MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION
PIROGOV RUSSIAN NATIONAL RESEARCH MEDICAL UNIVERSITY

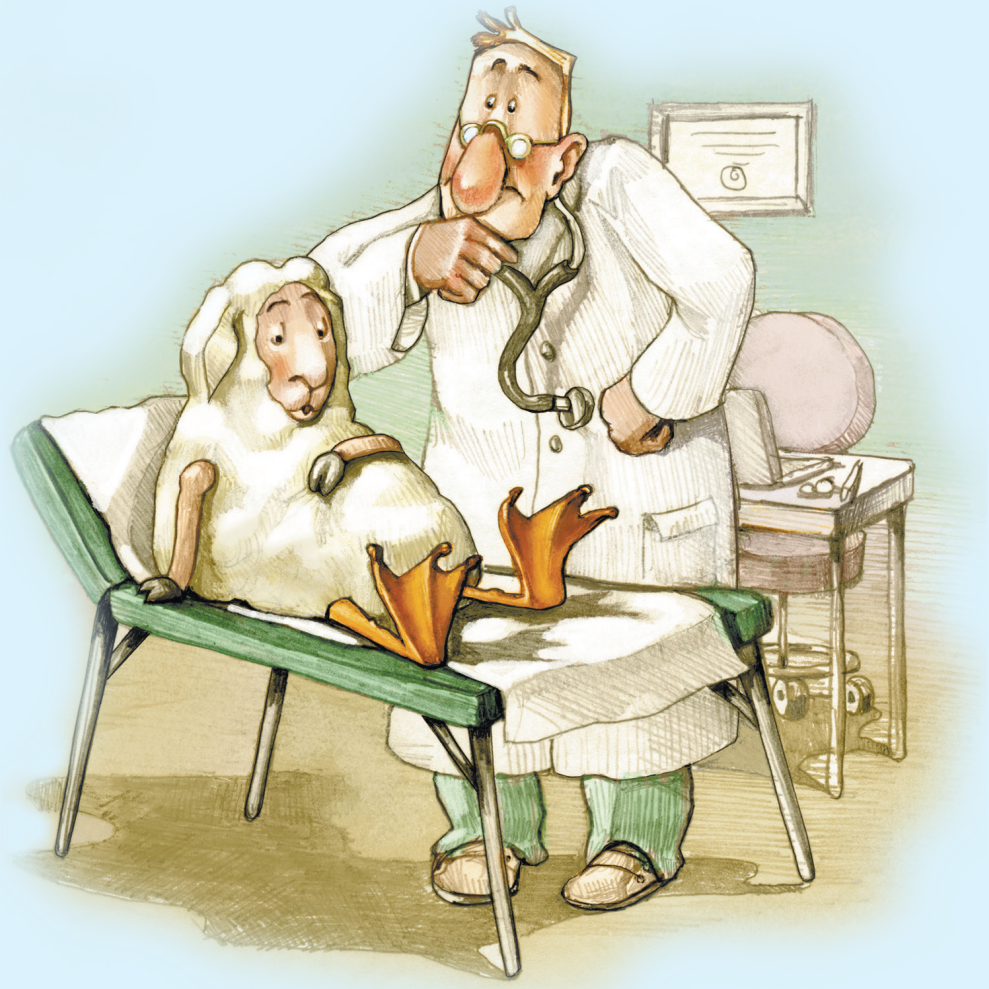
Department of Biology. Pediatrics Faculty

O.N. Khrushchova, E.I. Romashevskaya, Y.I. Voldgorn, E.A. Bogdanova

INTRODUCTION TO MEDICAL GENETICS

STUDENT WORKBOOK

Edited by prof. A.G.Mustafin



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The workbook is intended for students of medical universities enrolled in the educational program “General Medicine” to master the discipline “Biology”. It includes basic information and practical tasks that help to better understand medical genetics.

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TABLE OF CONTENT

TOPIC 1. MONOGENIC AUTOSOMAL INHERITANCE

Some genetic terminology

In general, every somatic cell has two sets of chromosomes, known as **homologous pairs**, one set from each parent. Thus, there are two copies (alleles) of each autosomal gene in the cell, one of maternal origin and one of paternal origin. They are in identical positions (or **loci**) on two homologous chromosomes.

The alternative forms of a gene that result of gene mutations are called **alleles**. The phenomenon when a gene has more than two alleles in population is called **multiple allelism**.

Any gene-determined characteristic is a **trait**. If the trait depends only upon one pair of autosomal gene, we say it is autosomal single-gene (monogenic) inheritance.

Pleiotropy is a phenomenon when a single gene determines a number of distinct characteristics. In humans, many monogenic syndromes demonstrate effect of pleiotropy.

Genotype in which two alleles of a gene are the same is said to be **homozygous** or pure-breeding for that gene. If the alleles are different then the organism is **heterozygous for that gene**.

If the trait is expressed in the heterozygote, then the trait is **dominant**, whereas if it is only expressed in the homozygote it is **recessive**. The alleles that an organism carries make up the genotype of that organism. All the traits that an organism possesses are referred to as a **phenotype**.

Methods in genetics

The first scientific method to study genetics was experimental breeding. Other methods are pedigree analysis, cytogenetic methods, biochemical and molecular methods (DNA analysis), twin studies and methods of population genetics.

Monohybrid cross. First Mendel law

Monohybrid cross is mating between individuals that differ in only one trait.

> **Mendel first law — the law of segregation.**

Mendelian inheritance is a type of biological inheritance that follows the laws originally proposed by Gregor Mendel in 1865 and 1866 and re-discovered in 1900. For experiments Mendel used peas that he had planted in the garden of his monastery. Between 1856 and 1863, Mendel cultivated and tested about 5,000 pea plants. From these experiments, he induced two generalizations which later became known as Mendel's Principles of Heredity or Mendelian Inheritance.

One of the pairs of traits that he studied was yellow versus green seeds. Parental plants (P) were pure bred, and Mendel performed cross-pollination between them. The F1 hybrid (first filial) plants were than allowed to self-pollinate. The progeny plants (F2) were like both of the original parental types: yellow and green. The phenotypes ratio was 3:1, genotype ratio — 1:2:1 (Fig. 1).

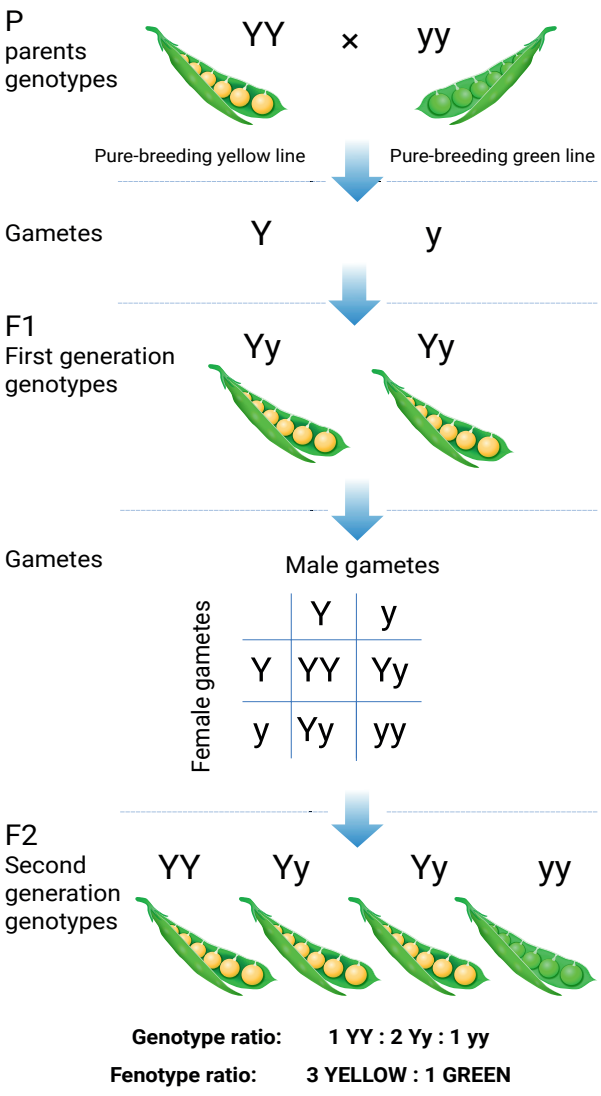


Fig.1. Monohybrid cross and two generations of progeny (Mendel's law of segregation).

Y – yellow seeds; y – green seeds.

Task 1.1 (example). Two short-haired cats mate and produced five short-haired and two longed-haired kittens. What does this information suggest about how hair length is inherited in cats? Which trait is dominant? Why the F1 ratio is not exactly 3:1?

Designations: A — short hair; a — long hair

P (parent genotypes): Aa × Aa

Gametes: A a A a

F1 (first generation genotypes): 1 AA : 2 Aa : 1 aa

Conclusion: Dominant trait in cats is short hair; the ratio is not exactly 1:3 because of chance meeting of gametes at fertilization.

Monogenic (single-gene) autosomal inheritance in human. Pedigree analysis

In humans, controlled crosses cannot be performed, so geneticists have to study family records. The investigator traces the history of some variant phenotype back through the history of the family and draws up a **family tree**, or **genealogical tree**, or **pedigree**, using the standard symbols given in Figure 2.

Pedigree analysis can help to determine whether the trait or disorder is dominant or recessive.

The traits whose genes are localized in the non-sexual chromosomes (autosomes) are referred to as autosomal traits.

There are two types of autosomal inheritance — dominant and recessive.

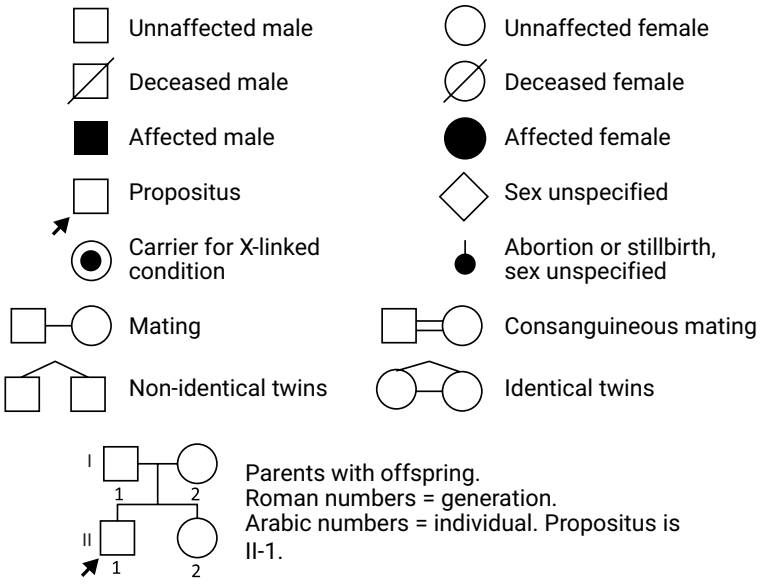


Fig.2. Symbols used in pedigree analysis.

Typical features of autosomal dominant (AD) inheritance are:

1. Both males and females are affected in approximately equal numbers.
2. Persons are affected in each generation.
3. Usually there is near 50% chance that each child of heterozygous parents will be affected.

Clinical examples of AD disorders in human:

1. Marphan's syndrome: Disorder of the connective tissue with a pleiotropic effect. Individuals are tall, thin, with long arm, legs, fingers and toes (arachnodactyly), flexible joints, skeletal and heart problem.
2. Huntington disease (HD, Huntington's chorea) is accompanied by the development of psychiatric symptoms, progressive chorea and dementia. Onset usually between 30 and 50 years. Progressive disability; death occurs on average 17 years from onset.
3. Achondroplasia is a form of short-limbed dwarfism. It's also an example of incomplete dominance because in homozygous state the gene is lethal.

Typical features of autosomal recessive (AR) inheritance are:

1. Both males and females are affected in approximately equal numbers.
2. Persons may be affected not in each generation.
3. The average proportion of affected offspring in a common case (both of the parents are heterozygous) is one to three (25%).

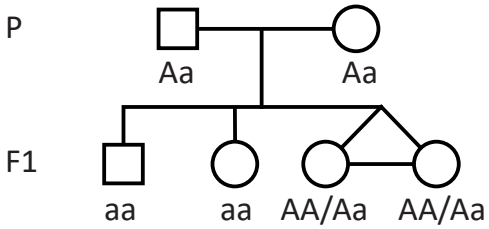
Clinical examples of AR disorders:

1. Albinism (oculocutaneous): Pink-red skin which fails to tan, white hair, blue or pink irises and a prominent red reflex.
2. Phenylketonuria: Elevated blood and urine phenylalanine due to deficiency of hepatic phenylalanine hydroxylase is usually detected as a result of neonatal screening. Prognosis: Normal development and lifespan with a diet low in phenylalanine and supplemented with tyrosine; mental retardation if untreated.
3. Cystic fibrosis: The disease that causes the body to produce thick and sticky mucus that can clog the lungs and obstruct the pancreas.

Fig.3. Dimple in a chin

Task 1.2 (example). Draw the genealogical tree of a family with four children where both parents have a dimple in the chin(Fig. 3), two eldest children (boy and girl) do not, and identical twin girls have a dimple.

Designations: A – with a dimple in a chin;
a – no dimple.



Task 1.3. Neurofibromatosis type 1 (benign tumors along nerves and "coffee-and-milk" spots on skin) is one of the most common autosomal dominant disorders. A woman with neurofibromatosis type 1 has an unaffected mother. Her partner is also unaffected. What is the probability for their children to have the disease? Draw the genealogical tree of a family.

Designations: _____

_____

Conclusion: _____

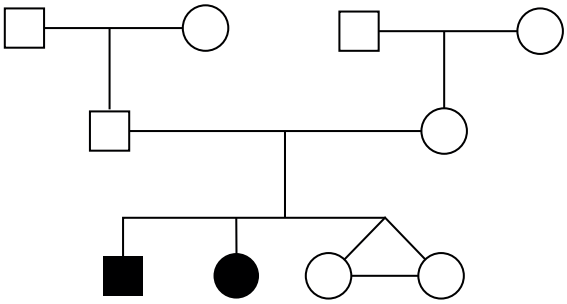
_____

Task 1.4. Study the pedigree of a family with PKU (phenylketonuria). Write down the genotypes. Is it dominant or recessive?

Symbol "A" is _____

Symbol "a" is _____

The trait is _____



Task 1.5. Achondroplasia (short limbs especially proximally (rhizomelia); normal length of the trunk; prominent forehead with depressed nasal bridge, normal IQ and lifespan) shows autosomal dominant inheritance. Is it possible for two achondroplastics to have a child with normal height? If so what is the probability?

Designations: _____

_____

Conclusion: _____

_____

Task 1.6. Determine which autosomal disorders are present in the people shown in the Fig. 4 below and indicate a type of inheritance.

A	B	C

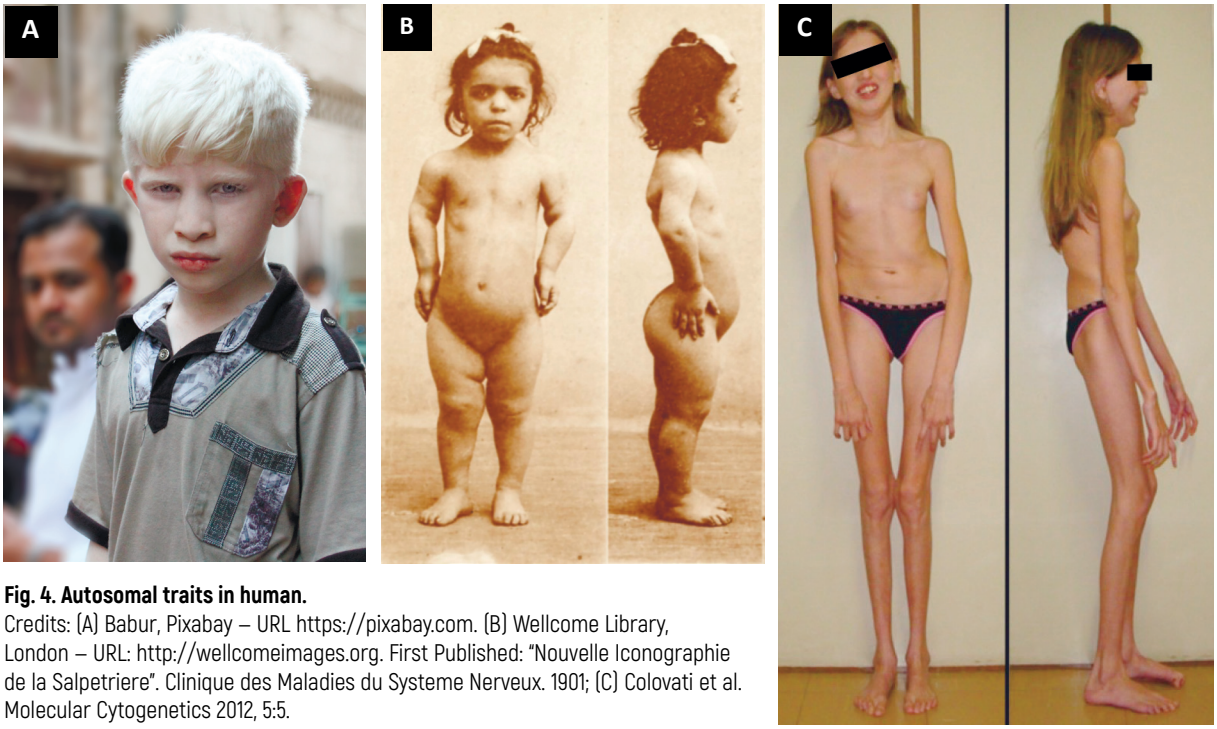


Fig. 4. Autosomal traits in human.
Credits: (A) Babur, Pixabay – URL https://pixabay.com. (B) Wellcome Library, London – URL: http://wellcomeimages.org. First Published: "Nouvelle Iconographie de la Salpetriere". Clinique des Maladies du Systeme Nerveux. 1901; (C) Colovati et al. Molecular Cytogenetics 2012, 5:5.

Multiple alleles and codominance

A diploid organism cannot have more than two alleles in the same locus. But in a population most of genes have more than two allelic forms.

The human ABO blood group system is an excellent example of multiple alleles. Human blood belongs to one of the A, B, AB or O groups. The alleles are designated by symbols IA, IB and I0. Alleles IA and IB are dominant to I^0, which is recessive; I^A and I^B are codominant alleles. AB group occurs when both alleles are expressed in the heterozygote, and two antigens are present.

Genotype(s)	Blood group
I^0I^0	I (0)
I^AI^0 or I^AI^A	II (A)
I^BI^0 or I^BI^B	III (B)
I^AI^B	IV (AB)

Task 1.7. Father has blood group A, mother – B, both are heterozygous. Draw the genealogical tree of a family. What blood groups may have their children?

Designations: I^A and I^B are codominant alleles; I^0 is recessive allele.

Task 1.8. The genotypes of a husband and wife are I^AI^B x I^AI^0. Among the blood types of their children, how many different genotypes and phenotypes are possible?

Designations: I^A and I^B are codominant alleles; I^0 is recessive allele.

Incomplete (partial) dominance

Incomplete dominance describes situation, in which the phenotype of heterozygote is intermediate between those of homozygotes. For example, when homozygous red and white snapdragon (antirrhinums) plants are crossed the F1 plants have pink flowers (intermediate in color between those of the parental varieties). When these are crossed the F2 has one part red, two parts pinks and one part white.

An example of incomplete dominance in human is sickle cell disease (sickle cell anemia). Heterozygotes have subclinical form of anemia, they are carriers of the mutant beta globin gene (HbA/HbS). Homozygotes for S hemoglobin die in the childhood, homozygotes for A hemoglobin are healthy. The sickle-cell gene has a so called pleiotropic effect — individuals with this allele are resistant to malaria.

Test cross is a breeding of an organism in question (with dominant phenotype) with a homozygous recessive partner in order to determine zygosity by analyzing the offspring.

Task 1.9. Parents both have sickle cell anemia in subclinical (light) form. One of their children died from anemia, the second died from malaria and the last one has anemia in subclinical form and is resistant to malaria. What are the genotypes of all the family? Draw the family tree.

Task 1.10. A blue-eyed man (recessive trait) was married twice. Both his wives had brown eyes (dominant trait). With his first wife, he had two daughters with blue eyes, but with his second wife he had ten children and all of them were brown-eyed. Draw a pedigree tree. What are the genotypes of the man and of his wives? What type of cross does this family illustrate?

Task 1.11. Match the terms in the column A with description in the column B.

COLUMN A	COLUMN B
(1) alleles	(a) having two identical alleles of a given gene
(2) phenotype	(b) the allele expressed in the phenotype of the heterozygote
(3) gametes	(c) alternative forms of a gene
(4) gene	(d) observable characteristic
(5) segregation	(e) reproductive cells containing only one copy of each genes
(6) heterozygote	(f) the allele that does not contribute to the phenotype of the heterozygote
(7) dominant	(g) the cross of an individual of ambiguous genotype with a homozygous recessive individual
(8) F1	(h) an individual with two different alleles of a gene
(9) test cross	(i) the heritable entity that determines a characteristic
(10) genotype	(j) the alleles an individual has
(11) recessive	(k) the separation of the two alleles of a gene into different gametes
(12) homozygote	(l) offspring of the P generation

A	1	2	3	4	5	6	7	8	9	10	11	12
B												

Task 1.12. Answer the questions (for the preparation use Chapters 12 and 13 [pp.71–78] in the textbook "ESSENTIAL MEDICAL BIOLOGY"):

1. If an individual is able to taste PTC (dominant trait), then what genotype does that person most likely to have?

2. What is the difference between terms "gene" and "allele"?

3. What is incomplete dominance? _____

4. What is codominance? _____

5. What is a test cross? _____

6. When there are three or more alleles of a gene, this is called _____

7. If two people who are both carriers for a genetically inherited fatal recessive disease decide to become parents, what will be the odds that their children will also be carriers?

TOPIC 2. MONOGENIC SEX-LINKED INHERITANCE

Sex determination in animals

Sex is a complex of characters of being a male or a female in animals and plants.

In animals, there are different models of sex determination (Fig. 5). In some fish, reptiles, amphibian sex-determination of the individual depends on the environment. But most of organisms have chromosomal (genetic) sex determination. It means that the sex of an embryo is determined be combination of chromosomes in zygote. The sex that has identical sex chromosomes is called **homogametic**, the other one – **heterogametic**. In humans and other mammals, the female is homogametic sex and the male the heterogametic sex, because they produce one or two types of gametes, respectively. The sex chromosomes in birds are designated Z and W, and the male is the homogametic sex (ZZ) and the female heterogametic (ZW).

In humans, X-chromosome is much bigger than Y. X chromosome belongs to C-group according to Denver nomenclature of chromosomes, while Y to smallest, G-group. The X and Y chromosomes have a homologous (so called pseudoautosomal) region where very few allele genes are situated and non-homologous regions (Fig. 6). Genes that are located on non-homologous regions of sex chromosomes are called sex-linked (X-linked or Y-linked, respectively). Because Y-linked genes are transmitted from father to sons and never to daughters they are referred to as **holandric**.

Females have two copies of X chromosomes and thus may either be homo-, or heterozygous. Males have only one X and Y chromosome and hence only one copy of each X-linked or Y-linked gene (i.e. **hemizygous**).

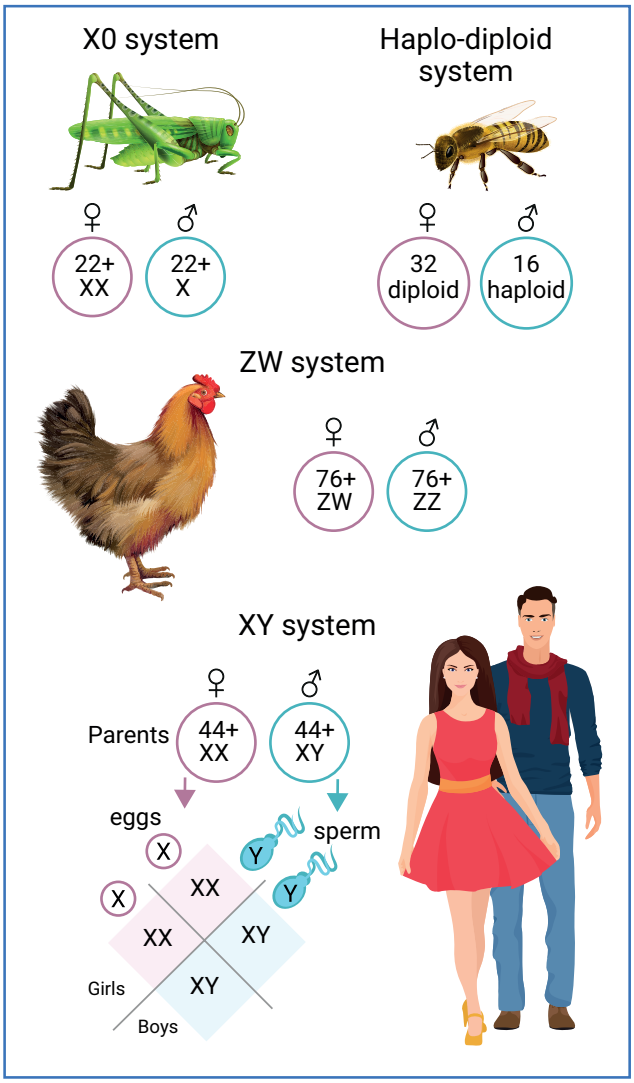


Fig.5. Sex determination in different animals

So, there are two types of X-linked inheritance (dominant and recessive) and Y-linked, or holandric, inheritance in human.

The typical features of X-linked dominant (XD) inheritance are:

1. Affected fathers transmit the disorder to all their daughters.
2. Daughters usually inherit more often than sons.
3. No variations in expression (all affected boys have a similar disease course).

Example of XD disorders:

- **Vitamin D resistant rickets (phosphate diabetes)** is a disorder of metabolism, due to failure of kidneys to absorb phosphate. Thus, males and females can be affected. However, whereas in males the condition is uniformly severe, the female heterozygote is more variably affected because of lyonization. **Lyonization** is a process of **random inactivation of X chromosomes** in mammal females discovered by Mary Layon. **Barr body** is an inactivated X chromosome.

The typical features of X-linked recessive (XR) inheritance are:

1. A marked discrepancy in the sex ratio: mostly boys have the disease.
2. No variations in expression (all affected boys have a similar disease course).
3. The disease is never transmitted by an unaffected male; heterozygous females are clinically unaffected but transmit the condition to the next generation.

Examples of XR conditions:

- **Haemophilia** is a condition in which the blood will not clot normally. The result is frequent, excessive bleeding. There are two forms of X-linked haemophilia, known as haemophilia A and haemophilia B.
- **Red-green colour blind** (daltonic) person sees the colours green, yellow, orange and red as the same colour. This condition affects about 8% of males, but only 0.4% of females in the human population.
- **Duchenne muscular dystrophy.** It is a rare progressive disease which affects all voluntary muscles and involves the heart and breathing muscles. The life expectancy is estimated to be around 25. DMD is due to mutations in dystrophin gene.

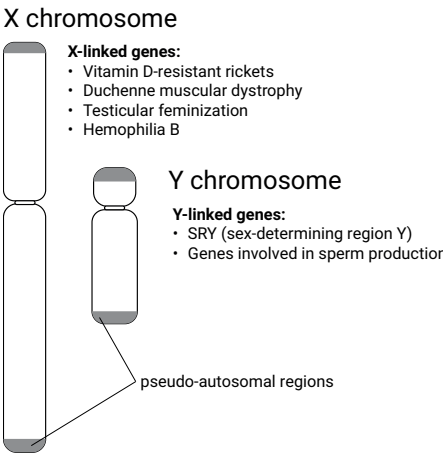


Fig.6. X- and Y-linked genes in human

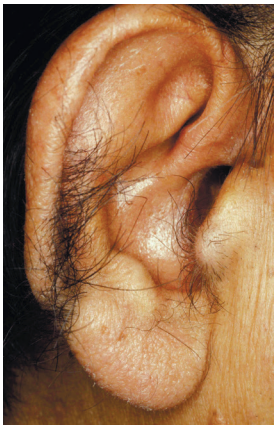


Fig.7. Hairy pinna of ear

Credit: http://otoscopy.hawkelibrary.com

Y-linked (holandric) inheritance

The inheritance of genes of Y chromosome is referred to as **holandric**. **Sex determining region gene (SRY gene)** provides an example of Y-linked inheritance. So, males transmit SRY:

1. To all of their sons, but not daughters.
2. 100% of sons inherit TDF-allele.
3. In every generation.

So far, no human examples of Y-linked diseases have been established. Sometimes hypertrichosis of ear is thought to be Y-linked, so called **hairy pinna of ear** (Fig. 7).

Task 2.1. Haemophilia A is a severe coagulation disorder that shows X-linked recessive inheritance. What offspring may have a hemophiliac man and woman-carrier?

Designations: X^H – normal blood clothing, X^h – haemophilia

P $X^hY \times X^HX^h$

Gametes:

F1

Conclusion: _____

Task 2.2. Red-green colour blindness (daltonism) shows X-linked recessive inheritance. The wife is daltonic and the husband has normal colour vision. Give the prognosis for their offspring.

Designations: X^D – normal colour vision, X^d – daltonism.

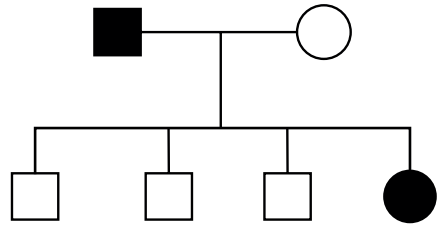
Task 2.3. Duchenne muscular dystrophy (DMD) is caused by X-linked recessive allele. It causes progressive muscular wasting and usually leads to death before age 20. What is the probability to have DMD for the second son of a woman whose brother and the first son were affected?

Designations: X^D – normal muscles, X^d – DMD

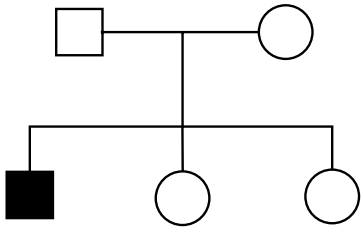
Task 2.4. Hypertrichosis, hairiness of the pinna (auricle) of the ear, is inherited as a Y-linked recessive in humans. If a man with hypertrichosis marries a normal woman, what children may they have? Draw a pedigree.

Task 2.5. The traits shown in bold in pedigrees below are X-linked. Decide if they are dominant or recessive and write down the genotypes for each member of the families. Put a question mark if the genotype cannot be undoubtedly determined.

A



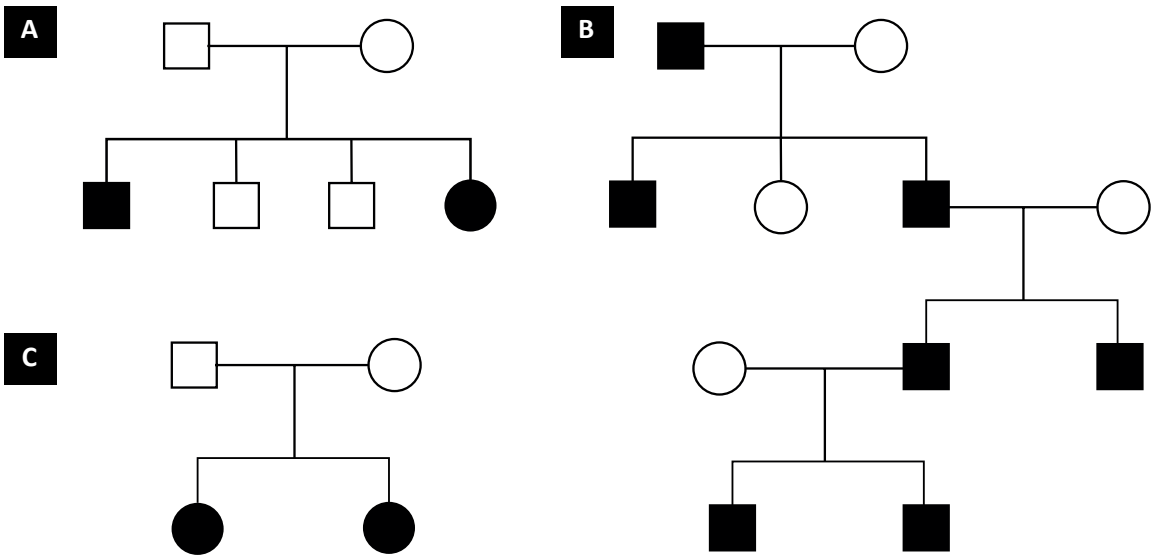
B



Task 2.6. A gene coding for testosterone receptor (X^T) is X-linked. Its recessive allele (X^t) causes androgen insensitivity syndrome (AIS) when male fetuses develop female external sexual characteristics – so called XY-female. Draw the pedigree. What phenotype may have the offspring of a couple where mother is heterozygous for AIS?

Task 2.7. In cats, fur colour gene is X-linked. X^B determines black colour, X^b – yellow. Heterozygous females have black and yellow spots (are tortoise-shell), males are either black or yellow. What fur colour will have the offspring of mating a black male and a tortoise-shell female cat?

Task 2.8. What type of inheritance do the following pedigrees illustrate (AD, AR, XD, XR, Y)? There may be more than one correct answer. Write down the genotypes.



D

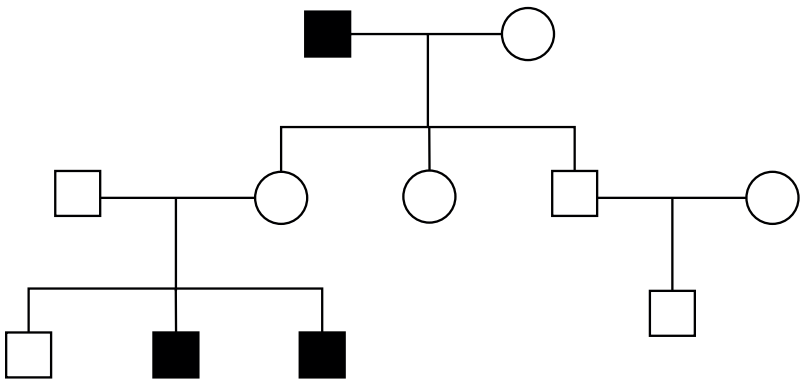


Figure	A	B	C	D
Type of inheritance:				

Task 2.9. Answer the questions (use Chapter 14 [pp.78–81] in the textbook "ESSENTIAL MEDICAL BIOLOGY"):

1. What is the difference between autosomal and sex-linked traits?

2. To which groups of chromosomes in human karyotype (from A to G) do sex chromosomes belong?

3. Give examples of X-linked traits in human: _____

4. How many different types of gametes may produce individuals with genotype AA; Aa; aa; X^hY; X^hX^h?

5. How is sex determined in different groups of animals?

6. What is lionization? Why is it called so? _____

7. What is a Barr body? Were can we see it?

TOPIC 3. DI- AND POLYHYBRID CROSS. MENDEL SECOND LAW (LAW OF INDEPENDENT ASSORTMENT)

Law of independent assortment states that allele pairs separate independently during gamete formation, and randomly unite at fertilization.

Law of independent assortment is true only if the genes of interest are situated on different pairs of chromosomes. In anaphase I of meiosis during gamete formation different pairs of alleles segregate independently of each other; then the gametes fuse randomly at fertilization and as a result produce all possible combinations of traits in the offspring.

Performing experiment on dihybrid cross, Mendel took parent pea plants that differ by two traits: colour and shape of the seeds (Fig.8).

Mendel also performed polyhybrid crosses where three or more traits were analyzed.

For example, let's try a cross between AaBbCc and aaBBCc parents. We can set up a **Punnett square**. The Punnett square is a square diagram that is used to predict the genotypes of a particular cross or breeding experiment. It is named after Reginald C. Punnett, who devised the approach.

General formula to find out how many types of gametes may an individual produce is 2^n, where n is number of gene pairs in heterozygous state.

So, the AaBbCc parent produces 2^3=8 types of gametes, and the parent aaBBCc produces 2^1=2 different types of gametes. So, we can get 16 genotypes in the end.

The Punnett square in this case will be:

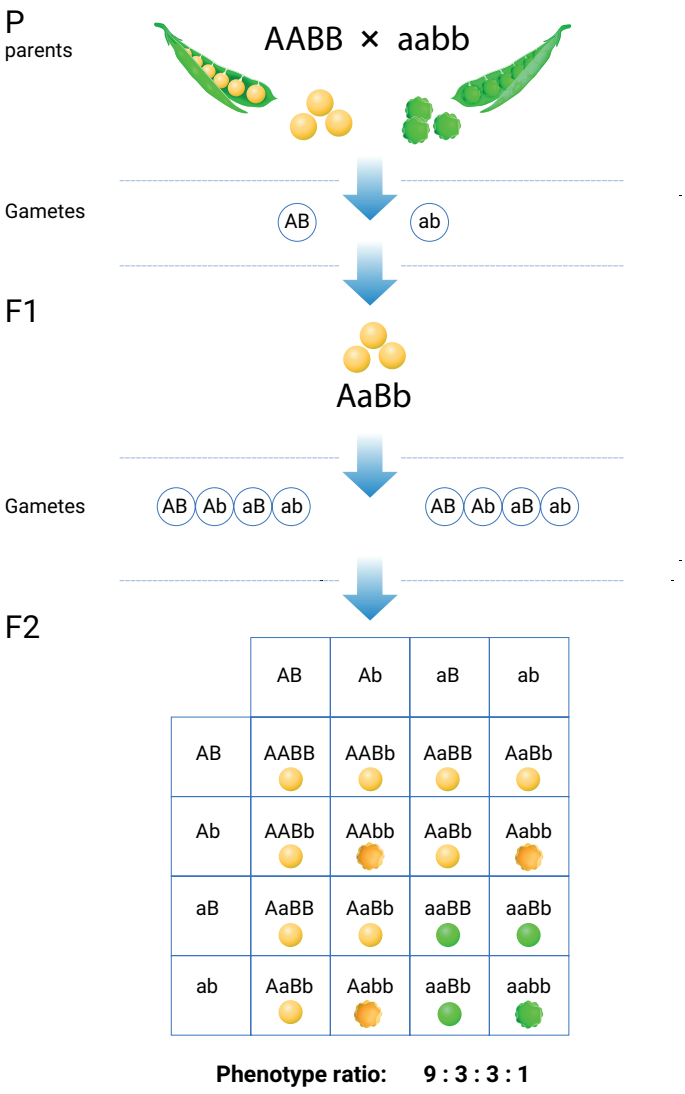


Fig.8. Dihybrid cross

Symbol A stands for yellow colour of seed, a – for green; B – smooth shape of seed; b – wrinkled. He mates true-breeding plants (P) and got in F1 only dominant phenotypes. Then he allowed them to self-fertilize and got in F2 phenotypic ratio 9: 3 : 3: 1.

gametes	ABC	aBC	AbC	abC	ABc	aBc	Abc	abc
aBC								
aBc								

Task 3.1. Write down the genotypes of the offspring into the Punnett square (see above).

Task 3.2. How many different types of gametes can produce individuals with following genotypes below (assume all the gene pairs are situated on non-homologous chromosomes). Write the gametes.

Genotype	Number of types of gametes	Gametes
aaccDD	$2^0=1$	acD
AaBbccddEe		
heterozygous brown-eyed hemophiliac male with blood group AB		

Task 3.3. What is the expected phenotypic ratio of the progeny of a AaBb x aabb test cross?

gametes				

Conclusion: _____

Task 3.4. What might be the parent's genotypes if phenotypic ratio in their offspring is 3:3:1:1? Assume it is a pea plant. Draw the Punnett square.

Designations: _____

_____

Conclusion: _____

_____

Task 3.5. There is a cross between a woman who is diheterozygous A(II)Rh+ and a man who is diheterozygous B(III) Rh+. Write the possible genotypes and phenotypes of their offspring. Draw the Punnett square.

Designations: _____

Task 3.6. In man, the achoo syndrome (sneezing in response to bright light) is an autosomal dominant trait. Daltonism (colour blindness) is X-linked recessive trait. What is the probability that the first child of diheterozygous mom and dad with normal vision and no achoo syndrome will have both abnormal traits? Draw the Punnett square.

Designations: _____

_____

Conclusion: _____

Task 3.7. In humans, polydactyly (having an extra finger on each hand) is dominant to the typical 5-finger arrangement. Tongue rolling is dominant to not being able to roll one's tongue. A man who is homozygous for 5-fingers and who cannot roll his tongue has children with a woman who is heterozygous for polydactyly and tongue rolling. Draw a Punnett square that represents the cross. What is the probability the couple will produce a polydactyl baby who cannot roll their tongue?

Designations: _____

_____

Conclusion: _____

TOPIC 4. GENE LINKAGE. MORGAN EXPERIMENTS

Mendel's second law, or law of independent assortment, failed to be universal. The exception was found in a fly *Drosophila melanogaster*. A system was first developed in Thomas Hunt Morgan laboratory in 1909. The genes for body color and wing size in drosophila were located on the same chromosome. Because of that they did not separate in meiosis and did not give the 1:1:1:1 ratio in the offspring (which was expected according to Mendel's law). Moreover, male fruit flies do not have a crossing over, and females do. Genes that are located on the same chromosome are referred to as **linked genes**.

The results were not the expected 1:1:1:1, but instead, two of the genotypes occurred at a frequency higher than the other two (Fig. 9). The total number of flies in the F1 generation was 2 300, and 391 (17%) of them were recombinant. These results make sense if the two loci are on the same chromosome, and thus their **inheritance is linked**. All the loci on a given chromosome make up a **linkage group**. *Drosophila* has 3 pairs of autosomes and one pair of sex chromosomes. The normal fly is diploid and has 8 chromosomes — 4 linkage groups. There are 23 linkage groups in humans.

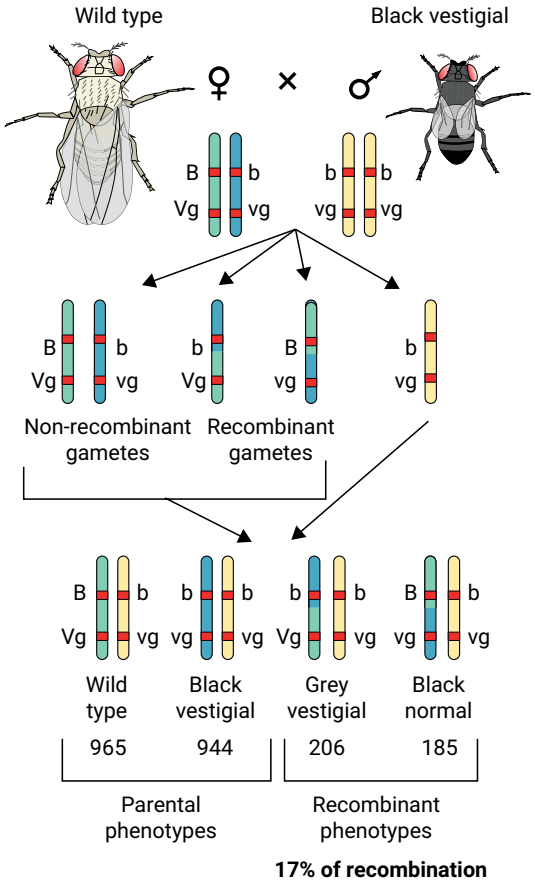


Fig.9. Morgan experiments on linkage of genes. A test cross.

The genotypes were designated as B Vg/b vg (grey body and normal wings – wild type) and b vg/b vg (black body, vestigial wings).

Credit: YassineMrabet – URL: https://ru.wikipedia.org/Sex-linked_inheritance.svg | GNU Free Documentation License (with changes)

Genes can be exchanged between chromatids in meiosis. When two homologous chromosomes physically exchange corresponding segments during **prophase I of meiosis**, geneticists call it **crossing over** (Fig. 10). If just a few exchanges occur, genes that are closer together tend to stay together. Absolute or total linkage of all loci is extremely rare, however. The farther apart on the same chromosome genes are, the more likely they will separate during recombination. In case of male *Drosophila* gene **linkage is complete** because there is no crossing over in *Drosophila* male. In case of *Drosophila* female and most of other organisms including human both males and females crossing over occurs and **linkage is incomplete**.

The **recombination unit** (LMU, Linkage Map Units) was named after Morgan — **centiMorgan** that is 1% of recombination frequency. It always refers to two genes located in the same chromosome. The larger the distance between the loci of two genes in a chromosome, the higher the recombination frequency between these genes. This is true because when alleles are closer together within the chromosome, it is more probable that they will be maintained united when chromosomal ends are exchanged by crossing over. On the other hand, if they are farther apart, it will be easier for them to separate by crossing over.

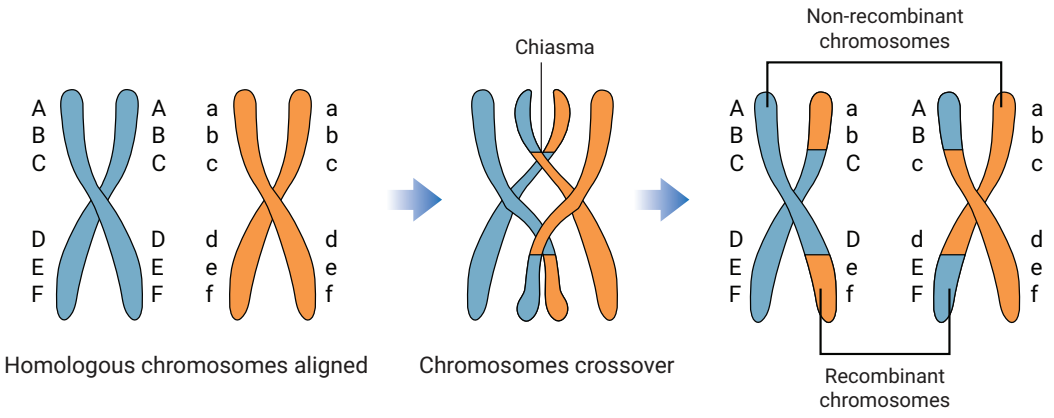


Fig.10. Scheme of crossing over.

Genetic mapping

After Morgan's experiments it became possible to localize genes on chromosomes and to construct gene (chromosome) maps. Genetic mapping is the determination of the location of genes on a chromosome.

By determining the recombination frequency between several different linked genes, it is possible to estimate the distance between them on the chromosome. For example, if a gene A has a recombination frequency of 20% with gene B, gene B has a recombination frequency of 5% with gene C, and gene C has a recombination frequency of 15% with gene A, it is possible to determine that gene A is located at a distance of 20 centimorgans from gene B and that between them lies gene C, located at a distance of 15 centimorgans from gene A.

All **linkage map distances** are calculated as the percentage of recombination between two loci. This is reflected in the percentage of recombinant offspring. If two genes are **completely linked**, all of the offspring will be **parental** (have the same linkage as the parents); there will be no **recombinant** offspring. Thus the linkage map distance between the two genes would be zero **LMU** (**Linkage Map Units**). If the genes are on **separate chromosomes** or on the same chromosome but far enough apart that crossing over between them occurs in virtually all meiosis, half of the offspring will be recombinant, the other half parental. Thus the distance between them would calculate as 50 LMU, and **50 LMU reflects independent assortment**.

Task 4.1. Make a map of a chromosome if it is known that the distance between gene A and gene B is 6 units, and between A and C is 4 units. Also it is known that all the genes belong to the same linkage group and that gene A is located very close to a telomere.

Task 4.2. How many different types of gametes and in what ratio can produce: (a) drosophila male AaBb, A and B linked; (b) drosophila female with the same genotype and recombination frequency 10 cM; (c) hemophiliac and colour-blind man?

#	Genotype	Number of types of gametes	Gametes	Ratio, %
(a)	$\frac{A\ B}{a\ b}$			
(b)				
(c)				

Task 4.3. Put the genes on chromosomes and write down gametes that can produce the following individuals: (a) Drosophila male with genotype AaBbCc if genes A and B are in one linkage group but gene C in another. (b) Drosophila female with the same genotype (recombination frequency 10 cM). (c) Hemophiliac and colour-blind man with blood group AB?

#	Genotype	Number of types of gametes	Gametes
(a)	$\frac{A\ B}{a\ b}\ \frac{C}{c}$		
(b)			
(c)			

Task 4.4. In human, the genes for Rhesus factor and for shape of erythrocytes are linked and belong to linkage group of chromosome 1. The distance between them is 3 cM. Rhesus "+" and oval shape of RBC (elliptocytosis) are dominant traits. A woman is heterozygous for both traits (she has got Rhesus "+" from her mother but elliptocytosis from her father) marries a man who is Rhesus-negative and with normal RBC. What offspring and in what ratio could they have got?

Designations: _____

_____

_____

Task 4.5. Answer the questions (use Chapter 15 [pp.81–85] in the textbook "ESSENTIAL MEDICAL BIOLOGY"):

1. Why do traits segregate independently? Does it always happen? When do they not?

2. Give examples of human traits that are inherited independently:

and

and

3. What is linkage? What is crossing over? How and at which phase in meiosis does this phenomenon happen?

4. What is a linkage group? How many linkage groups are there in humans? In drosophila fly?

5. What is total (complete) gene linkage? Incomplete linkage?

6. Why does the recombination frequency between genes vary depending on the distance between them in the chromosome?

7. How can the concept of recombination frequency be used in genetic mapping?

8. Explain the difference between terms "linked genes" and "sex-linked genes":

9. Give an example of genes in human that are both linked and sex-linked:

TOPIC 5. GENE INTERACTIONS (THE EFFECTS OF GENES ON THE EXPRESSION OF OTHER GENES)

Genes are able to interact in different ways. There are intra-allelic and inter-allelic gene interactions.

Interaction between the alleles of one gene (intra-allelic interactions, or allelic interactions of genes)

- full (complete) dominance
- incomplete (partial) dominance
- codominance
- allelic exclusion
- intra-allelic complementation

Full (or complete) dominance can be illustrated by such examples as yellow colour of pea seeds or Huntington disease in human. In case of complete dominance homo- and heterozygous individuals are phenotypically identical.

Incomplete (partial) dominance (Fig. 11) is seen in cases of snapdragon flowers or in sickle cell anemia in human. Heterozygous individuals have phenotype intermediate between true breeding (homozygous) individuals. Incomplete dominance is typical of quantitative traits.

Codominance (Fig. 12) is seen in qualitative traits and examples of this type of allele interactions are inheritance of blood groups in human – AB group, MN group and some other.

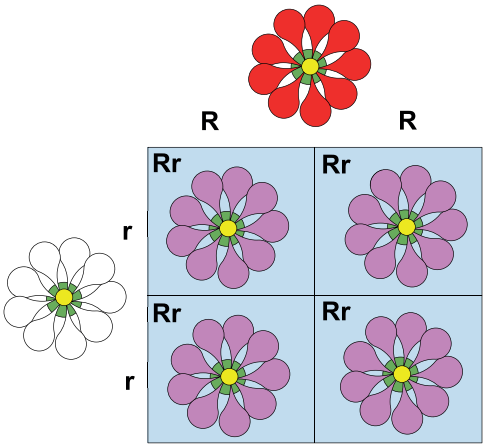


Fig.11. Incomplete (partial) dominance.

Credit: Spencerbaron – URL: https://en.wikipedia.org/wiki/File:Incomplete_dominance.svg. CC BY-SA 3.0 license

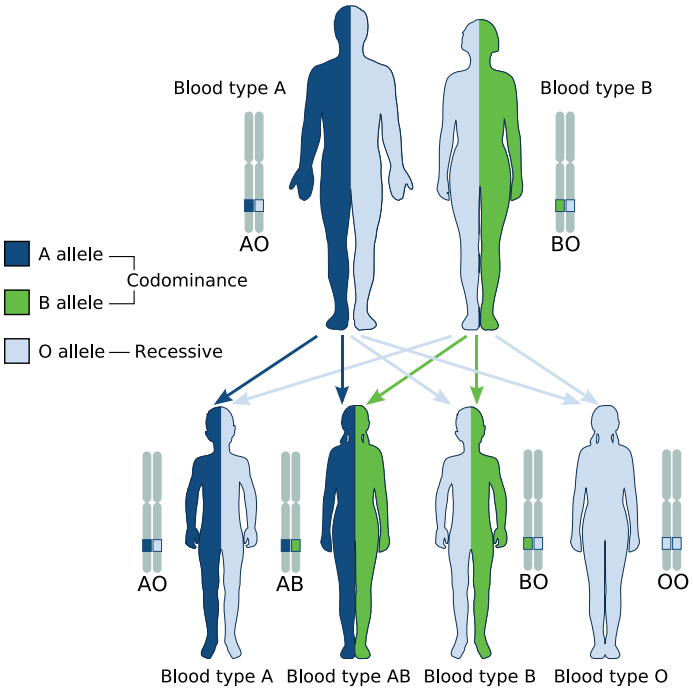


Fig.12. Codominance example.

Credit: National Institutes of Health.

Allelic exclusion is a process by which only one allele of a gene is expressed in particular cells while the other allele is expressed in other cells of the organism. We can say the individual is mosaic. Examples of allelic exclusion are X-linked traits in mammal female or genes coding for antibodies in B-lymphocytes of immune system.

Intra-allelic complementation is observed when proteins are built of identical subunits encoded by one gene. In a heterozygote of two different mutant alleles of this gene happens restoration of activity (or partial activity) of the protein. Examples are not common; in human heterozygote HbS/HbC have lighter form of anemia than homozygotes HbS/HbS or HbC/HbC. "S" and "C" stand for different mutant forms of hemoglobin.

Task 5.1. Which type of allelic interaction are the following examples?

Blood group B (genotype I^BI^0)	
Marfan's syndrome	
Woman heterozygous for hemophilia	
Wavy or gently curled hair in a child of a straight-haired and a curly-haired persons	

Interaction between the alleles of different genes (inter-allelic interactions, or non-allelic gene interactions).

- inter-allelic complementation
- epistasis
- polygenic inheritance (polymeric genes)
- effect of modifier genes
- position effect

Inter-allelic complementation is a very common type of non-allelic gene interactions. Dominant alleles of two or more genes interact to produce a particular phenotype.

An example of complementary gene interaction is flower colour in sweet pea. Interactions of the C and P genes will give purple colour of flowers. Otherwise the flowers are white (Fig. 13).

In human an example of inter-allelic complementation is normal hearing. In a simplified form, there are two genes — D and E that together produce normal hearing. If a person has only D or E he or she is deaf.

Epistasis means that allele of one gene can hide the trait caused by another gene(s). If dominant allele A masks the expression of gene B (A is an epistatic gene) the situation is referred to as dominant epistasis. If epistatic is recessive allele a — it is recessive epistasis.

An example of **dominant epistasis** is found for fruit colour in summer squash. There are three types of fruit colours in this cucumber, viz., white, yellow and green. Dominant gene W is epistatic to gene G (yellow) and its recessive allele g (green), so that fruits are white. Allele w does not suppress the colour of summer squash.

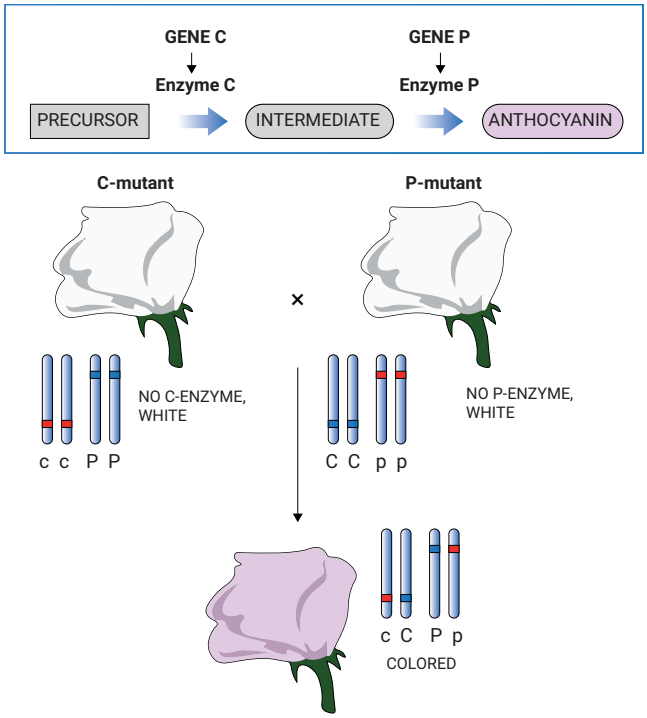


Fig.13. Inter-allelic complementation.

Task 5.2. What color will have sweet pea plants with following genotypes? What type of gene interaction is that?

ccpp	
Ccpp	
CCpp	
CcPp	
ccPP	

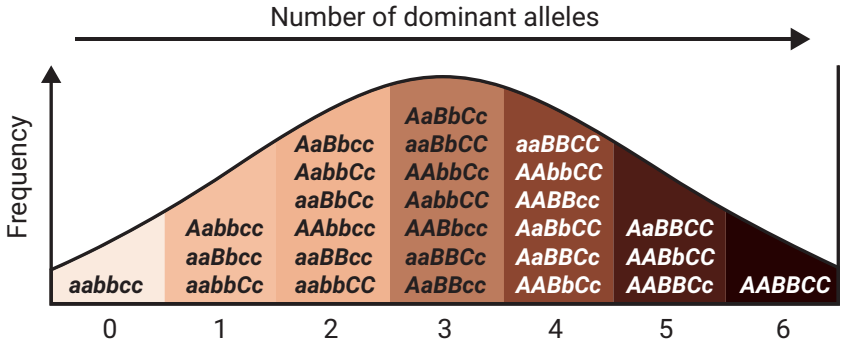


Fig.14. Polygenic inheritance example – skin color variations.

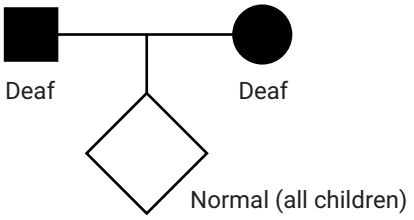
One of examples of r**ecessive epistasis** in human is known as **"Bombay phenomenon"**. The probability of finding a person with Bombay blood type is 1 for every 250,000 people. India has the highest number of people with the Bombay blood group where there is one Bombay blood type per 7,600 people. Geneticists believe that the high number of Bombay blood group people in India is the result of consanguineous marriage among members of a caste class. Higher caste class allows consanguineous marriage to maintain their position in the society and to protect their wealth. **In case of Bombay phenomenon recessive allele h in homozygous state masks A and B blood group phenotypes**. The H antigen is located on the surface of red blood cells and is the precursor of A and B antigens. A person with the Bombay blood group inherited the recessive form of the allele for the H antigen from each of his/her parents. As a result, the H antigen is not expressed in the red blood cell surfaces; consequently, the A and B antigens are not formed.

Polygenic inheritance means that two or more non-allelic genes result in the same phenotype. In humans, height, weight, and skin color are examples of polygenic inheritance. For instance, the height of an adult human is determined by more than 400 genes apart from the other non-genetic factors such as environment and nutrition.

Modifier genes produce secondary and more subtle effect on phenotype. For example, in horses the dominant allele E produces black pigment in the coat, while the recessive allele e produces red pigment. All horses with genotype ee are therefore red, yet there are many different types of red horses. These differences exist because of the action of modifier genes. One such modifier gene is called **cream dilution**. The cream dilution gene has two alleles: C^{CR} and C. The C^{CR} allele dilutes red to yellow in the heterozygous state and red to pale cream in the homozygous state. On the other hand, the C allele has no diluting effect on coat color. Thus, horses with genotype eeCC are chestnut colored, and they have reddish-brown coats, tails, and manes. In contrast, horses with one copy of the C^{CR} allele (genotype eeCC^{CR}) are palomino (i.e., they have a gold coat with a white mane and tail), while horses with two copies of the C^{CR} allele (genotype ee $C^{CR}C^{CR}$) are cremello (i.e., basically white or cream colored).

Position effect is the effect in which the expression of a gene is influenced by its interaction with adjacent genes on a chromosome. This has been demonstrated in *Drosophila* eye color. Because of a chromosomal translocation the gene for eye color is now close to a region of heterochromatin. The heterochromatin can spread stochastically and switch off the color gene resulting in the white eye sectors.

Task 5.3. Deaf parents have many children. All of them have normal hearing. Give an explanation for that and write down the genotypes of the parents and the offspring. What type of non-allelic gene interaction is that?



Task 5.4. What blood group will have the offspring of parents with genotypes HhI^AI^0 and HhI^BI^0? Make a Punnett square. What type of gene interaction is it?

Task 5.5. In horses, allele G is epistatic to gene E (hypostatic gene). All the individuals having G are grey. Allele g does not suppress either allele E (black coat of horse) or e (red coat). In numerous crosses of a grey stallion with black mares of the same genotypes the following phenotypic ratio was found in offspring: 4/8 grey: 3/8 black: 1/8 red. What are the genotypes of the parental horses?

Task 5.6. In humans, gene P is responsible for skin pigmentation. Its recessive allele p causes albinism. The type of gene interaction between P and p is a full (complete) dominance. On the other hand, the amount of pigment (A) is an example of polygenic inheritance with numerous non allelic genes that demonstrate interaction of incomplete dominance. If we limit ourselves to two genes A_1 and A_2 then black Africans will have the genotype $A_1A_1A_2A_2$, white Europeans $a_1a_1a_2a_2$, and individuals with different combinations of dominant and recessive A will be referred to as mulattos. What skin colour may have children if the parental genotypes are $PpA_1A_1A_2a_2$ and $PpA_1a_1a_2a_2$? Assume that 4A is black, 3A1a – dark mulatto, 2A2a – medium mulatto, 1A3a – light mulatto, 4a – white and pp genotype – albino. Draw a Punnett square. What type of gene interaction is it?

Task 5.7. What color might have the offspring of a cross $EeCC^{CR}$ x $eeCC^{CR}$? Draw the Punnett square. What type of gene interaction is it?

Task 5.8. For each of the terms in the column A, choose the best matching phrase in the column B.

COLUMN A	COLUMN B
(1) Epistasis	(a) One gene affecting more than one phenotype
(2) Modifier gene	(b) The alleles of one gene mask the effects of alleles of another gene
(3) Reduced penetrance	(c) Both parental phenotypes are expressed in the F1 hybrids
(4) Polygenic trait	(d) A heritable change in a gene
(5) Incomplete dominance	(e) Genes whose alleles subtly alter phenotypes produced by the action of other genes
(6) Codominance	(f) Less than 100% of the individuals possessing a particular genotype express it in their phenotype
(7) Mutation	(g) A trait is produced by the interaction of alleles of at least two genes
(8) Pleiotropy	(h) The heterozygote resembles neither homozygote

A	1	2	3	4	5	6	7	8
B								

Task 5.9. Answer the questions (as a help to answer the questions read in the textbook ESSENTIAL MEDICAL BIOLOGY Chapter 16 (pp.85–90) :

1. Explain the difference between allele and non-allele genes.

2. Define incomplete dominance and give examples of it.

3. Tortoiseshell cats are almost exclusively females. Tortoiseshell cats have coats with patches of yellow and black. The gene encodes these traits is X-linked. Which type of gene interaction do tortoiseshell cats illustrate?

4. Can two tortoiseshell cats have identical pattern of patches? How does Layon's hypothesis explain this?

5. Explain the difference between dominance and epistasis. How many loci are involved in each case?

6. Explain the difference between codominance and inter-allelic complementation. How many loci are involved in each case?

7. Is it possible for two mulattos have kids with skin lighter or darker than their parents'?

8. What type of gene interaction does the Bombay phenomenon illustrate?

TOPIC 6. GENETICS AND ENVIRONMENT. POPULATION GENETICS. TWIN STUDIES. GENETIC COUNSELING

Variable expressivity and penetrance

A gene itself carries only the possibility of development of a trait. Phenotypic variations may result from the effects of other genes or environmental conditions. Genes are said to have **variable expressivity** if they vary in the levels of expression in different individuals. The second form of variation in the expression of a gene is **variable penetrance**. Penetrance is defined as the proportion of individuals whose phenotype matches their genotype for a given trait. A genotype that is always expressed has a penetrance of 100 percent. These terms do not explain what exactly influences the gene expression; they just state the fact.

Suppose that ten individuals (Fig. 15) have the same hypothetical dominant gene ("coloured body") in their genotype. But three of them do not express it at all. In this case we can say that the penetrance of the gene is 70%. Other seven individuals have the trait but in different degree. We say that the trait demonstrates variable expressivity.

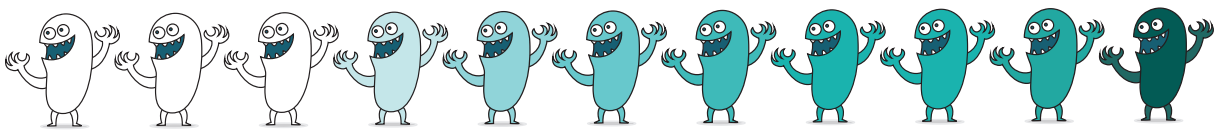


Fig.15. Variable expressivity and penetrance.

Task 6.1. In humans, gout is determined by an autosomal dominant allele that demonstrates 20% penetrance in males while in females its penetrance is 0%. What is the probability to have the disease for offspring of heterozygous parents?

Relationship between gene and trait

Phenotype of an organism is the result of the actions of many genes in combination with the environment. **Polygenic inheritance** refers to the inheritance of a phenotypic characteristic (**trait**) that is attributable to two or more genes and can be measured quantitatively. **Multifactorial inheritance** refers to **polygenic inheritance** that also includes interactions with the environment (Fig. 16).

Multifactorial inheritance

Many diseases are inherited as **multifactorial traits**. In such cases, a multifactorial predisposition to the disease is inherited, and the disease either occurs or does not occur, depending on the aggregate strength of the predisposing factors.

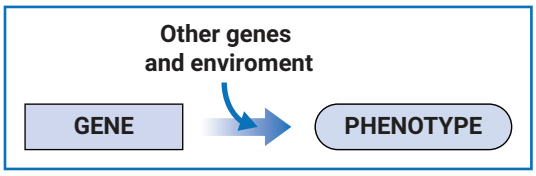


Fig.16. Gene(s) and environments.

Diseases Transmitted as Multifactorial Traits:

- Most isolated congenital anomalies appear to be multifactorial traits. Examples include cleft lip with or without cleft palate, congenital heart disease, and anencephaly.

- Many common diseases of adulthood also seem to be multifactorial traits. Non-insulin-dependent diabetes mellitus, arteriosclerotic heart disease, asthma, obesity, and psoriasis are examples of multifactorial traits.

Twin studies

Measuring the heritability of multifactorial traits in humans is a complex problem. The most useful approach is to compare the phenotypic differences between pairs of monozygotic and dizygotic twins (Fig. 17).

In humans, twins occur once in every 89 deliveries and there are two types of twins. **Monozygotic** (identical) contribute 33% of them and have identical genotypes, **dizygotic** (non-identical) contribute 67% and have on average one-half of their genes in common.

Twins are **concordant** if they both show a trait, and **discordant** if only one shows the trait. If a condition has no genetic component, for example road traffic accidents or highly contagious viral infection concordance rates are similar for both types of twins. The traits that are under a greater degree of genetic influence will show a high concordance rate in monozygous twins and low rate in dizygous twins. Example may be eye colour, or blood group. Environmental factors can alter the way our genes are expressed, making even identical twins different.

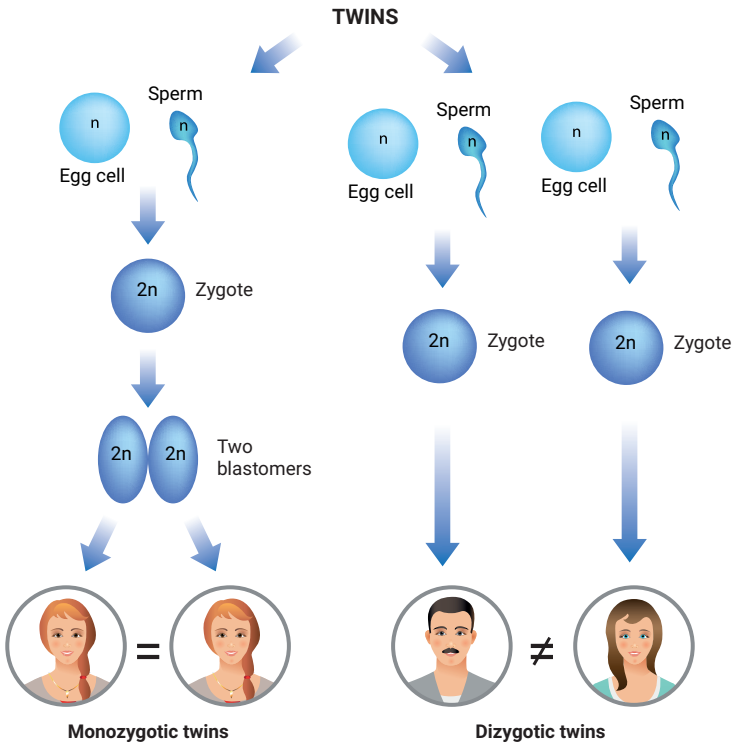


Fig.17. Mono- and dizygotic twins.

Task 6.2. Calculate the heritability coefficient of three different traits. Use the formula:

$$H = C_{MT} - C_{DT}/100\% - C_{DT}, \qquad C_{MT} + C_{DT} = 100\%,$$

where H – heritability coefficient, C_{MT} – concordance for monozygous twins, C_{DT} – concordance for dizygous twins. Make a conclusion about the predominant role of environment or heredity for the trait. If the result (H) is close to 1 – the trait has genetic cause; if the H is close to zero – the trait is caused by environment. if H is about 0.5–0.7 – there is high degree of genetic predisposition for the trait. Use the sample solution given below.

Trait	C_{MT}	C_{DT}	H	Conclusion
Endemic goiter	71%	70%	H = (71% – 70%)/ (100% – 70%)= 0.33	The external environment plays a predominant role in the formation of the trait
Eye colour	99%	28%	H = (99% – 28%)/ (100% – 28%)= 0.99	Genetics plays the main role in the formation of the trait
Measles	97%	96%		
Cancer	17%	11%		
Cleft lip ± cleft palate	35%	5%		

Epilepsy	37%	10%		
Tuberculosis	87%	26%		

Task 6.3. For each of the terms in the column A, choose the best matching phrase in the column B.

COLUMN A	COLUMN B
(1) Reduced penetrance	(a) One gene affecting more than one phenotype
(2) Multifactorial trait	(b) Is used to investigate the role of genetics and enviroments in phenotype of a trait
(3) Incomplete dominance	(c) A heritable change in a gene
(4) Mutation	(d) Less than 100% of the individuals possessing a particular genotype express it in their phenotype
(5) Pleiotropy	(e) A trait produced by the interaction of alleles of at least two genes
(6) Mendelian trait	(f) They have identical genotypes (identical twins)
(7) Polygenic trait	(g) Variation in traits caused by genetic and environmental factors
(8) Monozygotic twins	(h) The heterozygote resembles neither homozygote
(9) Dizigotic twins	(i) A trait completely determined by a single gene
(10) Method of twin study	(j) They share environment and 50% of genes, fraternal twins

A	1	2	3	4	5	6	7	8	9	10
B										

Task 6.4. Answer the questions (as a help to answer the questions read in the textbook ESSENTIAL MEDICAL BIOLOGY Chapters 17 (pp.90 – 94):

1. What is the difference between identical and non-identical (fraternal) twins?

_____

_____

2. What can twin concordance method tell about the relative role of environmental and genetic influences on traits?

_____

3. In what case the concordance rates are similar for both types of twins?_____

_____

4. What is polygenic inheritance? _____

5. Give examples of polygenic traits in human: _____

6. Give examples of multifactorial traits in human: _____

7. What is a multifactorial trait?

Population genetics

The Hardy-Weinberg law is used to relate the frequencies of alleles and genotypes at a single mendelian locus to the **phenotype frequencies in an "ideal" population**. In the population the relative frequencies of different alleles tend to be maintained constant from one generation to the next.

The assumptions upon which the Hardy-Weinberg law is based are:

- There is no mutation occurring at the locus.
- There is no selection for any of the genotypes at the locus.
- Mating is completely random.
- There is no migration into or out of the population being considered (Migration is the movement of individuals between populations. Migration can result in exchange of genes between populations and alteration of gene frequencies.).
- Population is very large.

If there are two alleles of a gene in a population, there are three possible genotypes — homozygous (*AA, aa*) for each of the two alleles and heterozygous (*Aa*). The frequency of the two alleles in the population is usually represented by the letters ***p(A)*** and ***q(a)***. The total frequency of the alleles in the population $\boldsymbol{p} + \boldsymbol{q} = \mathbf{1}$. If there is random mating in a population, the chance of inheriting two copies of allele *A* is $\boldsymbol{p} \times \boldsymbol{p}$. The chance of inheriting two copies of allele *a* is $\boldsymbol{q} \times \boldsymbol{q}$. The expected frequency of the two homozygous genotypes is therefore $\boldsymbol{p^2(AA)}$ and $\boldsymbol{q^2(aa)}$. The expected frequency of the heterozygous genotype is $\mathbf{2}\boldsymbol{pq(Aa)}$. The sum of all of these frequencies is 1, so $\boldsymbol{p^2} + \mathbf{2}\boldsymbol{pq} + \boldsymbol{q^2} = \mathbf{1}$.

Evolution consists of changes in allele frequency over time. Some populations are not very large, individuals do not always mate at random, new mutations do arise, there is migration into and out of the population, and different genotypes do have differences in fitness.

Task 6.5. Phenylketonuria (PKU) shows autosomal recessive inheritance with an incidence of 1 in 10 000. Assume that the population is in Hardy-Weinberg equilibrium. What is the carrier frequency in the population?

Task 6.6. Which of the following populations are in Hardy–Weinberg equilibrium?

Population	AA	Aa	aa
A	0.25	0.50	0.25
B	0.10	0.74	0.16
C	0.64	0.27	0.09
D	0.81	0.18	0.01

Task 6.7. Answer the questions (as a help to answer the questions read in the textbook ESSENTIAL MEDICAL BIOLOGY Chapter 18 (pp.94–97).

1. Define the Hardy-Weinberg law _____

2. What factors can cause a departure of the population from the Hardy–Weinberg equilibrium?

Congenital anomalies

Congenital anomalies are defects of development found at birth. **Frequency of congenital anomalies** is about 2% of newborns. Congenital anomalies in different individuals may have different causes. This phenomenon is called **etiologic heterogeneity**. In general, etiology is unknown in up to 60% of cases, 20–25% birth defects are multifactorial, 7–10% caused by environmental factors (teratogens), 7–8% monogenic (caused by a mutation of a single gene) and 6–7% have chromosomal origin (numerical or structural chromosomal mutations).

A **congenital physical anomaly** is an abnormality of the structure of a body part.

- Many people have one or more **minor physical anomalies** if examined carefully (Fig. 18). Examples of minor anomalies can include curvature of the 5th finger (clinodactyly), a third nipple (polythelia), tiny indentations of the skin near the ears (preauricular pits), or dimples over the lower spine (sacral dimples). Some minor anomalies may be clues to more significant internal abnormalities.
  - **Birth defect** is a widely used term for a congenital anomaly which is recognizable at birth, and which is **significant enough to be considered a problem**. An example of a birth defect is cleft palate, which occurs during the fourth and seventh week of gestation. Body tissue and special cells from each side of the head grow toward the center of the face. They join together to make the face. A cleft means a split or separation.
- When **multiple effects** occur in a specified order, it is known as a sequence. When the order is not known, it is a syndrome.

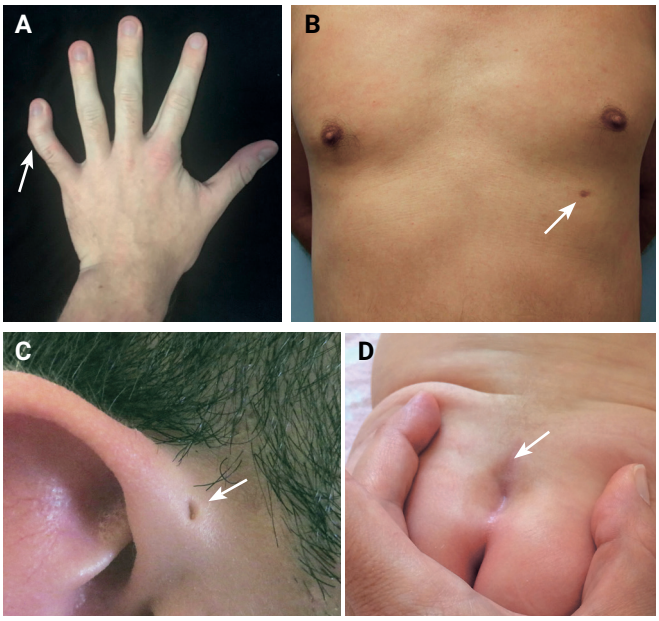


Fig. 18. Minor anomalies:
(A) clinodactyly; (B) polythelia; (C) preauricular pit; (D) sacral dimple.

Credits: (A) TheFrenchTickler1031 – URL: https://commons.wikimedia.org/wiki/File:SampleClinodactyly.jpg – License CC BY-SA 4.0. (B) Grimshaw E.C. & Cohen P.R. (2013). Supernumerary nipple and seminoma: Case report and review of polythelia and genitourinary cancers. Dermatology Online Journal, 19(1). (C) Smooth_O – https://commons.wikimedia.org/wiki/File:Preauricular_sinus.jpg – License CC BY-SA 3.0. (D) Sacral Dimple. Diseases & Conditions 2018. – URL: https://medicalfoster.com/sacral-dimple.

Examples of congenital disorders:

- A limb anomaly is called a **dysmelia**. These include all forms of limbs anomalies, such as polydactyly, syndactyly, oligodactyly, brachydactyly, achondroplasia, and others (Fig. 19).
- **Congenital anomalies of heart** include patent ductus arteriosus, atrial septal defect, ventricular septal defect, and others.
- **Congenital anomalies of the nervous system** (Fig. 20) include neural tube defects such as spina bifida, anencephaly and others.

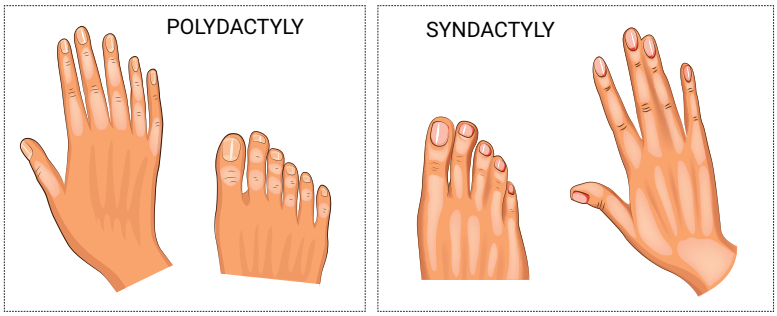


Fig. 19. Dysmelia examples.

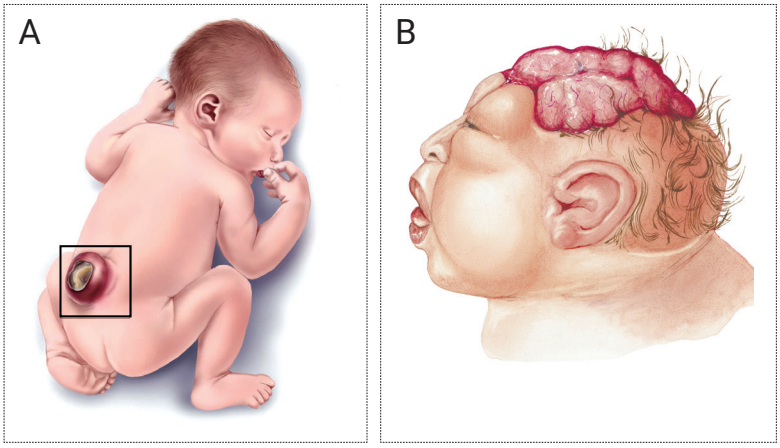


Fig. 20. Congenital anomalies of the nervous system.

(A) Spina bifida. Credit: Centers for Disease Control and Prevention, US Department of Health and Human Services
(B) Anencephaly. Credit: Medicalartinc | Dreamstime.com

Task 6.8. For each of the terms in the column A, choose the best matching phrase in the column B.

COLUMN A	COLUMN B
(1) Polydactyly	(a) Number of fingers less than normal
(2) Syndactyly	(b) Excessive number of fingers and/or toes
(3) Brachydactyly	(c) Incomplete closing of the spine and membranes around the spinal cord
(4) Achondroplasia	(d) Fusion of fingers
(5) Patent ductus arteriosus	(e) Absence or underdevelopment of the brain
(6) Oligodactyly	(f) Abnormally short fingers and toes
(7) Atrial septal defect	(g) The presence of a duct between the aorta and the pulmonary artery
(8) Spina bifida	(h) A form of dwarfism in which the arms and legs are short, while the torso is typically of normal length
(9) Anencephaly	(i) Foramen ovale is not closed in this condition

A	1	2	3	4	5	6	7	8	9
B									

Genetic counseling

Genetic counseling is the communication of information and advice about inherited conditions. **The counselor** in medical genetics generally uses nondirective counseling. For a couple or a **family seeking the counseling (consultands)**, the information received may have long-term consequences and will often be used as part of the information necessary for decision-making.

Different methods of human genetics may be used for genetic counseling:

- making a genealogical tree
- cytogenetic study
- DNA analysis methods
- prenatal diagnosis techniques

Indications for genetic counseling may change with time as new methods of diagnostics become available or as specific therapies are developed. The most common indications include:

1. Advanced maternal age (prenatal diagnosis is offered to pregnant women at the age of 35 years or older)
2. Known or suspected hereditary condition in the family.
3. A fetus or child with birth defects, including both single and multiple malformations.
4. Mental retardation of a child.
5. Recurrent spontaneous abortions.
6. Exposure to known or suspected teratogens.
7. Consanguinity.

The purpose of genetic counseling is to enable a consultand to understand:

- The medical diagnosis and its implications in terms of prognosis and possible treatment
- The mode of inheritance of the disorder and the risk of developing and/ or transmitting it
- The choices or options available for dealing with the risks

Steps in genetic counseling:

1. Establishing the diagnosis.

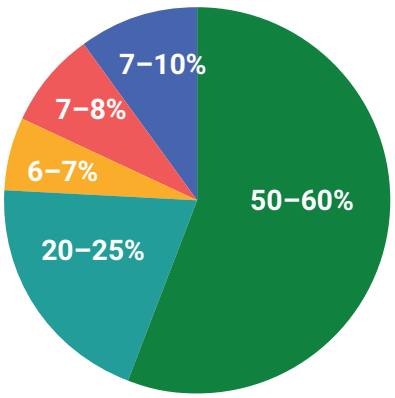
   Generally, there are three main groups of genetic disorders:

   - **Monogenic diseases** (achondroplasia, cystic fibrosis, hemophilia, PKU, and others). In this case, to calculate the recurrence risk a **family tree construction** is needed. A more accurate method is direct **DNA analysis**.
   - **Chromosomal diseases** (Down's syndrome, Patau syndrome, different structural abnormalities of chromosomes, and others). To decide the risk biochemical tests and **cytogenetic study** has to be performed. Recently, highly effective methods based on **DNA (genome) sequencing technologies** for testing fetal chromosomal abnormalities have been developed.
   - **Multifactorial diseases** (diabetes mellitus, rheumatoid arthritis, and others) The risk is calculated on **base of empiric data**.
2. Calculating and presenting the risk.
3. Discussing the options.

Consultands should be provided with all of the information necessary for them to make their own informed decisions. The decision could be:

- to have children despite the risk;
- not to have children at all;
- to use donor sperm,
- to use donor egg cell,
- to break the marriage and enter into another;
- to adopt a child;
- to use in vitro fertilization with the selection of a healthy embryo;
- to have a prenatal diagnosis during pregnancy.

Task 6.9. Guess which group of congenital disorders (unknown; multifactorial; chromosomal; monogenic; environmental) are shown in the diagram.



Color	Group of congenital disorders
Green	
Red	
Blue	
Yellow	
Cyan	

Task 6.10. Put the following conditions into one of three columns. Achondroplasia, Down's syndrome, hypertonia, "Cat cry" syndrome, Patau syndrome, Turner's syndrome, Marfan's syndrome, hemophilia, sickle cell disease, cleft lip and/or palate, congenital heart disease, neural tube defect, diabetes mellitus, cystic fibrosis, cancer, Edwards' syndrome.

Monogenic diseases	Chromosomal diseases	Multifactorial diseases

Task 6.11. Calculate the genetic risk for the next children in the family in case of monogenic disorder:

1. A 28-year old woman has a son suffering from Duchenne muscular dystrophy (DMD). Her husband, two her brothers and her sister are healthy, but her uncle (mother's brother) died at age 20 of DMD. Do a counseling session to the family. Draw a family tree. What is the risk of disease for next child in the family?

2. A couple comes to ask you about the probability to have children with normal height. They both are achondroplastic. Consult the family.

Task 6.12. Calculate the genetic risk for the next children in the family in case of chromosomal disorder:

1. Two couples have babies with Down syndrome (karyotype47, XY, 21+). The first couple is at the age of 20, and the second – 41. Consult the families.

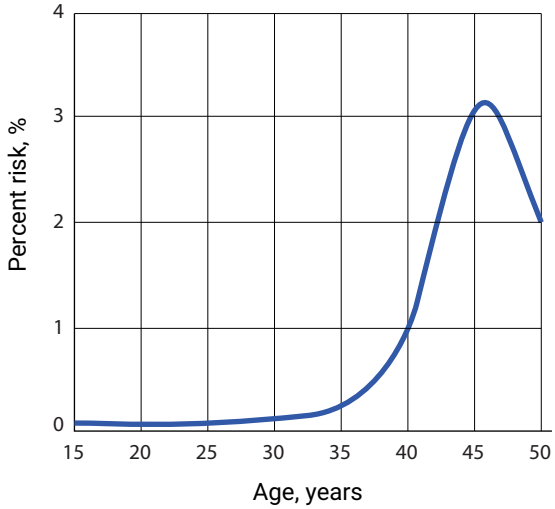


Fig. 20. The risk of having a Down syndrome pregnancy in relation to a mother's age.

[Morris et al. Journal of Medical Screening. 2002. 9 (1): 2–6.]

2. A young woman with normal chromosomal complex comes to a genetic counselor. Her first pregnancy finished at 12th week with spontaneous abortion. Two years later she delivered a girl with multiple congenital malformations (karyotype 46, XX, del 5p). The woman's husband has a balanced translocation (karyotype 46, XY, t (5p-/10p+). Provide consultation to the family.

Task 6.13. Calculate the genetic risk for the next children in the family in case of multifactorial disorder. Use the tables of empiric risk.

1. A young and healthy couple would like to know the risk of having a baby with neural tube defect. One of their first-degree relatives has spina bifida. Provide consultation to the family. The type of neural tube defect can differ the second time. For example, a family's first baby could be born with anencephaly. A second baby could have spina bifida instead.

Table 1. Risk for having a neural tube defect for newborn

Malformation	Incidence in general population	Incidence relative to general population		
		Monozygotic twins	First degree relatives	Third degree relatives
Neural tube defect	0.002	x200	x8	x2

2. A couple has a child who suffers from a serious heart disorder – tetralogy of Fallot. The parents are anxious if their next child could have the same disease. Provide consultation to the family.

Table 2. Risk for sibling of an individual with a congenital heart defect to have the same heart defect

Congenital heart defect	Risk (%)
Patent ductus arteriosus	3
Ventricular septal defect (all types)	3
Transposition of the great vessels	2
Coarctation of the aorta	2
Tetralogy of Fallot	2

Methods of prenatal diagnosis

Prenatal diagnosis employs a variety of techniques to determine the health and condition of an unborn fetus.

Preimplantation genetic testing: The technique is used on embryos created through **in vitro fertilization (IVF)** before pregnancy. Preimplantation genetic diagnosis (PGD) refers specifically to when one or both genetic parents has a known genetic abnormality and testing is performed on an embryo to select healthy embryos without this genetic abnormality.

Non-invasive methods:

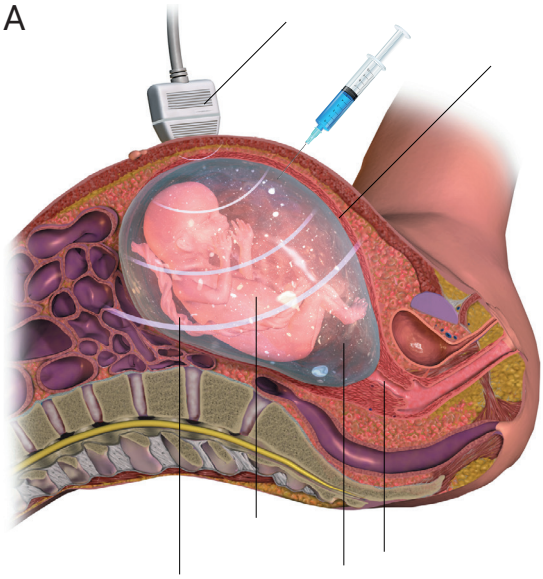
- **Ultrasound examination** helps to diagnose dating of pregnancy, investigating of bleeding, determining viability of fetus, determining the presence of twins, determining placental position, screening for fetal anomalies, and so on.
- **Biochemical analisys of maternal blood** allows to set gestational age and indicate some abnormalities of a fetus: α-fetoprotein (MSAFP), pregnancy-related plasma A-protein (PAPP-A), chorionic gonadotropin (hCG), etc.
- **Fetal cell screening in maternal blood.** Screening is performed using fetal cells isolated from maternal peripheral blood samples.

Invasive methods:

- **Chorionic villus sampling** (CVS) is a first-trimester method of prenatal diagnosis involving either transcervical or transabdominal biopsy of the developing placenta.
- **Amniocentesis** involves the aspiration of amniotic fluid with a fine gauge spinal needle for amniotic fluid cell culture and analysis of it. As with CVS, the technique should be done under ultrasound control. Amniocentesis is performed between the 15th and 20th week of pregnancy..
- **Chordocentesis**, or fetal blood sampling, involves percutaneous puncturing of the umbilical cord near the placental insertion with a spinal needle under ultrasound guidance. The procedure is done from 17 weeks of gestation to near term.

Samples obtained using invasive methods are tested for genetic disorders by cytogenetic analysis, biochemcal analysis, or DNA analisys, like allele-specific polymerase chain reaction (PCR), DNA sequencing, etc. The option to continue or abort a pregnancy is the primary choice after most prenatal testing. Rarely, fetal intervention corrective procedures are possible.

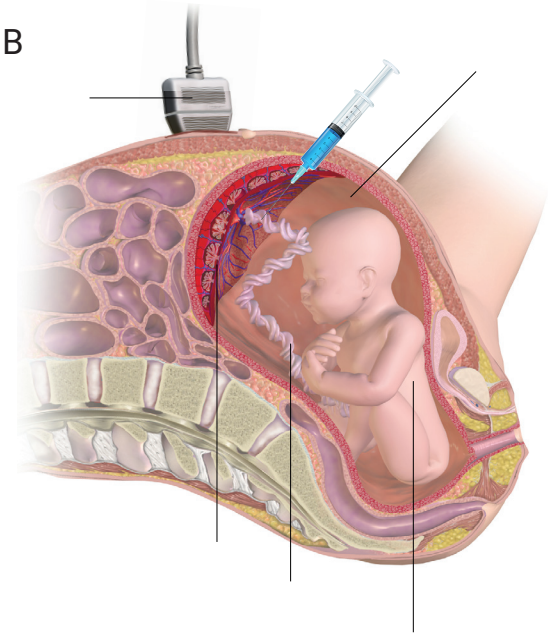
A



Task 6.14. Determine what types of invasive procedures are shown in the figures* below. At what stage of pregnancy are these methods used. Mark the (1) placenta, (2) amniotic fluid, (3) chorion, (4) fetus, (5) cervix, (6) ultra-sonograph, and (7) umbilical cord.

Method of sampling	
Gestational age when the method is used	

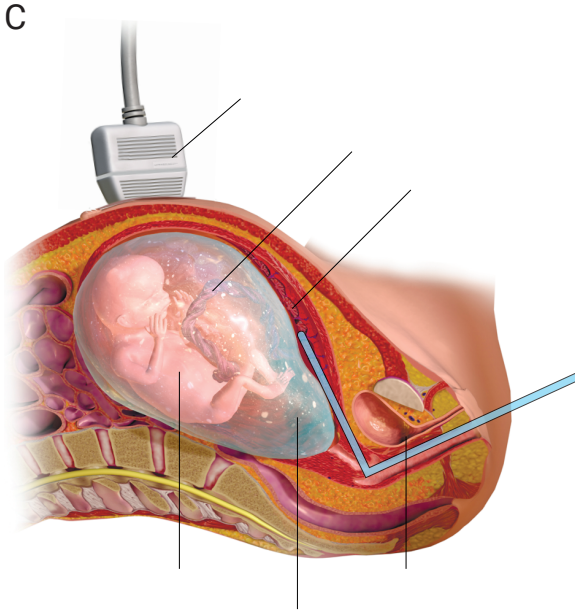
B



Method of sampling	
Gestational age when the method is used	

* Credit: BruceBlaus | commons.wikimedia.org | CC BY-SA 4.0

C



Method of sampling	
Gestational age when the method is used	

Task 6.14. Answer the questions (as a help to answer the questions read in the textbook ESSENTIAL MEDICAL BIOLOGY Chapters 19, 20 and 21 (pp.97–105)::

1. What is genetic counseling? What are the goals of genetic counseling?

2. What are the indications for genetic counseling?

3. How to calculate genetic risk for monogenic disorders; chromosomal disorders; multifactorial disorders?

4. What methods of prenatal testing do you know?

5. Explain amniocentesis and CVS.

6. Why the advanced maternal age is an indication for genetic counseling?

7. Discuss the feelings that a family may have and think how to help them.

8. Genetic counseling is said to be nondirective. What do you think of this?

9. What options are available to individuals and couples at risk for a genetic disease?

10. Females with Down syndrome are sometimes fertile. A 20-year-old woman has Down syndrome due to trisomy for chromosome 21. She wants to have a child. What is the probability that the child will have Down syndrome?

11. Huntington disease is a rare fatal, degenerative neurological disease in which individuals start to show symptoms, on average, in their 40s. It is caused by a dominant allele. Joe, a man in his 20s, just learned that his father has Huntington disease. What is the probability that Joe will also develop the disease? Joe and his wife are anxious to have children. There are genetic tests developed to find out if the person has the defective allele. Discuss the options that the couple has.

QUESTIONS TO THE COLLOQUIUM

1. Define: genes, alleles, multiple allelism, heterozygote, homozygote, hemizygote.
2. Mendel's first law – the principle of segregation.
3. Multiple allelism. ABO blood group inheritance
4. Test cross and back cross.
5. Mendel's second law – the principle of independent assortment.
6. Autosomal dominant inheritance. Typical features. Clinical examples.
7. Autosomal recessive inheritance. Clinical examples.
8. Sex-linked inheritance. Sex determination in animals and humans.
9. X-linked dominant inheritance. Clinical examples.
10. Y-linked holandric inheritance.
11. X-linked recessive inheritance. Clinical examples.
12. Non-Mendelian inheritance. Cytoplasmic (mitochondrial) inheritance) and others.
13. Linkage and recombination of genes in chromosome. Complete and incomplete linkage.
14. Linkage groups. Crossing over and chromosome mapping.
15. Interaction of allelic genes. Examples.
16. Interactions of non-allelic genes. Examples.
17. Multifactorial inheritance. Variable expression and penetrance of genes.
18. Twin studies method in human genetics.
19. Frequency and etiology of congenital abnormalities.
20. Genetic counseling. Indications for genetic counseling.
21. Prenatal diagnostic techniques.
22. Population genetics. Hardy-Weinberg law.

FOR NOTES

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