the phenotype, not accompanied by changes in the genotype. The mechanism of occurrence of modifications lies in the fact that environmental conditions affect the enzymatic reactions (metabolic processes) occurring in a developing organism, and to a certain extent change their course, and, consequently, the result - the state of the trait formed on their basis.

8.2. Genotypic variation and its types.

Genotypic variation is modification of the phenotype due to changing the genotype. It is inherited. It includes a combinative and mutational variation.

8.2.1. Combinative variation

Combinative variation (or Genetic recombination) is associated with recombination of parental genes in filial generations without changing the structure of genetic material. The exchange of genetic material between different organisms leads to production of offspring with combinations of traits that differ from those found in either parent. Most recombination is naturally occurring.

For example, appearance of a blue-eyed child in heterozygous brown-eyed parents.

Mechanisms of combinative variation:

1. Free random combination of chromosomes and chromatids during meiosis.
2. Crossing-over in meiosis (recombination of genes).
3. Random combination of different types of gametes during fertilization.

8.2.2. Mutational variation

Mutational variation (mutations) is a sudden uneven changing of genetic material under the influence of environmental factors. It is inherited.

Properties of mutations:

- Inherited, because genotype is changed
- Individual
- Appear suddenly, unevenly
- Constant
- Mostly harmful for the organism. Only sometime mutations may be useful. Useful mutations are matter for natural selection

Classification of mutations.

Mutations can be classified in two major ways:

- **Hereditary mutations** are inherited from a parent and are present throughout a person's life in virtually every cell in the body. These mutations are also called germline mutations because they are present in the parent's egg or sperm cells, which are also called germ cells. When an egg and a sperm cell unite, the resulting fertilized egg cell receives DNA from both parents. If this DNA has a mutation, the child that grows from the fertilized egg will have the mutation in each of his or her cells.
- **Acquired (or somatic) mutations** occur at some time during a person's life and are present only in certain cells, not in every cell in the body. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if an error is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed to the next generation.

According to the origin the mutations can be classified in two ways:

- spontaneous mutations;
- induced mutations.

Based on their phenotype:

a) **Recessive mutations** requiring two copies of the mutated allele to manifest the phenotype

b) **Dominant**, i.e. one or two copies of the mutated allele produces the phenotype

c) **Semidominant**, i.e. one mutant allele produces an intermediate phenotype

Based on the effect of mutation on the gene structure:

- small-scale mutations (gene mutation, point mutation);
  - Insertions
  - Deletions
  - Substitution
    - transitions
    - transversions

- large scale mutations (chromosome mutation)
    - Chromosome Structure Changes
        - Deletion
        - Duplication
        - Inversion
        - Translocation
    - Chromosomal Number Mutations
        - Haploidy
        - Polyploidy
        - (Aneuploidy)
            - Monosomy
            - Trisomy

QUESTIONS FOR SELF-CONTROL.

1. *Give the definition to the "variability".*
2. *Name the main types of variability and show their biological essence.*
3. *Non-hereditary(phenotype) variability.*
4. *What is the base of combinative variability? Give the examples.*
5. *The role of combinative variability in the formation of variety of living matter.*
6. *Mutagenesis and its types. Factors of mutagenesis and their characteristics.*
7. *Mutations as the main material for evolution.*
8. *The levels of origin of mutations and their characteristics.*
9. *Biological role of generative and somatic mutations.*

Chapter 9. Human Being as an Object of Genetic Analysis.

9.1. Deficiencies and Advantages of Human Genetics.

The recognition of the role of genetic factors in the causation of human disease has made clinical genetics one of the most rapidly developing fields in medicine. Important genetic contributions to the etiology of major diseases such as coronary artery disease, diabetes mellitus , hypertension, and the major psychoses have been identified. At the same time, there has been a veritable explosion of knowledge in basic genetics. Much of this progress has been propelled by recent advances in the area of molecular genetics, which un turn have been applied directly to a better understanding of the pathogenesis of disease and to improved diagnosis and management of patients. Appropriately, a major contribution of these new developments in genetics has been in the area of prevention and/or avoidance of disease, the aspect of medicine that must be-come the focus of modern medicine. Genetic screening programs to detect individuals at risk, genetic counseling, and prenatal diagnosis are some of these current applications of new genetic knowledge to medical practice.

The main deficiencies of human genetics study are following:

1) the great number of groups of linkage (karyotype);
2) impossibility of crossing;
3) slow change of generations;
4) slight number of progeny (offsprings) in every family.

The advantages of human genetics are:

- high level of studying of human biology, biochemistry, physiology etc.;
- the large size of population in the earth (more than 5 milliards) in all the territorial zones with the varieties of gene pool (normal and unnormal signs).

9.2. Methods of Human Genetics.

- Genealogical Method
- Cytogenetic Method

- Biochemical Method
- Twins Method
- Populational Method

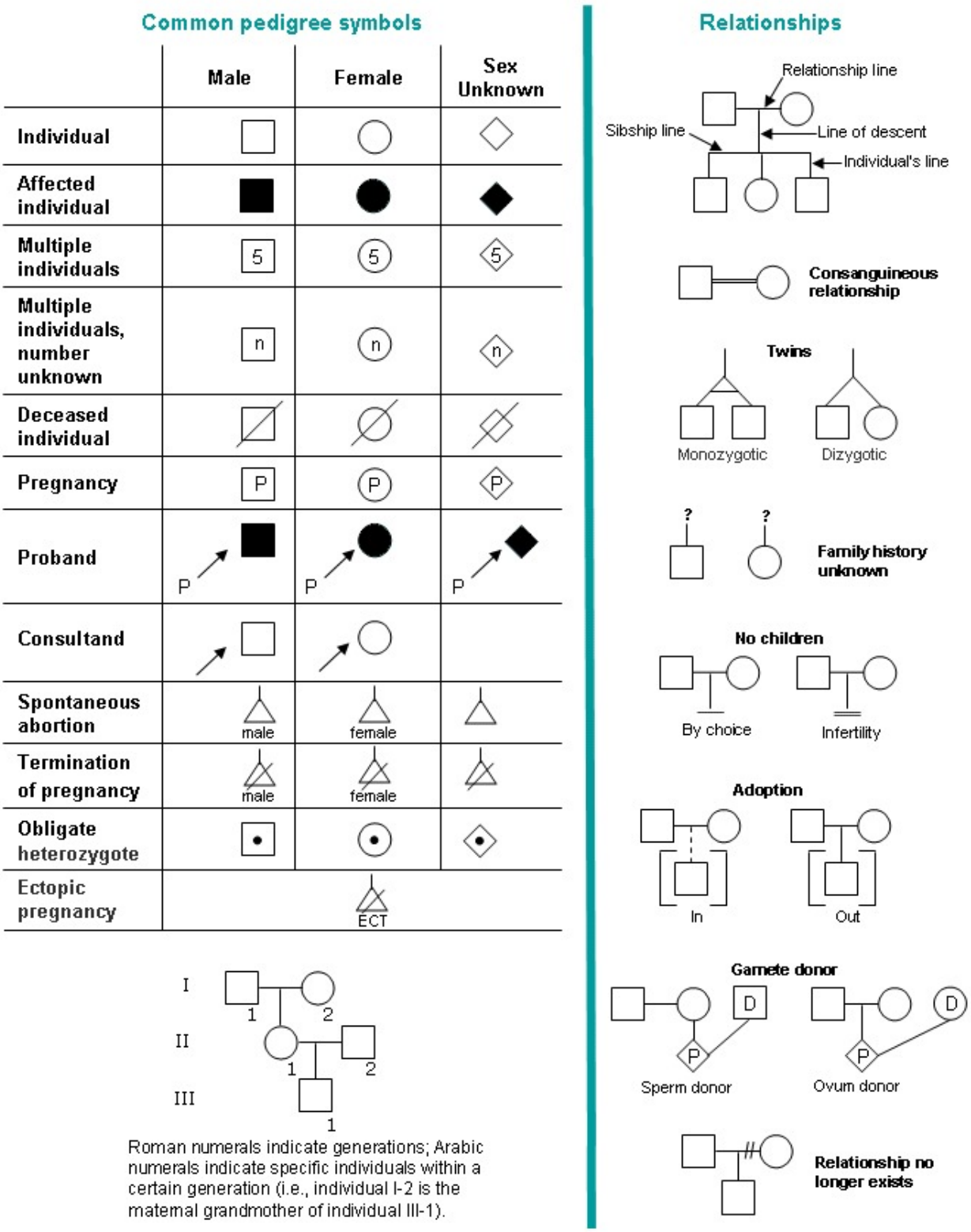
9.2.1. THE GENEALOGICAL METHOD. HUMAN PEDIGREE ANALYSIS

Modes of Inheritance

There are 5 main modes of inheritance:

1. Autosomal Dominant Inheritance
2. Autosomal Recessive Inheritance
3. X-Linked Dominant Inheritance
4. X-Linked Recessive Inheritance
5. Y-linked inheritance (or holandric inheritance).

Genealogical method is used for studying of inheritance of a trait by examining the segregation of alleles in several generations of related individuals. This is typically done with a family tree that shows the phenotype of each individual; such a diagram is called a **pedigree**. Information about a family is obtained by oral interviews (e.g. by a clinical geneticist, any other physician or a genetic couselor), from medical and historical records, (previous) genetic analysis, and other relevant sources. An important application of probability in genetics is its use in pedigree analysis.



A pedigree results in the presentation of family information in the form of an easily readable chart. Pedigrees use a standardized set of symbols, squares represent males and circles represent females. Pedigree construction is a family history, and details about an earlier generation may be uncertain

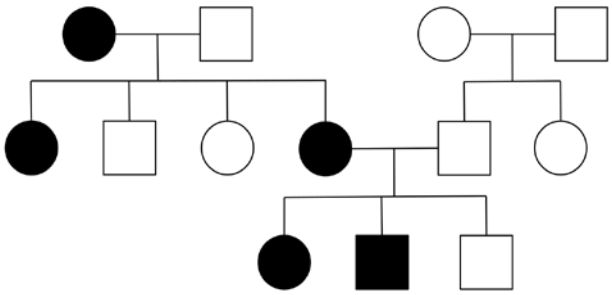
as memories fade. If the sex of the person is unknown a rhombus is used. Someone with the phenotype in question is represented by a filled-in (darker) symbol. Sometime heterozygotes, when identifiable, are indicated by a shade dot inside a symbol or a half-filled symbol.

Relationships in a pedigree are shown as a series of lines. Parents are connected by a horizontal line and a vertical line leads to their offspring. The offspring are connected by a horizontal sibship line and listed in birth order from left to right. If the offspring are twins then they will be connected by a triangle. If an offspring dies then its symbol will be crossed by a line. If the offspring is still born or aborted it is represented by a small triangle.

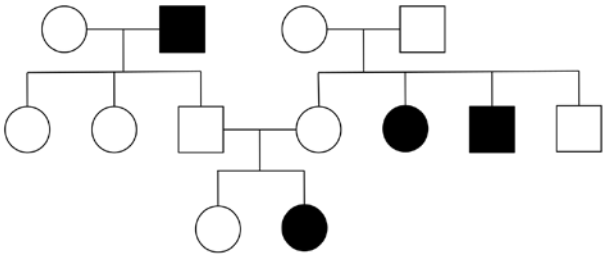
Each generation is identified by a Roman numeral (I, II, III, and so on), and each individual within the same generation is identified by an Arabic numeral (1, 2, 3, and so on). Analysis of the pedigree using the principles of Mendelian inheritance can determine whether a trait has a dominant or recessive pattern of inheritance. Pedigrees are often constructed after a family member afflicted with a genetic disorder has been identified. This individual, known as the proband, is indicated on the pedigree by an arrow.

CHARACTERISTICS OF MODES OF INHERITANCE:

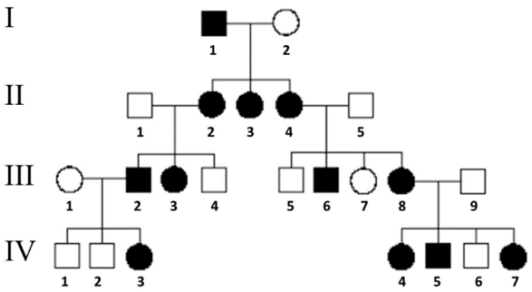
Autosomal Dominant disorders don't skip a generation, so affected offspring have affected parents. At least one parent must have the disorder for its offspring to be affected. Both males and females are equally likely to be affected, so it is an autosomal disorder.



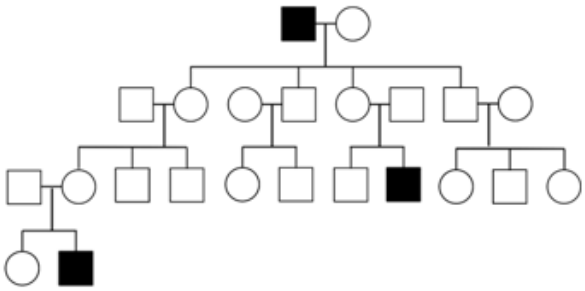
In an **Autosomal Recessive** Disorder, both parents can not express the trait, however, if both are carriers, their offspring can express the trait. Autosomal recessive disorders typically skip a generation, so affected offspring typically have unaffected parents. With an autosomal recessive disorder, both males and females are equally likely to be affected.



In a **X-Linked Dominant** disorder, if the father is affected all daughters will be affected and no sons will be affected. It doesn't skip a generation and if the mother is affected she has a 50% chance of passing it onto her offspring.

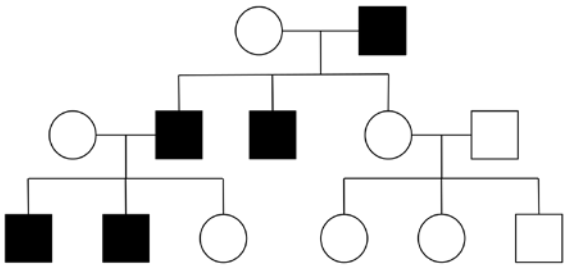


In a **X-linked Recessive** Disorder, males are more likely to be affected than females. Affected sons typically have unaffected mothers. The father also must be affected for daughter to be affected and the mother must be affected or a carrier for the daughter to be affected. The disorder is also never passed from father to son. Only females can be carriers for the disorders. X-linked



recessive disorders also typically skip a generation.

In a **Y-linked** disorder, only males can be affected. If the father is affected all sons will be affected. It also does not skip a generation.



QUESTIONS FOR SELF-CONTROL.

1. Characterize the main types of inheritance (autosomal-dominant, autosomal-recessive, X-linked dominant, X-linked recessive, Y-linked).

2. Family Studies, Pedigree Analysis.

a) autosomal dominant inheritance

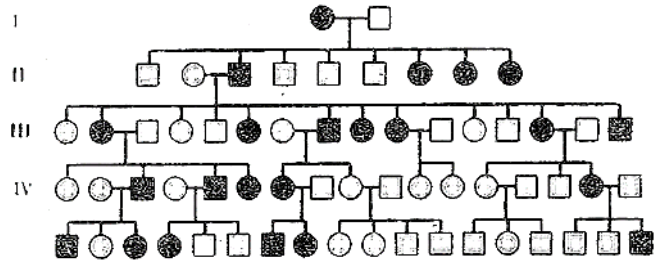
b) autosomal recessive inheritance

c) X-linked inheritance (dominant and recessive)

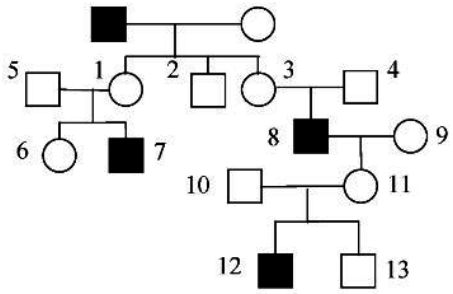
d) Y-linked inheritance

HUMAN PEDIGREE ANALYSIS

Problem 1. Analyze the Pedigree. Determine the type of trait inheritance



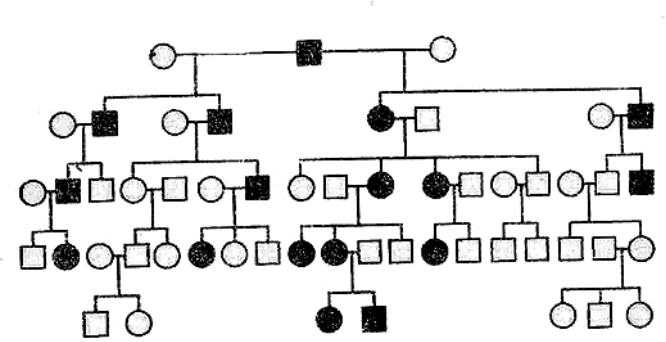
Problem 2. Analyze the Pedigree.



1) What is the most likely mode of inheritance for this pedigree?

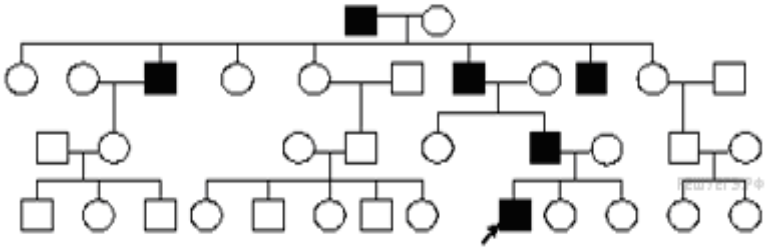
2) State the genotypes of individuals №1-13 in the following table

Problem 3. Analyze the Pedigree.



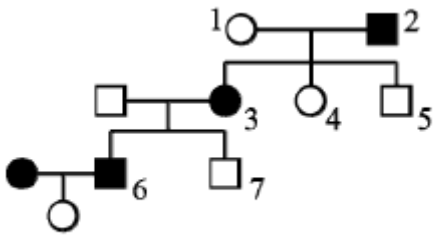
What is the most likely mode of inheritance for this pedigree?

Problem 4. Analyze the Pedigree.



What is the most likely mode of inheritance for this pedigree?

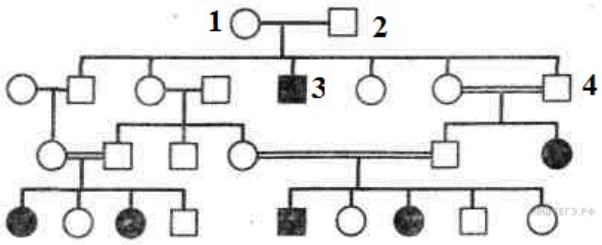
Problem 5. Analyze the Pedigree.



1) What is the most likely mode of inheritance for this pedigree?

2) State the genotypes of individuals №1-6 in the following table

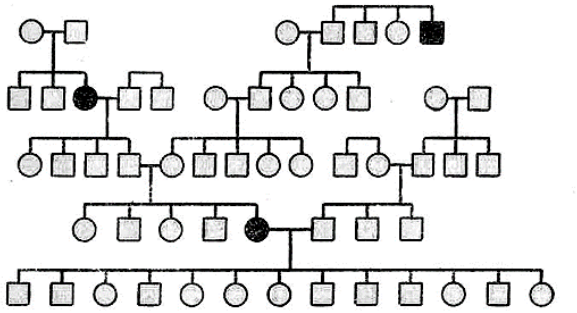
Problem 6. Analyze the Pedigree.



1) What is the most likely mode of inheritance for this pedigree?

2) State the genotypes of individuals №1-4 in the following table

Problem 6. Analyze the Pedigree.



What is the most likely mode of inheritance for this pedigree?

Problem 7.

Draw and analyze the Pedigree

Two normally-pigmented parents have 3 children. The first child (a girl) and their second child (a boy) have normal pigmentation. Their third child (a girl) has albinism. That girl marries a normally pigmented male and they have four children. The first three (two girls and a boy) have normal pigmentation. Their fourth child (a girl) has albinism like her mother. Determine the type of trait inheritance

9.2.2. Cytogenetic method

Cytogenetic method is used for indicating of the chromosomal diseases and disorders which are connected with chromosomal mutations (chromosome structure changes and chromosomal number mutations).

Metaphase chromosomes are examined under microscope after the process of cultivating of peripheral human blood lymphocytes (or cells from amniotic fluid or chorion) and using of special staining. Chromosomes become unlike each other and every aberrations become discovered.

The complete set of chromosomes in a species or in an individual organism that detected in nucleus of somatic cell is called **karyotype**.

The karyotype is analyzed under a light microscope. Attention is paid to their length, the position of the centromeres, banding pattern, any differences between the sex chromosomes, and any other physical characteristics.

Human karyotype

The normal human karyotypes contain 22 pairs of autosomal chromosomes and one pair of sex chromosomes. Normal karyotypes for females contain two X chromosomes and are denoted 46,XX; males have both an X and a Y chromosome denoted 46,XY.

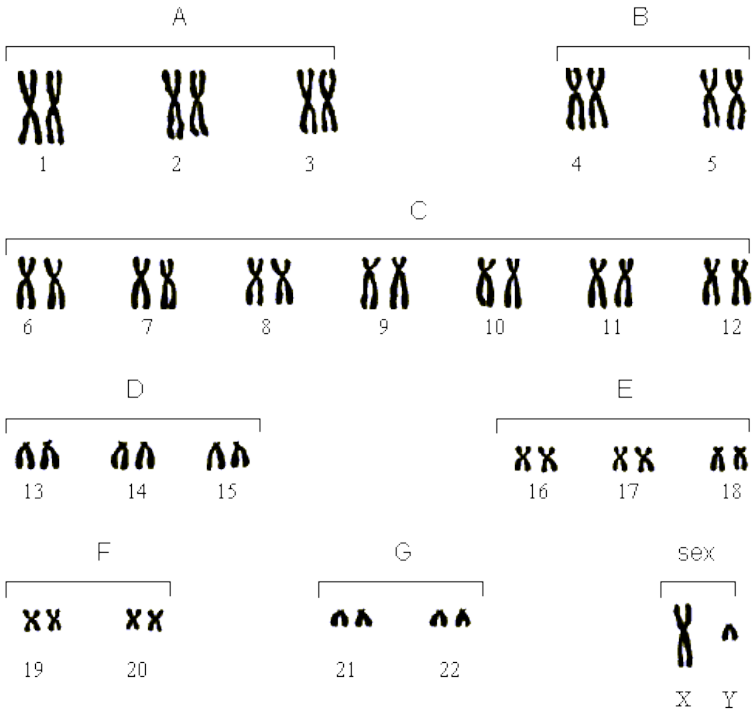
CLASSIFICATION OF HUMAN CHROMOSOMES.

The classification and nomenclature were determined by a convention of experts held at Denver, Colorado in 1960. In according to this recommendation:

1. The chromosomes are arranged in order of decrease of their size, except the sex chromosomes.
2. The chromosomes with similar sizes within one group are arranged in order of decrease of their centromere indexes. Centromere indexes - is expressed by length of short arm to length of all chromosomes ratio. It is expressed in percentages.
3. The autosomes are numbered 1 to 22.
4. The sex chromosomes of human and mammalies XX and XY are not numbered and placed at the end.

DENVER CLASSIFICATION OF CHROMOSOMES (DENVER, 1960)

GROUP NUMBER	NUMBER OF CHROMOSOMES IN KARYOTYPE	DESCRIPTION OF CHROMOSOMES
A (I)	1, 2, 3	These are largest in size, metacentric, and near metacentric.
B (II)	4, 5	These are largest in size, submetacentric.
C (III)	6 - 12 and X-chromosome	These are medium-sized, submetacentric.
D (IV)	13, 14, 15	These are short-sized and acrocentric
E (V)	16, 17, 18	These are short-sized, submetacentric.
F (VI)	19, 20	These are short-sized, metacentric.
G (VII)	21, 22, Y-chromosome	These are smallest in size and acrocentric



Any variation from the normal structure or number of chromosomes may lead to developmental abnormalities.

9.2.3. Biochemical method

Biochemical method is used for indicating the hereditary diseases of metabolism. Biochemistry is carried out at the cellular or subcellular level, generally on cell extracts. Biochemical methods are applied to the main chemical compounds of genetics—notably DNA, RNA, and protein. Biochemical techniques are used to determine the activities of genes within cells and to analyze substrates and products of gene-controlled reactions.

Special techniques (e.g., chromatography and electrophoresis) are used to separate the components of proteins so that inherited differences in their structures can be revealed. For example, more than 100 different kinds of human hemoglobin molecules have been identified. Radioactively tagged compounds are valuable in studying the biochemistry of whole cells. For example, thymine is a compound found only in DNA; if radioactive thymine is placed in a tissue-culture medium in which cells are growing, genes use it to duplicate themselves. When cells containing radioactive thymine are analyzed, the results show that, during duplication, the DNA molecule splits in half, and each half synthesizes its missing components.

Chemical tests are used to distinguish certain inherited conditions of humans; e.g., urinalysis and blood analysis reveal the presence of certain inherited abnormalities—phenylketonuria (PKU), cystinuria, alkaptonuria, gout, and galactosemia. Genomics has provided a battery of diagnostic tests that can be carried out on an individual's DNA. Some of these tests can be applied to fetuses in utero.

9.2.4. Twins method

Twins method is based on the signs of monozygotic and dizygotic twins.

Monozygotic ('identical') twins develop from one zygote, which splits during cleavage and forms two embryos. During cleavage cells divide by mitosis, that's why monozygotic twins are genetically identical.

Dizygotic (fraternal) twins develop from a different eggs and each egg is fertilized by its own sperm cell. That's why they share half their DNA, just like any siblings.

Scientists study twins to understand how genes and the environment work together to affect traits.

Concordance - similarity of twins in analyzing sign:

> *The concordance of monozygotic twins (Mc) - number of similar pairs of monozygotic twins / total number of pairs of monozygotic twins × 100%*
>
> *The concordance of dizygotic twins (Dc) - number of similar pairs of dizygotic twins / total number of pairs of dizygotic twins × 100%*

Discordance means that only one twin has definite sign while another one hasn't.

Both characteristics are used in studying of hereditability.

To calculate the role of heredity (H), Holzinger's formula is used:

$$H = \frac{\%Mc - \%Dc}{100\% - \%Dc}$$

Mc - Concordance in monozygotic twins

Dc - Concordance in dizygotic twins

If **H** approximately equal to **1**, it means the most contribution of genotype;

if $\mathbf{H_a}$ is less than **0,5** till **0**, it means the environmental contribution.

Concordance rates between MZ and

Trait	Concordance %	
	MZ	DZ
Blood types	100	66
Eye colour	99	28
Mental retardation	97	37
Measles	95	87
Idiopathic epilepsy	72	15
Schizophrenia	69	10
Diabetes	65	18
Identical allergy	59	5
Tuberculosis	57	23

Source: Klug, W.S. and Cummings, M.R., *Concepts of Genetics* (2nd edition). Glenview, IL: Scott, Foresman, 1986.

9.2.5. POPULATION-STATISTICAL METHOD

Application of genetic principles to entire populations of organisms constitutes the subject of population genetics.

The term population refers to a group of organisms of the same species living within a prescribel geographical area. Such a group of interbreeding individuals is called a local population.

Within a population a complete set of genetic information carried by the individuals is called the gene pool. This pool includes not only the genes but all alleles present in the population.

For the medical geneticist, the most important concept in population genetics is the Hardy-Weinberg equilibrium. Independently described in 1908 by the English mathematician Y.H. Hardy and the German physician W. Weinberg. A was derived to explain why dominant traits do not automatically replace recessive traits in the population. Its utility for medical genetics, however, is in explaining why, in a large population with random mating, allele frequencies

do not change from generation to generation and how, for any genetic locus, the genotype frequencies are determined by the relative frequencies of the alleles at that locus.

Consider a single autosomal locus with two alleles (**A** and **a**), whose population frequencies in both sperm and eggs are **p = frequency of allele A**, and **q = frequency of allele a**. Because there are only two alleles, **p + q = 1**. Random, mating without regard to genotype, is mathematically equivalent to random, mixing and union of sperm and eggs.

The genotype frequencies in the progeny are thus:

genotype**:** **AA, 2Aa, aa**
frequency: **p, 2pq, q**

In the next generation, each of the three paternal genotypes can mate with each of the three maternal genotypes. Thus the frequency of each genotype (**AA, Aa** and **aa**), is stable over successive generation and the population is said to be in Hardy-Weinberg equilibrium.

Of course, this principle depends upon certain assumptions of which the most important are the following:

1. Mating in random.

2. Allele frequencies are the same in males and females.
3. The genotypes are all equal in viability and fertility (that is selection does not occur).
4. Mutation does not occur.
5. Migration into population does not occur.
6. The population is sufficiently large that the frequencies of alleles will not change from generation because of chance.

The most important medical application of the Hardy- Weinberg equilibrium is the determination of allele frequency and heterozygote carrier frequency in a population for which the frequency of a trait is known.

Chapter 10. Glossary of Terms.

Allele An allele is one of two or more versions of DNA sequence (a single base or a segment of bases) at a given genomic location. An individual inherits two alleles, one from each parent, for any given genomic location where such variation exists. If the two alleles are the same, the individual is homozygous for that allele. If the alleles are different, the individual is heterozygous.

Allelic gene Allelic gene are located in the same locus of homologous chromosomes.

Alternative traits Alternative (or contrasting) traits are different variants of one trait that are encoded by different alleles of one gene.

Amino acid An amino acid is the fundamental molecule that serves as the building block for proteins. There are 20 different amino acids. A protein consists of one or several chains of amino acids (called polypeptides) whose sequence is encoded in a gene.

Aneuploidy Aneuploidy is an abnormality in the number of chromosomes in a cell. In humans, aneuploidy would be any number of chromosomes other than the usual 46.

Anticodon An anticodon is a trinucleotide sequence located at one end of a transfer RNA (tRNA) molecule, which is complementary to a corresponding codon in a messenger RNA (mRNA) sequence.

Autosome An autosome is one of the numbered chromosomes, as opposed to the sex chromosomes. Humans have 22 pairs of autosomes and one pair of sex chromosomes (XX or XY). Autosomes are numbered roughly in relation to their sizes. The largest autosome — chromosome 1 — has

	approximately 2,800 genes; the smallest autosome — chromosome 22 — has approximately 750 genes.
Carrier	A carrier is an individual who "carries" and can pass on to its offspring an allele associated with a disease that is inherited in an autosomal recessive or sex-linked manner, and who does not show symptoms of that disease (or features of that trait).
Centimorgan (cM)	A centimorgan (abbreviated cM) is a unit of measure for the frequency of genetic recombination. One centimorgan is equal to a 1% chance that two markers on a chromosome will become separated from one another due to a recombination event during meiosis (which occurs during the formation of egg and sperm cells).
Centromere	is a constricted region of a chromosome where the cell's spindle fibers attach. Following attachment of the spindle fibers to the centromere, the two identical sister chromatids that make up the replicated chromosome are pulled to opposite sides of the dividing cell
Chromatid	A chromatid is one of the two identical halves of a chromosome that has been replicated in preparation for cell division.
Chromatin	Chromatin refers to a mixture of DNA and proteins that form the chromosomes.
Chromosomes	Chromosomes are threadlike structures made of protein and a single molecule of DNA that serve to carry the genomic information from cell to cell.
Codominance	Codominance refers to a type of inheritance in which two versions (alleles) of the same gene are expressed separately to yield different traits in an individual.

Codon	A codon is a DNA or RNA sequence of three nucleotides (a trinucleotide) that forms a unit of genomic information encoding a particular amino acid
Crossing Over	Crossing over, as related to genetics and genomics, refers to the exchange of DNA between paired homologous chromosomes (one from each parent) that occurs during the development of egg and sperm cells (meiosis). This process results in new combinations of alleles in the gametes (egg or sperm) formed, which ensures genomic variation in any offspring produced.
DNA Replication	DNA replication is the process by which the genome's DNA is copied in cells.
Dihybrid cross	is a cross between two different organisms that differ in two genes (two observed traits).
Dominant Traits and Alleles	The dominant allele express the dominant trait always independently of the second allele. The effect of the other allele (the recessive allele) is masked by the dominant allele. An individual who carries two copies of a dominant allele exhibits the same trait as those who carry only one copy.
Epigenetics	is a field of study focused on changes in DNA that do not involve alterations to the underlying sequence. The DNA letters and the proteins that interact with DNA can have chemical modifications that change the degrees to which genes are turned on and off.
Epistasis	Epistasis is a circumstance where the expression of one gene is suppressed by the expression of other gene.

Gamete	A gamete is a haploid reproductive cell of an animal or plant. In animals, female gametes are called ova or egg cells, and male gametes are called sperm.
Gene	is the basic unit of inheritance. It's a sequence of DNA that codes for specific protein.
Gene expression	Gene expression is the process by which the information encoded in a gene is used to either make RNA molecules that code for proteins or to make non-coding RNA molecules that serve other functions.
Gene mapping	Gene mapping refers to the process of determining the location of genes on chromosomes.
Genome	The genome is the entire set of DNA instructions found in a cell.
Genotype	A genotype is a scoring of the type of variant present at a given location (i.e., a locus) in the genome.
Haploid	Haploid refers to the presence of a single set of chromosomes in an organism's cells.
Hemizygous	Hemizygous organism has only a single copy of a gene instead of two.
Heredity	Heredity is the ability of living organism to transmit characteristics and properties to next generation during reproduction
Heterozygous	Heterozygous, as related to genetics, refers to having inherited different alleles of a gene from each biological parent. Heterozygous organism produces 2 types of gametes.

Homozygous	Homozygous means that an individual has the same allele for a gene. If both alleles are dominant the individual is a homozygous dominant (AA). If both alleles are recessive the individual is a homozygous recessive (aa). Homozygous organism forms only 1 type of gametes.
Hybridization	Hybridization is crossing of individuals differing on genotype and phenotype, followed by further analysis of individuals obtained in filial generations (hybrids).
Inheritance	Inheritance is the way in which characteristics are passed from one generation to the next
Karyotype	A karyotype is an individual's complete set of chromosomes.
Linkage	Is the closeness of genes or other DNA sequences to one another on the same chromosome. The closer two genes or sequences are to each other on a chromosome, the greater the probability that they will be inherited together.
Locus	A locus, as related to genomics, is a physical site or location within a genome
Mitosis	Mitosis is the process by which a cell replicates its chromosomes and then segregates them, producing two identical nuclei in preparation for cell division.
Monogenic inheritance	Monogenic inheritance refers to the kind of inheritance whereby a trait is determined by the expression of a single gene or allele
Monohybrid cross	is a mating between two organisms with different variations at one gene.

Mutation	A mutation is a change in the DNA sequence of an organism.
Pedigree	A pedigree is a chart that diagrams the inheritance of a trait or health condition through generations of a family. The pedigree particularly shows the relationships among family members and, when the information is available, indicates which individuals have a trait(s) of interest.
Phenotype	is a complex of all traits of organism that are resulted of gene expression and depended of environment.
Polygenic inheritance	Means that a trait is determined by the expression of several genes
Polydactyly	Polydactyly is a condition in which a person has more than the normal number of fingers or toes.
Recessive allele	Recessive allele produces its characteristic phenotype only when its paired allele is identical. This allele is not expressed if a dominant allele is present.
sex chromosome	A sex chromosome is a type of chromosome involved in sex determination. Humans and most other mammals have two sex chromosomes, X and Y, that in combination determine the sex of an individual. Females have two X chromosomes in their cells, while males have one X and one Y.
Sex-linked	Sex-linked refers to characteristics (or traits) that are influenced by genes carried on the sex chromosomes.
Somatic Cells	Somatic cells are the cells in the body other than sperm and egg cells (which are called germ cells). In humans, somatic cells are diploid,

	meaning they contain two sets of chromosomes, one inherited from each parent.
Syndrome	A syndrome, as related to genetics, is a group of traits or conditions that tend to occur together and characterize a recognizable disease.
Trait	A trait, as related to genetics, is a specific characteristic of an individual. Traits can be determined by genes, environmental factors or by a combination of both.
Transcription	Transcription is the process of making an RNA copy of a gene's DNA sequence.
Translation	Translation, as related to genomics, is the process through which information encoded in messenger RNA (mRNA) directs the addition of amino acids during protein synthesis.
Variability	- the ability of organisms to acquire new features and properties during the life

Bibliography

Bekish, O.-Y. L. Medical biology : textbook for student of higher educational establishments / O.-Y. L. Bekish. Vitebsk : VSMU Press, 2003. 346 p.

Biology for international students 1st year : курс лекций /В.Э. Бутвиловский [и др.] ; пер. с рус. яз. Т. Ф. Данилова. – Минск : БГМУ, 2012. – 75 с.

Cell biology [Electronic resource]// Anatomy & Physiology Made Incredibly Easy. – Lippincott Williams & Wilkins, 2009. – URL: http://ovidsp.tx.ovid.com.

Chatterjee, K. D. Parasitology (Protozoology and Helminthology): in relation to clinical medicine / K. D. Chatterjee. – 12th ed. – Calcutta: [S. n.], 2001. – 238 p.

Cytology&Genetics: учеб. пособие, для самост. внеауд. раб. обучающихся /Сост.: Т. В. Викторова, К. В. Данилко. — Уфа: ФГБОУ ВО БГМУ Минздрава России, 2016. — 182 с. — on-line. — Режим доступа: http://library.bashgmu.ru/elibdoc/elib668.pdf.

Cytology. Biology of reproduction and development: метод. рекомендации //Tver State Medical Academy; ed. G. V. Khomullo. – Tver : Publishing house "Triada", 2006. – 32 p.

General and medical genetics: метод. Рекомендации // Tver State Medical Academy; ed. G. V. Khomullo. – Tver : Publishing house "Triada", 2007. – 56 p

Medical biology and genetics for international students 1st year : lecture course /I.V. Rachkovskaya [et al.]. Minsk : BSMU, 2012. 205 p.

Medical parasitology: метод. Рекомендации / Tver State Medical Academy ; ed. G. V. Khomullo. – Tver: Publishing house "Triada", 2007. – 91 p.

Medical Parasitology: учеб. пособие / сост.: Ф. Ф. Мусыргалина, О. А. Майорова. – Уфа: ФГБОУ ВО БГМУ Минздрава России, 2017. – 214 с.– online.– Режим доступа: http://library.bashgmu.ru/elibdoc/elib665.pdf.

Бочков Н.П. Клиническая генетика. Учебник для ВУЗов. - М.:«ГЭОТАР-Медиа», 2004, 480с.

Волгарева Г.М. Основы мутагенеза (учебная лекция). - М., 2007.

Гайнутдинов И.К., Юровская Э.Д. Медицинская генетика. Учебник. - М.: «М.», 2008, 336с.

Генова О.А., Филиппова В.В., Морозова Н.В., Козлов В.К. Руководство к практическим занятиям по медицинской генетике. Руководство. - Хабаровск: Издательство Дальневосточного государственного медицинского университета, 2008, 163с.

Инге-Вечтомов С.Г. Общая генетика. Методическое пособие. - С-Пб., 2008.

Козлова С.И., Демикова Н.С. Наследственные синдромы и медико-генетическое консультирование. Атлас-справочник. Учебное пособие. - М., 2007, 448 с.

Козлова С.И., Ижевская В.Л. Медико-генетическое консультирование. - М., 2005.

Медицинская биология и общая генетика : сборник задач / В.Э. Бутвиловский [и др.]. – 2-е изд. - Минск : БГМУ, 2010. 264 с

Медицинская биология и общая генетика : терминологический словарь для иностранных студентов / В.Э. Бутвиловский [и др.]. Минск : БГМУ, 2007. 55 с.

Медицинская биология и общая генетика : тесты / В.Э. Бутвиловский [и др.].Минск : БГМУ, 2006. 228 с

Медицинская биология и общая генетика : учебник/ Заяц Р. Г. [и др.]. – Минск :Выш. школа, 2011. 495 с.

https://anatomypubs.onlinelibrary.wiley.com/doi/full/10.1002/dvdy.23924

https://web2.mendelu.cz/af_291_projekty2/vseo/print.php?page=279

https://bccampusbiology.pressbooks.tru.ca/chapter/mendels-experiments-and-the-laws-of-probability/

https://opened.cuny.edu/courseware/lesson/662/overview

https://pressbooks-dev.oer.hawaii.edu/biology/chapter/mendels-experiments-and-the-laws-of-probability/

http://www.mendelweb.org/Mendel.plain.html

https://slcc.pressbooks.pub/humanbiology/chapter/__unknown__-6/

https://pressbooks.umn.edu/introbio/chapter/inheritancelaws/

https://view.genial.ly/60184a5a8e938a0d79d63d67/horizontal-infographic-review-biology

https://www.docsity.com/ru/biologia-de-la-celula-2/4464612/

https://studyres.com/doc/16233673/medical-biology-and-general-genetics

http://rep.bsmu.by/bitstream/handle/BSMU/14301/978-985-567-543-4.Image.Marked.pdf?sequence=1

https://papers.gceguide.com/A%20Levels/Biology%20(9700)/2003/9700_s03_er.pdf

https://www.thelancet.com/action/showPdf?pii=S2352-3964%2819%2930838-2