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С. А. Жадан, Д. М. Попутников, Ф. И. Висмонт

РОЛЬ НАСЛЕДСТВЕННОСТИ В ПАТОЛОГИИ

THE ROLE OF HEREDITY IN PATHOLOGY

Учебно-методическое пособие

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Жадан Светлана Анатольевна
Попутников Дмитрий Михайлович
Висмонт Франтишек Иванович

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Ответственный за выпуск Ф. И. Висмонт
Переводчик С. А. Жадан
Компьютерный набор С. А. Жадан
Компьютерная верстка Н. М. Федорцовой

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MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

Teaching manual is designed to optimize the learning process and is offered to prepare students for laboratory lesson on the topic. The expediency of this edition is connected with outlining of the number of issues, which have not been reflected in the relevant academic literature on pathological physiology.

Lesson purpose: to investigate the pathophysiological aspects of hereditary forms of pathology, types of inheritance, to get acquainted with the most common hereditary diseases and congenital malformations, the principles of their prevention and treatment.

Lesson objectives: the student should:

1. Know:

– general classification and etiology of hereditary forms of diseases, the causes of phenocopies;

– the main pathogenetic mechanisms of genetically related diseases;

– causes, classification and general patterns of genetic diseases pathogenesis.

– clinical manifestations of some hereditarily determined genetic metabolic diseases;

– causes, classification and general patterns of chromosomal diseases pathogenesis;

– characteristics and clinical manifestations of some chromosomal diseases;

– methods of medical genetics, principles of prevention and treatment of hereditary diseases.

2. Learn the basic hereditary syndromes, their manifestations and clinical signs.

3. Acquire solving skills of situational tasks relating to the topic of the lessons.

Requirements for the initial level of knowledge. For complete mastering of the theme the student must go over the next notions from Medical Biology and General Genetics again: heredity and variation, types of inheritance, genotype and phenotype, research methods in medical genetics.

The control questions from related disciplines:

1. Concept of human genetics, its subject matter, methods and tasks.
2. Concepts of heredity and variation.
3. Concepts of genotype and phenotype of an organism.
4. The concept of the types of inheritance of hereditary diseases.
5. The concept of the research methods of medical genetics.

Control questions:

1. Medical genetics, its tasks.

2. Hereditary and congenital forms of pathology. Phenocopies. The definition, causes of development. Examples.

3. Classification of diseases taking into account the specificity of heredity and environment in their development.

4. Etiology of hereditary forms of pathology. Mutation, the definition of the notion. Kinds of mutations.

5. Antimutagenesis. Mechanisms of antimutagen factors action.

6. Classification principles of hereditary forms of pathology.

7. Gene diseases. Etiology. General patterns of the pathogenesis. Hereditarily determined metabolic diseases: alcaptonuria, phenylketonuria, hepatocerebral dystrophy, family hypercholesterinemia, galactosemia, etc.

8. Chromosomal diseases. Etiology. General patterns of pathogenesis. Karyotype, clinical manifestations of some chromosomal syndromes (Down's syndrome, Patau's syndrome, Edwards' syndrome, Klinefelter's syndrome, a trisomy syndrome of X-chromosomes, Shereshevsky–Turner's syndrome, a syndrome of «the cat's cry».

9. Methods of studying of hereditary forms of pathology.

10. Principles of prophylaxis and treatment of hereditary diseases and developmental defects, diseases with hereditary predisposition.

GENERAL CHARACTERISTICS OF HEREDITARY PATHOLOGY

MEDICAL GENETICS AND ITS TASKS

Heredity is a feature of living beings and the body's cells transmit their characteristics (anatomical and physiological features) to descendants. It provides a relatively stable species. Material carriers of hereditary information are genes — DNA molecules.

Variability is a feature of the organism and its cells, which manifests itself in the appearance of new symptoms.

Currently there are about 4000 species of hereditary pathology and genetically determined syndromes. The number is constantly growing. Every year tens of new forms of hereditary diseases are described. The main reasons of hereditary diseases growth are:

– significant medical achievements in the treatment and prevention of many infectious diseases;

– increased pollution of the environment due to mutagenic agents;

– increasing of the average human lifetime.

Medical Genetics is the specialty of medicine that involves the diagnosis and management of hereditary disorders.

It considers laws of hereditary diseases transference from generation to generation, develops methods of diagnostics, treatment and prevention of hereditary and not hereditary diseases.

The main tasks of medical genetics are:

1. Study of inherited forms of pathology. This means the study of their etiology, pathogenesis, improvement of diagnosis, methods of prevention and treatment. Fatal nature of hereditary diseases exists only as long as the specific causes and mechanisms of their development remain unknown. Investigation of the mechanisms of hereditary diseases will allow not only treat these diseases, but also to some extent to prevent them.

2. Study of the causes and mechanisms of hereditary predisposition and determined resistance to various (including infectious nature) diseases.

3. Establishing of the role and importance of the genetic apparatus in the development of responses of adaptation, compensation and decompensation.

4. A detailed comprehensive study of the processes of mutagenesis and anti-mutagenesis, and their role in the development of disease.

5. Researching of a number of biological problems: molecular and genetic mechanisms of carcinogenesis, the role of the genetic apparatus in the phenomena of tissue incompatibility, autoimmune reactions of the organism, etc.

CONCEPT OF HEREDITARY AND CONGENITAL PATHOLOGY. PHENOCOPIES

There is a classification in medical genetics according to which all diseases are classified as: *congenital, hereditary and not hereditary*.

The concepts of «hereditary disease» and «congenital disease» are not the same.

The term a ***congenital disease*** or malformation refers to any abnormality present at birth (congenital = with birth) though it may not be detected just after birth. Congenital defects develop during prenatal life and can be hereditary and non-hereditary.

Hereditary diseases are caused by genetic factors (single-gene, multifactorial inheritance or chromosomal aberrations). These diseases can be transmitted from parents to offspring. They may also become apparent at different age.

Non-hereditary diseases are caused by environmental factors occurred during embryonic or fetal development.

Phenocopies are environmentally induced changes in an organism considered to be hereditary but in fact they are not hereditary. A *phenocopy* is a variation in phenotype (generally referring to a single trait) which is caused by environmental conditions (often, but not necessarily, during the organism's development), such that the organism's phenotype matches a phenotype which is determined by genetic factors. It is not a type of mutation, as it is non-hereditary.

For example, anomalies such as «cleft palate», «cleft lip» can be both hereditary (Patau syndrome) and non-hereditary, resulting from violations of embryonic development. Early deafness may be inherited as a recessive or dominant trait, and can occur as a phenocopy in children born to women who had been ill with rubella during pregnancy. Hypothyroidism is inherited as an autosomal-recessive trait, but can occur as a phenocopy in people living in areas where drinking water is poor in iodine.

The main reasons of phenocopies are:

– fetus hypoxia (intrauterine hypoxia), causing the development of serious structural defects of the brain and skull, microcephaly;

– infections of the pregnant woman (toxoplasmosis, rubella, syphilis, etc.), especially in early pregnancy, causing severe malformations (microcephaly, deaf-mutism, cleft palate, etc.);

– severe mental trauma and prolonged emotional stress during pregnancy in women;

– harmful drugs and chemicals (thalidamide) taken by pregnant women; endocrine diseases of pregnant women;

– parents chronicle alcoholism (malformations in children of non-drinking parents make up about 2 %, in moderate drinkers — up to 9 % in heavy drinkers — 74 %), etc.

CLASSIFICATION OF DISEASES ACCORDING TO SPECIFIC CONTRIBUTION OF HEREDITY AND ENVIRONMENT IN THEIR DEVELOPMENT. CONCEPT OF PENETRANCE AND EXPRESSIVITY

In the development of any disease the etiologic factor both the environment (external factors) and heredity (internal factor) are a constituent part of the pathogenesis. Specific weight of each of them is different at various diseases.

Given the proportion of heredity and environment there are 4 groups of diseases (N. P. Bochkov, 2002):

– hereditary diseases;
– single-gene diseases;
– multifactoral inherited diseases;
– disorders caused by environmental factors.

The first group is strictly hereditary diseases. The main reasons of origin and development of these diseases are changes in the genetic apparatus. This group includes monogenic diseases (homogentisuria, phenylketonuria, hepatolenticular disease, hemophilia, etc.) and all chromosomal diseases. Environment in the first group of diseases defines a penetration (from Lat. penetro — penetrating, reach) and an expressivity. A *penetration* — is the exposure of gene action in the population of individuals who have this gene (homozygous — in the case of recessive genes, or heterozygous — in the case

of dominant genes). An *expressivity* — is a degree of gene expression in a particular individual.

Heredity also plays a crucial role in the development of the *second group* of diseases, as well as in the first, but their appearance is due to specific action of the environment, without which the disease, despite the presence of pathological mutations, is not clinically manifested. Thus, the appearance of clinical symptoms of gout, in which malfunction of metabolism of uric acid is genetically determined, is caused by systematic overeating, excessive consumption of animal food, wines and other substances, the metabolism of which leads to the formation of excessive amounts of uric acid which is deposited in the joints, causing their defect.

The main etiologic factors in *the third group* of diseases are environmental factors. These are diseases with a hereditary predisposition, multi-factor polygenic diseases. These include the vast number of diseases of the mature and elderly age: hypertension, atherosclerosis, coronary heart disease, gastric ulcer, duodenal ulcer, cancer, etc.

There is no clear difference between the second and third group of diseases. They are often combined into a group of diseases with hereditary predisposition by distinguishing monogenic and polygenic predisposition.

The fourth group comprises the disease, the development of which is fully determined by environmental factors, to the action which the body has no means of protection — extreme factors. These are injury (mechanical, electrical), the action of ionizing radiation, burns, frostbite, particularly dangerous infection. Genetic factor in these cases determines the severity of the disease, its outcome, in some cases — the probability of occurrence.

CLASSIFICATION OF THE HEREDITARY PATHOLOGY

There are two main classification principles of hereditary disease: clinical and genetic.

Clinical classification principle implies the division of inherited forms of diseases depending on the organ or system most involved in the pathological process. In accordance with this criterion, there are genetically caused diseases of the nervous system, of the musculoskeletal system, of the skin, of the blood system, etc.

The basis of the *genetic classification* of hereditary diseases is an etiological principle, i. e. type of mutation and the nature of interaction with the environment. In accordance with this criterion, the hereditary pathology can be divided into 5 groups:

1) *genetic diseases* caused by gene mutations;

2) *chromosomal diseases* appeared as a result of chromosomal or genomic mutations;

3) *diseases with hereditary predisposition* (multifactorial) — develop in individuals with the appropriate combination of «predisposing» hereditary and «showing» external factors;

4) *genetic diseases of somatic cells*;

5) *diseases of genetic incompatibility between mother and fetus*.

In turn each of these groups is subdivided in accordance with the more detailed genetic characteristics and the type of inheritance.

ETIOLOGY OF HEREDITARY FORMS OF PATHOLOGY. MUTATIONS, THEIR KINDS. MUTAGENS

Individual genes, chromosomes and genome as a whole are constantly undergoing various changes. Despite the fact that there are mechanisms for DNA repair some of the damage and errors are stored. Changes in the number and sequence of nucleotides in DNA are called *mutations*.

Mutation is a randomly derived change in the nucleotide sequence of the genetic material of an organism.

All mutations are classified according to several criteria:

I. *By reasons*:

– *spontaneous* mutations have purely natural, spontaneous causes;

– *induced* mutations appear as a result of different factors exposure. These factors are called *mutagens* and are divided into three groups: physical, chemical and biological.

The major *physical mutagens* are ionizing radiation and ultraviolet rays. Ionizing rays may cause all known mutations types — genomic, chromosomal and genic. They can be located in sexual and somatic cells. Among the somatic cells, the most sensible to radiations are those, which intensively get divided (bone marrow cells, mucous epithelium, incretion glands cells). The ultraviolet rays induce gene mutations.

Chemical mutagens are compounds increasing the frequency of some types of mutations. They vary in their potency since this term reflects their ability to enter the cell, their reactivity with DNA, their general toxicity, and the likelihood that the type of chemical change they introduce into the DNA will be corrected by a repair system.

To *biological mutagens* belong measles viruses, rubella viruses, hepatitis viruses and retroviruses.

II. *By the type of cells*:

– *somatic mutation* forms a clone of cells in one individual which are genetically slightly different from the rest cells in the body. They do not cause hereditary diseases but are important in the genesis of cancers and some congenital malformations;

– *associated with germ cells* mutation which are transmitted to the progeny and may give rise to inherited diseases;

– *mosaic mutation* (mosaicism is the presence in one individual of two or more cell lines characterized by distinctive karyotypes).

III. *Depending on value*:

– *pathogenic* mutations can cause death or severe disease. They are divided into lethal, half-lethal and non-lethal mutations. Mortality can occur at the level of gametes, zygotes, embryos, fetuses, and after birth;

– *neutral* mutation. Most of mutations are neutral; they either make no change in the expression of any gene or the changes made do not affect the function of any gene product;

– *beneficial* mutations increase the vitality of the body (e. g., dark skin color among residents of the African continent).

IV. *Depending on the extent of genome damage:*

– *genome mutations* involve loss or gain of whole chromosomes, giving rise to monosomy, trisomy or polysomy;

– *chromosome mutations* are the result of rearrangement of genetic material and give rise to visible structural changes in the chromosome;

– *gene mutations* result in partial or complete deletion of a gene or, more often, affect a single base.

ANTIMUTAGENESIS. MECHANISMS OF ANTIMUTAGENS

Antimutagenesis is the suppression of spontaneous and induced mutations. Substances having these properties are called antimutagens.

There are different classification principles of antimutagens: 1) by origin: exogenous and endogenous, intracellular and extracellular, 2) by the mechanism of action, 3) by chemical structure and anti-carcinogenic properties of antimutagens.

Exogenous antimutagens include:

1. *Antimutagens contained in food and are ingested with food*:

– essential amino acids (methionine, histidine, arginine, glutamic acid, etc.);

– vitamins and pro-vitamins (especially A, E, C, K);

– polyunsaturated fatty acids;

– trace elements (Se), cobalt chloride;

2. *Antimutagens penetrating into the body through the respiratory system (volatile).*

3. *Antimutagens, ingested orally in the pharmacotherapy, or prophylactic uses*:

– drugs (streptomycin, levomitsitsin etc., used in small doses);

– specially synthesized drugs (bemitil);

– dietary supplements (indole-3-carbinol, etc.);

– synthetic antimutagens (ionol, BHT, etc.).

Endogenous antimutagens include:

1) system repair of damaged DNA;

2) antioxidant system;
3) enzyme systems;
4) cellular metabolites;
5) thyroid hormone, melatonin;
6) embryonic material (Co);
7) C-containing compound (glutathione).

Mechanisms of antimutagens action:

1. *Inactivation of external origin mutagens and prevention of their DNA damaging effect (dismutageny).* In most cases dismutageny stably associated with mutagen and remove it from the body (extracts of parsley, beets, radishes, celery, cabbage, plums, blueberries, apples).

2. *Suppression of the formation of true mutagens from preceding non-mutagenic substances* (vitamins C, E, tannins, some phenols).

3. *Suppression activity of free radicals that can damage DNA* (antioxidants: superoxide dismutase, glutathione peroxidase, catalase, vitamin C, A, α-tocopherol, β-carotene, E, melatonin, etc.).

4. *Increase in activity of the enzyme systems, detoxifying mutagens, carcinogens and other genotoxic compounds.* Universal mechanism for the inactivation of xenobiotics provides microsomal liver enzymes that metabolize up to 75 % of all medicines.

5. Antimutagens reducing errors of DNA repair and replication, the activation of repair and correction (reparageny).

6. *Antimutagens with unknown mechanism of action.* In recent years polyfunctionality of some antimutagens is installed. Antimutagens act as interceptors of free radicals, inhibit the synthesis of metabolic activation of xenobiotics, stimulate their detoxification, modulate DNA reparation, suppress inflammation and angiogenesis.

Thus, the main antimutagens include:

1) the compounds neutralizing the mutagen prior to its reaction with the DNA molecule;

2) substances that eliminate damage of DNA molecule caused by the mutagen, or increase its resistance to mutagen;

3) compounds that interfere with the conversion of indirect mutagens in the true body.

GENE DISEASES

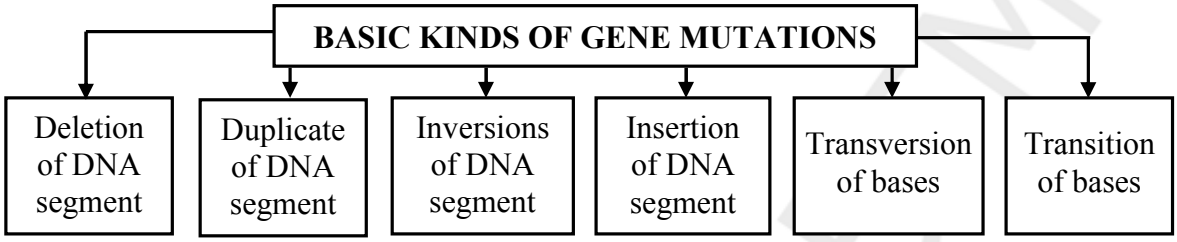
Gene diseases — a heterogeneous by clinical manifestation group of diseases caused by mutations on the gene level. Basis for combining them into a single group are the etiological and genetic characteristics and patterns of inheritance in families and populations.

ETIOLOGY OF GENE DISEASES

The main reason of gene diseases is **gene mutations**. *Gene mutations* are molecular changes in DNA structure. They are caused by changes in the chemical structure of the gene, namely the specific sequence of the purine and pyrimidine bases of a DNA region.

By type of molecular changes there are following kinds of gene mutations:

Basic kinds of gene mutations



Deletion — is a mutation when a portion of the gene is missed or deleted.

Duplicate — is a mutation when segment of DNA is duplicated, resulting in extra genetic material.

Inversion — is a mutation when an entire section of DNA is reversed.

Insertion — is a mutation when the addition of DNA into a genetic sequence.

Transversion mutations involve replacing a purine with a pyrimidine (and its partnering pyrimidine with a purine), or replacing a pyrimidine with a puring (and its partnering purine with a pyrimidine).

Transition mutations involve replacing a purine with another purine (and its partnering pyrimidine with another pyrimidine), or replacing a pyrimidine with a pyrimidine (and its partnering purine with another purine).

CLASSIFICATION OF GENE DISEASES

There are three main classification principles of gene diseases.

According to the **genetic** principle all gene diseases are divided into several types of inheritance, including:

1) *autosomal-dominant*;
2) *autosomal-recessive*;
3) *dominant X-linked*;
4) *recessive X- linked*;
5) *Y- linked*;
6) *mitochondrial.*

Examples of diseases and developmental abnormalities with different types of inheritance there are in the Appendix.

According to the **clinical** principle of classification all gene diseases are classified into few groups depending on the organ or system involved in

pathological process: *hereditary skin disease; hematological diseases; ear diseases and so on.*

And finally, according to the **pathogenical** principle all diseases are classified as:

1) *hereditary diseases of metabolism*;
2) *congenital developmental anomalies*;
3) *combined disorders.*

PATHOGENESIS OF GENE DISEASES

Basic links of gene diseases pathogenesis can be represented as follows: mutant allele → pathological primary product (qualitatively or quantitatively) → subsequent chain of biochemical processes → cells → organs → body.

Mechanism of genetic diseases should be considered at the *molecular, cellular, organ and organism levels* of the body structure.

At the molecular level the primary effects of mutant alleles can be manifested in 3 versions:

1. *The lack of synthesis of the polypeptide chain (protein).*
2. *Quantitatively insufficient synthesis of the polypeptide chain (protein).*
3. *Synthesis of abnormal protein.*

The lack of synthesis of the polypeptide chain (protein). In the absence or insufficient amount of this protein the processes at some stages of which this protein plays a key role are broken. Antihemophilic globulin A (factor VIII), B (factor IX), the precursor of plasma thromboplastin (factor XI) are of exceptional significance for accomplishing various stages of the intrinsic mechanism of the 1st blood clotting phase. Their impaired synthesis results in hemophilia (respectively: A, B and C). Clinical manifestations of the disease are hematoma bleeding type with the involvement of the musculoskeletal system. Hemorrhages into large limb joints, profuse bleeding even in case of minor injuries and hematuria prevail. Hemophilia A and B are inherited linking with X-chromosome in a recessive way. Hemophilia C is inherited according to dominant or semidominant type in an autosomal way.

Quantitatively insufficient synthesis of the polypeptide chain (protein). Phenylpyruvic oligophrenia, for example, associated with impaired synthesis of phenylalanine hydroxylase which catalyzes the conversion of normal dietary intake of phenylalanine into tyrosine. Enzyme deficiency leads to excessive content of phenylalanine in blood, changes in the of tyrosine metabolism, production of significant amounts phenylpyruvic acid, brain damage associated with microcephaly and mental retardation. The disease is inherited in autosomal recessive way. The diagnosis can be made in the first days after birth, even before the appearance of severe symptoms of the disease by detecting phenylpyruvic acid and phenylalaninemia in the urine. Early

diagnosis and timely initiation of treatment (diet low in phenylalanine) allow avoiding the disease and its most severe manifestations — mental deficiency.

Synthesis of abnormal protein. The most striking example of such kind of pathology is sickle-cell anemia, in which in the 6^{th} position of hemoglobin β-chain glutamic amino acid is replaced by valine, and an unstable HbS formed. Its solubility decreases dramatically in the reduced state and its ability to polymerize increases. Crystals impairing the shape of red blood cells are formed. They are easily hemolyzed, especially under conditions of hypoxia and acidosis, leading to anemia development. Inheritance is autosomal recessive or semidominant.

An important condition for mutation appearing and implementing is the **failure of DNA repair system**, it can be determined genetically or develop in the course of life, under the influence of external or internal environment adverse factors.

Thus, in the genotype of healthy people there is a gene with the program code of synthesizing enzyme exonuclease which ensures «cutting out» of pyrimidine dimers, that are formed under the influence of ultraviolet radiation. This gene anomaly expressed in the loss of the exonuclease synthesis program code increases the sensitivity of the skin to sunlight. Under even brief sun exposure dry skin, its chronic inflammation, abnormal pigmentation occurs, later neoplasms undergoing malignant transformation appear. Two-thirds of patients die before the age of 15 years. The disease — xeroderma pigmentosum — is inherited in autosomal recessive way.

Functional potency of DNA repair system weakens with age.

A certain role in the pathogenesis of hereditary forms of diseases seems to belong to the persistent **impairment of gene activity regulation**, which, as noted, may be one of the possible causes of manifesting symptoms of hereditary disease until years after birth.

So the basic mechanisms of developing hereditary pathology in molecular level are associated with:

1) mutations resulting in:
   a) lack of normal hereditary information;
   b) decrease of the volume of normal hereditary information;
   c) replacement of normal hereditary information by pathological one;
2) impairments of DNA repair system;
3) persistent changes in the gene activity regulation.

The cellular level of the pathogenesis of gene disease is connected with the development of pathological processes characteristic of specific forms of disease.

Organ level pathogenesis of hereditary diseases is derived from the molecular and cellular levels. Different organs are damaged at various

diseases — sometimes as a result of the primary pathological processes, sometimes — secondary one.

Organismal level is manifested at the molecular, cellular and organ levels. Thus, the pathogenesis of any hereditary disease in different individuals formed strictly individually.

CLINICAL MANIFESTATIONS OF SOME HEREDITARY DISEASES OF THE METABOLISM

Phenylketonuria (PKU) is an autosomal-recessive metabolic genetic disorder characterized by a mutation in the gene for the hepatic enzymephenylalanine hydroxylase (PAH), rendering it nonfunctional. This enzyme is necessary to metabolize the amino acid phenylalanine (Phe) to the amino acid tyrosine. When PAH activity is reduced, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which can be detected in the urine.

*Clinical symptoms***:** increase in excitability and muscle tone; hyperreflection, tremor, convulsive epileptic attack; infringements of the supreme nervous activity; intellectual insufficiency; «mouse» smell.

For the diagnosis newborn infants are usually screened for abnormal levels of serum phenylalanine. It is important that blood samples for PKU screening are obtained at least 12 hours after birth to ensure accuracy.

Untreated PKU can lead to intellectual disability, seizures, and other serious medical problems. The mainstream treatment for classic PKU patients is a strict PHE-restricted diet supplemented by a medical formula containing amino acids and other nutrients. Patients who are diagnosed early and maintain a strict diet can have a normal life span with normal mental development.

Alkaptonuria is a rare inherited genetic disorder of *phenylalanine* and *tyrosine* metabolism. It is an autosomal-recessive disorder in which the lack of *homogentisic oxidase* blocks the metabolism of phenylalanine-tyrosine at the level of homogentisic acid. Thus, homogentisic acid accumulates in the body. A large amount is excreted, imparting a black color to the urine if allowed to stand and undergo oxidation.

The retained homogentisic acid selectively binds to collagen in connective tissues, tendons, and cartilage, imparting to these tissues a blue-black pigmentation (ochronosis) most evident in the ears, nose, and cheeks. The most serious consequences of ochronosis, however, stem from deposits of the pigment in the articular cartilages of the joints. In some obscure manner, the pigmentation causes the cartilage to lose its normal resiliency and become brittle and fibrillated.

In healthy subjects, homogentisic acid is absent in both blood plasma and urine. In alkaptonuria, plasma levels are 6.6 micrograms/ml on average, and urine levels are on average 3.12 mmol/mmol of creatinine

Clinical symptoms: the eye sclera (may be pigmented); skin (may be darkened in sun-exposed areas and around sweat glands); sweat (may be coloured brown); urine (may turn brown if collected and left exposed to open air, especially when left standing for a certain period of time).

Commonly recommended treatments include dietary restriction of phenylalanine and tyrosine and large doses of ascorbic acid (vitamin C).

Galactosemia, is the most common type of galactosemia, an inborn error of galactose metabolism, caused by a deficiency of the enzyme galactose-1-phosphate uridylyltransferase. It is an autosomal recessive metabolic disorder that can cause liver disease and death if untreated.

In undiagnosed and untreated children, the accumulation of precursor metabolites due to the deficient activity of *galactose 1-phosphate uridylyltransferase* (GALT) can lead to feeding problems, failure to thrive, liver damage, bleeding and infections.

Clinical symptoms. The first presenting symptom in an infant is often prolonged jaundice. Without intervention in the form of galactose restriction, infants can develop hyperammonemia and sepsis, possibly leading to shock. The accumulation of galactose-1-phosphate (Gal-1-P) can lead to cataracts which are similar to those seen in galactokinase deficiency

Treatment of galactosemia is most successful if initiated early, and includes dietary restriction of lactose intake.

CHROMOSOMAL DISEASES

Chromosomal diseases are the special group of diseases associated with structural and numerical changes in the genetic material. They are classified as hereditary by convenience. The fact is that in the vast majority of cases chromosomal diseases are not passed to descendants since their carriers are most often infertile.

Chromosomal diseases are due to genomic or chromosomal mutations that have occurred in the gamete of a parent, or in the zygote formed by gametes with a normal set of chromosomes. In the first case, all the cells of a child will have an abnormal chromosome set (*the complete form of chromosomal disease*), in the second one, a mosaic organism having only some cells with an abnormal set of chromosomes is formed (*mosaic disease*). The degree of pathological signs expression in the mosaic form of the disease is less clearly marked than in the complete one.

Phenotypic basis of chromosomal diseases are disorders of early embryogenesis, due to which a disease is always characterized by multiple developmental malformations.

The incidence of chromosomal abnormalities is high: 4–3 of every 1000 live-birth infants have chromosomal diseases, in still-born children they make

up 6 %, about 40 % of spontaneous abortions are due to chromosome imbalance (N. P. Bochkov, 2002). The imbalance affecting all pairs of chromosomes causes so significant disorders in the body that they tend to be incompatible with life in the early or later stages of embryogenesis. Changes in the number or structure of individual chromosomes are more frequent. Lack of genetic material causes more significant defects than its excess. Complete monosomies due to autosomes hardly have been detected. This imbalance is likely to cause death already in gametogenesis or zygote stage and early blastula.

The basis for the development of chromosomal diseases associated with changes in the number of chromosomes is formed in gametogenesis, during the first or second meiotic divisions or during cleavage of fertilized ovum, often as a result of nondisjunction of chromosomes. Prerequisites for the development of chromosomal disease occur on fertilizing an abnormal ovum by a spermatozoon with normal set of chromosomes or a normal ovum by an abnormal spermatozoon, sometimes with a combination of two gametes containing changed chromosome number.

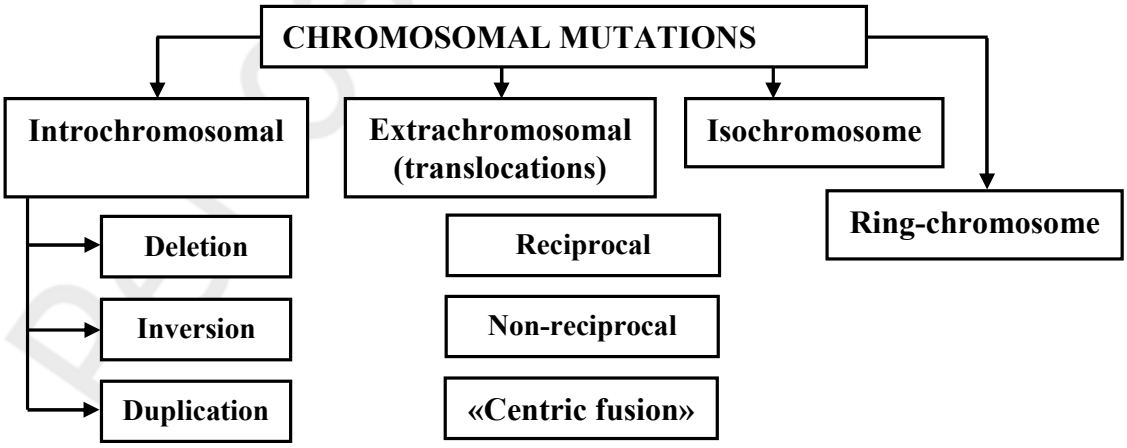
The probability of such disorders, and the birth of children with chromosomal diseases increases with parents' age, especially that of the mother.

ETIOLOGY OF CHROMOSOMAL DISEASES

Etiologic factors of chromosomal aberrations are all kinds of chromosomal mutations and some genomic mutations.

Chromosomal mutations are the structural changes of separate chromosomes. Alterations in the chromosomal structure occur when there is a break in one or more chromosomes.

All chromosomal mutations are divided into four groups: *intrachromosomal; extrachromosomal; isochromosome and Ring-chromosome.*



Intrachromosomal mutations are aberration within a single chromosome. These include:

1) *deletion* of the part of a chromosome. It leads to the loss of genetic material and shortening of the chromosome (fig. 1);

2) *inversion* — is a mutation, which requires two breaks in a single chromosome with inversion (180° change in direction) (fig. 2);

3) *duplication* — occurs mainly as a small supernumerary chromosome (fig. 3).

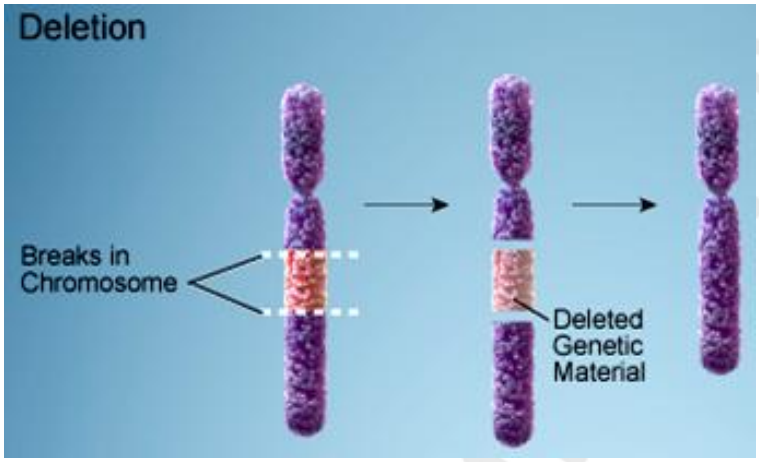


Fig. 1

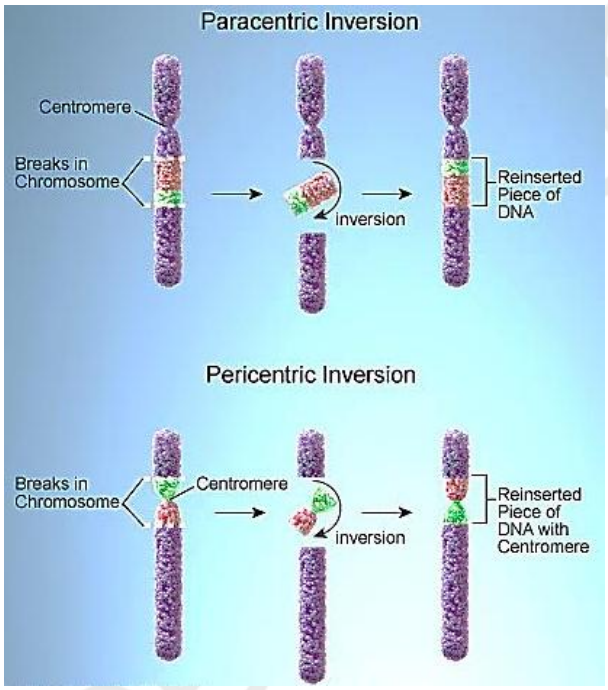


Fig. 2

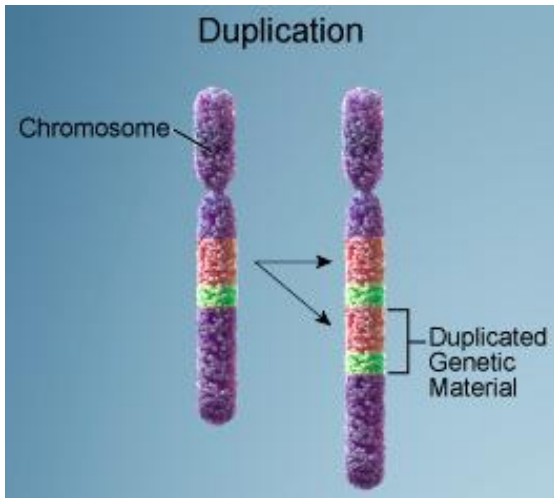


Fig. 3

Extrachromosomal mutations are exchange between non-homologous chromosomes fragments. These include:

– *reciprocal translocations* — are the most typical type of translocation. They occur when chromosomal segments are exchanged between two non-

homologous chromosomes. Because there has been no loss of genetic material, the individual is likely to be phenotypically normal. A balanced translocation carrier, however, is at increased risk for producing abnormal gametes (fig. 4);

– *non-reciprocal translocations* involve the transference of genes from one chromosome to another, non-homologous chromosome (fig. 5).

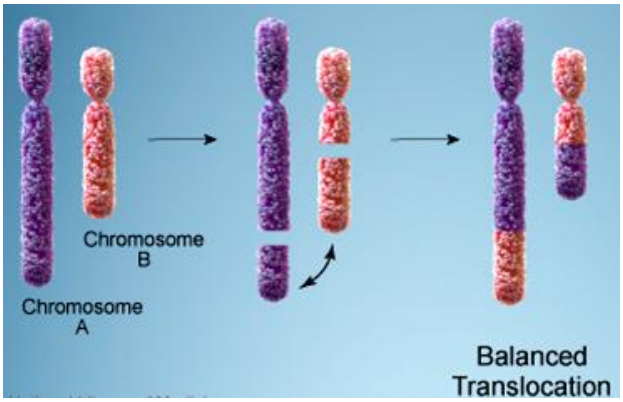


Fig. 4

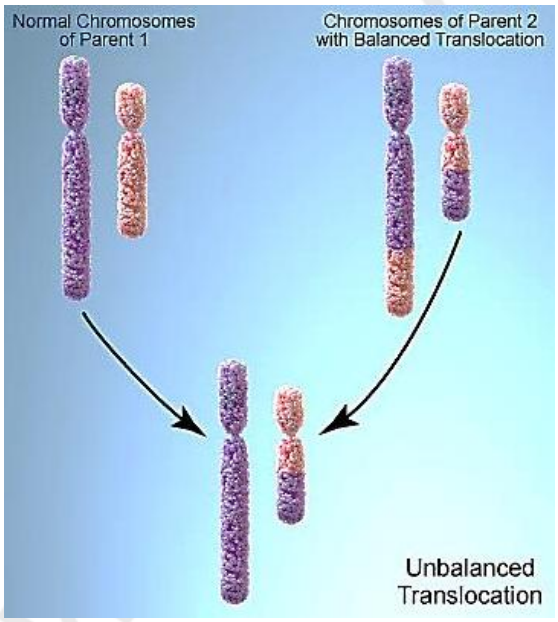


Fig. 5

– *centric fusion* or Robertsonian translocation involves two acrocentric chromosomes in which the centromere is near the end. Typically, the break occurs near the centromere affecting the short arm in one chromosome and the long arm in the other. Transference of the chromosome fragments leads to one long and extremely short chromosome. The short fragment is commonly lost. In this case, the person has only 45 chromosomes, but the amount of lost genetic material is so small that it is often unnoticed.

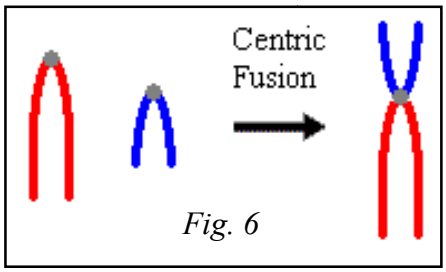


Fig. 6

Isochromosome formation occurs when the centromere, or central portion, of the chromosome is separated horizontally but not vertically (fig. 7). *Isochromosome* formation results when one arm of a chromosome is lost and the remaining arm is duplicated, resulting in a chromosome consisting of two short arms only or of two long arms. An isochromosome has morphologically identical genetic information in both arms.

Ring-chromosome results when deletion is followed by uniting of the chromatids to form a ring (fig. 8). A *ring chromosome* is a special form of deletion. It is produced when a break occurs at both ends of a chromosome with fusion of the damaged ends (fig. 8). If significant genetic material is lost,

phenotypic abnormalities result. This might be expressed as *46,XY,r(14)*. Ring chromosomes do not behave normally in meiosis or mitosis and usually result in serious consequences.

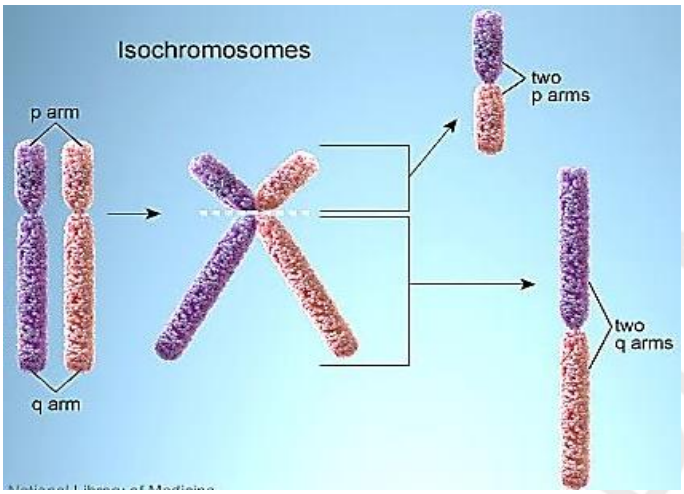


Fig. 7

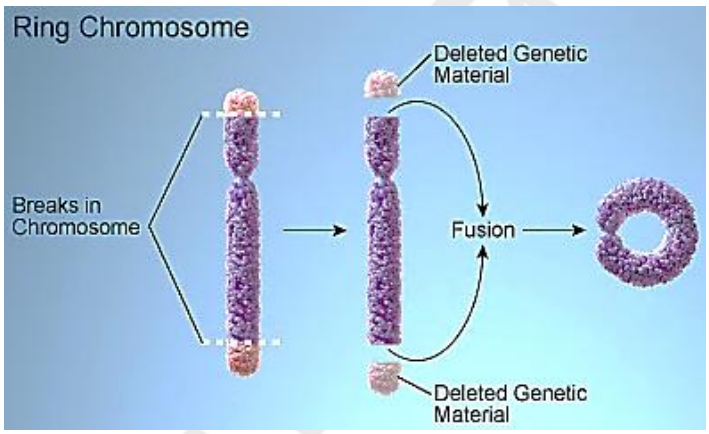


Fig. 8

Genomic mutations consist of chromosomes amount changes. A few mechanisms of genome mutations are established. Major of them is undivergence of chromosomes. Normally amount of chromosomes in time of cultural division increases twice in somatic cells there will be 92 of them, in sexual 46. In anaphase the sisters chromosomes must be divided, and go for different poles. Then a necessary amount of chromosomes is found 46 and 23 in daughter's cells.

But there are the cases, when both daughters chromosome remain coupled and move away to one pole. This phenomenon meets frequent during meiosis that is fission of sexual cells. The superfluous chromosome hits one gamete and the other one goes without chromosome. After the fecundation the zygote will perform as trisomia (47), or monosomia (45).

If happened in somatic cell on early stages of embrion development, this would bring to mosaicism. There would be three cell populations presence in

such organism: normal (46), trisomia (47) and monosomia (45). Such faces are named as *mosaicisms*.

Following mechanism of genome mutations is *anaphase deficiency*. During the anaphase moving from equator down to the pole one of chromosomes gets retarded and lost. One from daughter gametes gets the normal amount of chromosomes, and the other one less. After the impregnation zygote can be normal (46), or monosomic (45).

Two variants of genomic mutations are possible:

– *aneuploidy* is separate chromosomes deficit or surplus (monosomy, trisomy and polysomy);

– *polyploidy* is aliquot augmentation of genome.

Aneuploidy is a deviation of the normal chromosome number. It leads to loss or gain of one or several individual chromosomes from the diploid set.

Three states of aneuploidy can be distinguished:

1. *Polysomy is* presence of more than two additional chromosomes in a set. This mutation refers to the autosomes and the sex chromosomes. Polysomy occurs when a germ cell containing more than 23 chromosomes is involved in conception.

2. *Trisomy* is the mutation, when three chromosomes instead of two present in one pair. Additional chromosome may be present in autosomes or in sex chromosomes.

3. *Monosomy* refers to the presence of only one member of a chromosome pair. The defects associated with monosomy of the autosomes are severe and usually cause abortion. Monosomy of the X chromosome (45,XO) or Turners syndrome causes less severe defects.

Polyploidy is a chromosomal aberration when a cell contains several chromosome sets. There are:

1. *Triploidy* is the mutation when all chromosomes present in triplicate (fig. 9). Triploidy is one of the most frequent chromosomal aberrations in man, causing 17 % of spontaneous abortions. Only 1 in 10 000 triploid zygotes results in a liveborn infant, but with severe congenital malformations invariably leading to early death (69,XYY; 69 XXY; 69XXX).

2. *Tetraploidy* is the mutation when all chromosomes present in quadruplicate. Tetraploidy occurs even more rarely than triploidy.

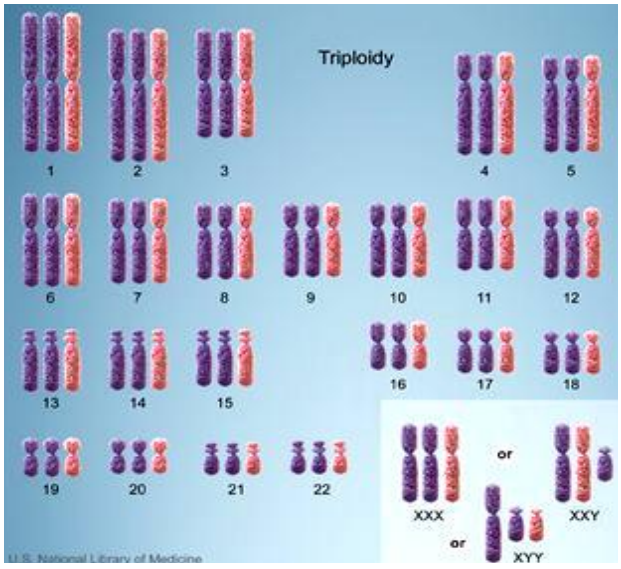


Fig. 9

CLASSIFICATION OF CHROMOSOMAL DISEASES

There are three main classification principles of chromosomal aberrations that can accurately describe the form of chromosomal abnormalities in the individual, as well as its variants.

1. *Characteristic of chromosomal or genomic mutations (etiological principle)*:

– *polyploidy* (triploidy and tetraploidy);

– *aneuploidy* (lack or excess of chromosomal material on autosomes and sex chromosomes).

2. *Determination of the type of cells in which the mutation has arisen (gamete or zygote)*:

– *germ cells* cause complete forms of chromosomal diseases;

– *somatic cells* — the organism develops from cells of different chromosomal constitution (mosaicism);

3. *Identification of a generation in which the mutation has arisen*:

– *sporadic chromosomal diseases* (appear in gametes healthy parents firstly);

– *inherited chromosomal diseases*.

PATHOGENESIS OF CHROMOSOMAL DISEASES

Pathogenesis of chromosome diseases is not fully studied. A general scheme of the complex pathological processes caused by chromosomal abnormalities and leading to the most complex phenotypes of chromosomal diseases is not developed.

It is supposed the main link of pathogenesis of chromosomal disorders is imbalance of genotype due to genomic and chromosomal mutations that are manifested by intrauterine death of embryos and fetuses, the development of specific syndromes that can cause impairment of physical and mental health.

CLINICAL CHARACTERISTIC OF SOME CHROMOSOMAL SYNDROMES

Clinical-cytogenetic characterization of syndromes associated with numerical abnormalities of sex chromosomes

XYY-syndrome («Super-male syndrome») is a chromosome disorder that affects males. XYY syndrome occurs when an extra Y chromosome is present in the cells of an affected individual. The error that causes appearance of the extra Y chromosome can occur in the fertilizing sperm or in the developing embryo.

Karyotype: 47, XYY. Frequency: 1:1000 newborn males.

Clinical symptoms: tall stature, rough face features, the increased bottom jaw, big auricles, the intelligence is reduced or in norm; emotional infringements; a tendency to aggressive acts.

Since many males with XYY syndrome look like other males without XYY-syndrome, many males are never identified.

«Superwomen» syndrome. *Karyotypes*: syndrome trisomy X-karyotype: 47,XXX; syndrome tetrasomy X-karyotype: 48,XXXX; syndrome pentasomy X-karyotype : 49,XXXXX. Frequency: 1 : 1000 newborn girls.

Most of these women are entirely normal. A variety of random findings, however, may be present. As mentioned, there is an increased tendency to mental retardation in proportion to the number of extra X chromosomes. Thus, mental retardation is seen in all with the 49,XXXXX karyotype, whereas most with 47,XXX are unaffected. Some women have amenorrhea or occasionally other menstrual irregularities.

Clinical symptoms: tall stature, learning problems, delayed development of further skills (sitting, walking), weak muscle tone, behavioral and emotional difficulties.

These characteristics vary widely among affected girls and women. In is unclear why an extra copy of the chromosome is associated with these features.

Klinefelter syndrome is a condition that occurs in men as a result of an extra X chromosome. *Karyotypes*: 47,ХХУ; 48,ХХХУ; 49ХХХХУ/

It is one of the most frequent forms of genetic disease involving the sex chromosomes as well as one of the most common causes of hypogonadism in the male. The incidence of this condition is approximately 1 in 850 live male births. It can rarely be diagnosed before puberty, particularly because the testicular abnormality does not develop before early puberty.

Clinical symptoms: tall stature; small, firm testes; a small penis; sparse pubic, armpit and facial hair; enlarged breast (called gynecomastia); abnormal body proportions (long legs, short trunk). The mean IQ is somewhat lower than normal, but mental retardation is uncommon.

Treatment: testosterone therapy is used to increase strength, promote muscular development, grow body hair, improve mood and self-esteem, increase energy and improve concentration.

Turner syndrome results from complete or partial monosomy of the X-chromosome and is characterized primarily by hypogonadism in phenotypic females. *Frequency*: 1 : 2000–5000.

It is the most common sex chromosome abnormality in females. With routine cytogenetic methods, three types of karyotypic abnormalities are seen in patients with Turner syndrome. Approximately 57 % are missing an entire X-chromosome, resulting in a 45,XO karyotype. Of the remaining, approximately one third (approximately 14 %) have structural abnormalities of the X-chromosomes, and two thirds (approximately 29 %) are mosaics.

Clinical symptoms: growth of infertility problems; physical abnormalities; low growth; short stature (1 m 30 cm – 1 m 50 cm infertility); webbed neck, low hairline; broad chest; hand and feet swelling.

Treatment of patients with Turner's syndrome is complex: 1) reconstructive surgery (congenital malformations internal organs), 2) plastic surgery (removal of the wing-folds), 3) hormonal (estrogen, growth hormone), 4) psychotherapy.

Clinical-cytogenetic characterization of syndromes associated with numerical abnormalities of autosomes

Down Syndrome 47,XX(XY),+21 is the most common of the chromosomal disorders and a major cause of mental retardation. The incidence in newborns is about 1 in 700.

Approximately 95 % of affected individuals have trisomy 21, so their chromosome count is 47,XX(XY),+21; most others have normal chromosome numbers, but the extra chromosomal material is present as a translocation 46,XY,14-,t(21/14). As mentioned earlier, the most common cause of trisomy and therefore of Down syndrome is meiotic nondisjunction. The parents of such children have a normal karyotype and are normal in all respects. Maternal age has a strong influence on the incidence of trisomy 21. It occurs once in 1550 live births in women under the age of 20 years, in contrast to 1 in 25 live births for mothers over 45 years of age.

Approximately 1 % of Down syndrome patients are mosaics, usually having a mixture of cells with 46 and 47 chromosomes 46,XX/47XX,+21. This mosaicism results from mitotic nondisjunction of chromosome 21 during an early stage of embryogenesis. Symptoms in such cases are variable and milder, depending on the proportion of abnormal cells.

Clinical symptoms: the diagnostic clinical features of this condition are usually readily evident, even at birth. The flat facial profile; oblique palpebral fissures; «mongolism»; hypotonia (floppiness); small head with brachicephaly; epicanthic folds across the inside corners of the eyes; small mouth; small ears; big tongue; wide space with a deep fissure between the first and second toes; a deep («monkey») fissure on the hand (fig. in Appendix).

Despite all these problems, improved medical care has increased the longevity of patients with trisomy 21. Currently more than 80 % survive to age 30 or beyond.

Patau Syndrome 47,XX(XY),+13 is a very rare but the most severe of the possible autosomal trisomies. It is the second most frequent pathology (1 : 5000–7000 births) caused by changes in the number of autosomes is Patau's syndrome (trisomy 13; 47,XX(XY),+13). The syndrome is characterized by severe malformations of the brain and face (defects of cranial and facial parts of the skull, brain, eyes, microcephaly, cleft lip and palate), polydactyly (often — hexadactylism), defects of the heart walls, incomplete intestinal rotation, polycystic kidney, developmental malformations of other organs (fig. in Appendix).

90 % of children born with this disease die within 1 year of life. In the majority of cases the survival is up to 3 days.

Edwards Syndrome 47,XX(XY),+18 is a chromosomal abnormality due to the gaining of chromosome 18 extra copy. Trisomy 18 (Edwards' syndrome) ranks the third (1:7000 births) among autosome polysomy.

The main *clinical manifestations* of the disease are the numerous defects of the skeletal system (pathology in the structure of the facial part of the skull: micrognathia, epicanthus, ptosis, hypertelorism, cleft lip/cleft palate, low-set, malformed ears, clenched hands, clubfoot or Rocker bottom feet*;* cardiovascular malformations (ventricular septum defect, defects of pulmonary artery and aorta valves), hypoplastic nails, horseshoe kidney, cryptorchidism in boys (fig. in Appendix).

The syndrome has a very low rate of survival, resulting from heart abnormalities, kidney malformations, and other internal organ disorders. 90 % children with this syndrome die in the 1st year of life.

Clinical-cytogenetic characterization of syndromes associated with structural rearrangements

Crying Cat Syndrome 46,XX(XY),5p- is a disorder caused by the partial loss of the short (p) arm from chromosome 5.

It is also called the cri du chat (or cri-du-chat) syndrome. The condition is characterized by a high-pitched cry which is similar to a cat's cry. Frequency: 1 : 45 000.

Clinical symptoms: microcephaly (small head), round face, hypertelorism (wide-spread eyes), micrognathia (small chin), epicanthal folds (inner eye folds), low-set ears, hypotonia (poor muscle tone), motor and mental retardation. The majority of patients die in early childhood

Wolf–Hirshhorn syndrome 46,XX(XY),4p- is caused by a partial deletion of the short arm of chromosome 4. About 87 % of cases represent a de novo deletion, while about 13 % are inherited from a parent with a chromosome translocation. The symptoms and phenotype do not differ based on the size of the deletion.

The most common abnormalities seen include severe to profound mental retardation, microcephaly (small head), seizures, poor muscle tone, and cleft lip and/or cleft palate. Characteristic facial features, include strabismus, hypertelorism, down-turned «fishlike» mouth, short upper lip and philtrum, small chin, ear tags or pits, and cranial asymmetry. Occasional abnormalities include heart defects, hypospadias, scoliosis, ptosis, fused teeth, hearing loss, delayed bone age, low hairline with webbed neck, and renal anomalies.

PRINCIPLES OF THERAPY

Treatment of hereditary pathology is based on three principles: etiological, pathogenetic and symptomatic.

Etiological therapy is aimed at addressing the causes of the disease. For this purpose, methods of genetic defect correction are used (gene therapy). The purpose of gene therapy is to introduce normally expressed «healthy gene»into the cellular genome of affected organs.

Pathogenetic therapy aims to break the different links of pathogenesis. To achieve this, several methods are used:

– *Replacement therapy* — the administration of a scarce substance (insulin in diabetes mellitus);

– *Correction of metabolism* by: 1) restriction of intake substances which are not involved in metabolism, e. g., phenylalanine, or lactose; 2) excretion of metabolites that accumulate in excess (e. g., cholesterol); 3) regulation of enzyme activity (for example, suppression of creatine phosphokinase (CPK) at certain types of muscular dystrophy);

– *Surgical correction* of defects (e. g., creation of a shunt between the vena cava inferior and portal veins in patients with «hepatotropic» glycogenosis.

Symptomatic therapy is aimed at eliminating the symptoms, aggravating the patient's condition (e. g., the use of substances that reduce the viscosity of secretions of the endocrine glands in cystic fibrosis, surgical removal of extra fingers and/or skin bridges between them in poly-and syndactyly; perform plastic surgery with facial deformities, heart defects and large vessels).

METHODS OF PREVENTION

There are the following types of hereditary diseases prevention: primary, secondary and tertiary.

Primary prevention is aimed at preventing birth to a sick child. This is accomplished through:

1) planning childbearing by choosing the optimal reproductive age (for women it is 21–35 years). More early and late pregnancy increases the chance of a child birth with congenital disorders and chromosomal diseases);

2) rejection of childbearing in cases of high risk of hereditary and congenital abnormalities (including in marriages with blood relatives and heterozygous carriers of the abnormal gene).

3) tight control of mutagens and teratogens content in the environment (20 % of all hereditary diseases in each generation due to new mutations).

Secondary prevention is accomplished by interrupting pregnancy in the case of a high probability of fetal disease or prenatally diagnosed illness.

Secondary prevention is accomplished by: 1) genetic counseling, 2) screening of pregnant women using biochemical methods (for example, determining the concentration of alphafetoprotein (AFP) in the blood of pregnant women), 3) ultrasound — diagnosis, 4) the application of certain invasive examination methods (such as chorionic villus sampling (up to 13 weeks), amniocentesis (16–19 weeks)).

Tertiary prevention of hereditary disease is a correction of pathological manifestations of genotypes by treatment assignment when detecting pathology. As a result, it is possible to achieve full normalization or reduction of the severity of the pathological process. Tertiary prevention is done by newborn screening to detect certain hereditary forms of pathology (e. g. phenylketonuria, hypothyroidism, adrenogenital syndrome etc.), as well as early initiation of corrective treatment.

METHODS OF MEDICAL GENETICS

There are the following main methods of genetic.

Genetic genealogy involves the use of genealogical DNA testing to determine the level and type of the genetic relationship between individuals.

Cytogenetic method. It is a microscopic examination of genetic components of the cell, including chromosomes, genes, and gene products

Biochemical methods. 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.

Molecular diagnostics involves the discovery and laboratory testing for DNA mutations underlying many single gene disorders. Although overlapping with biochemical techniques, molecular genetics techniques are deeply involved with the direct study of DNA. This field has been revolutionized by the invention of recombinant DNA technology. The DNA of any gene of interest from a donor organism (such as a human) can be cut out of a chromosome and inserted into a vector to make recombinant DNA, which can then be amplified and manipulated, studied, or used to modify the genomes of other organisms by transgenesis.

Experimental methods are connected with use of animals in the experiment for reveal of possible genetic defects in humans. Genetically diverse lines of organisms can be crossed in such a way to produce different combinations of alleles in one line. Many of the plants and animals used by humans today (e. g., cows, pigs, chickens, sheep, wheat, corn (maize), potatoes, and rice) have been bred in this way.

SITUATIONAL TASKS

№ 1

What is the probability of a child birth with syndactylism (accreted fingers) in the family, where the father has this developmental defect, while the mother and the first child have a normal structure of fingers?

Character	Gene	Genotype

№ 2

Determine the birth probability of short-fingered children in the family where parents have a developmental defect and are heterozygotes.

Character	Gene	Genotype

№ 3

In the family, where both spouses suffer from achondroplasia, a normal child was born. What is the birth probability of healthy children?

Character	Gene	Genotype

№ 4

Determine the birth probability of children with otosclerosis in the family, in which parents are heterozygous by the analyzed character (penetrance of 30 %).

Character	Gene	Genotype

№ 5

Determine the birth probability of children with astigmatism in the family, where father is heterozygous and mother does not suffer astigmatism.

Character	Gene	Genotype

№ 6

Homozygous individuals by a gene of crescent-cellularity usually die before puberty, heterozygotes are viable, anemia is revealed in hypoxia. What

is the birth probability of phenotypically and genotypically healthy children, if both parents are heterozygous by the analyzed character?

Character	Gene	Genotype

№ 7

What is the birth probability of sick children in the family where one of the parents is heterozygous by a gene of phenylketonuria, and another is healthy (his parents, brothers and sisters were healthy)?

Character	Gene	Genotype

№ 8

Successes of modern medicine allow to prevent the development of galactosemia and to avoid consequences of metabolic impairments. What is the birth probability of sick children in the family where one of the spouses is homozygous by a gene of galactosemia, but the development of his disease is prevented by diet, and the other is heterozygous on a galactosemia gene?

Character	Gene	Genotype

№ 9

What descendants can be expected from heterozygous parents on a gene of alcaptonuria?

Character	Gene	Genotype

№ 10

Determine the birth probability of sick children with hepatocerebral dystrophy (Wilson's illness) in the family where the father is sick, and the mother is healthy (her parents, brothers and sisters were healthy).

Character	Gene	Genotype

№ 11

The man, ill with hemophilia A, married a healthy woman whose father suffered from hemophilia A. Determine the birth probability of healthy children in this family?

Character	Gene	Genotype

№ 12

In the family where the parents have hypoplasia of dental enamel, a son was born with normal teeth. What is the birth probability of sons with normal teeth?

Character	Gene	Genotype

№ 13

What is the birth probability of children with the absence of lateral incisors if the parents have this dental abnormality and they are heterozygous by the analyzed character?

Character	Gene	Genotype

№ 14

How many bodies of sex chromatin are there in people with genotype ОХ? ХХУ? ХХХ? ХХХУ? What is the sex of these people and what are they ill with?

№ 15

The karyotype of the given patient is characterized by the presence of 3 sex chromosomes. It is associated with a large stature, eunuch-like constitution, spermatogenesis impairment, microorchia, psychic impairment. What is the name of the given syndrome? What is the karyotype of the given syndrome?

№ 16

In patient М., height of 153 cm, is a skin fold on the neck, «sphinx» neck, primary amenorrhea, sterility. There are congenital defects of the heart and kidneys. What is the name of the given syndrome? What is the karyotype of the given syndrome?

ANSWERS TO SITUATIONAL TASKS

Task 1. 50 %.
Task 2. 75 %.
Task 3. 33.3 %.
Task 4. 40 %.
Task 5. 50 %.
Task 6. 25 %.
Task 7. 0 %.
Task 8. 50 %.
Task 9. 75 % — healthy; 25 % — sick.
Task 10. 0 %.
Task 11. 50 %.
Task 12. 50 %.
Task 13. 75 %.
Task 14. 1) Barr bodies — 0; female gender; Turner's syndrome;
2) Barr bodies — 1; male; Klinefelter syndrome;
3) Barr bodies — 2; female gender; syndrome «Superwoman»;
4) Barr bodies — 3; male; Klinefelter syndrome.
Task 15. Klinefelter syndrome.
Task 16. Turner's syndrome.

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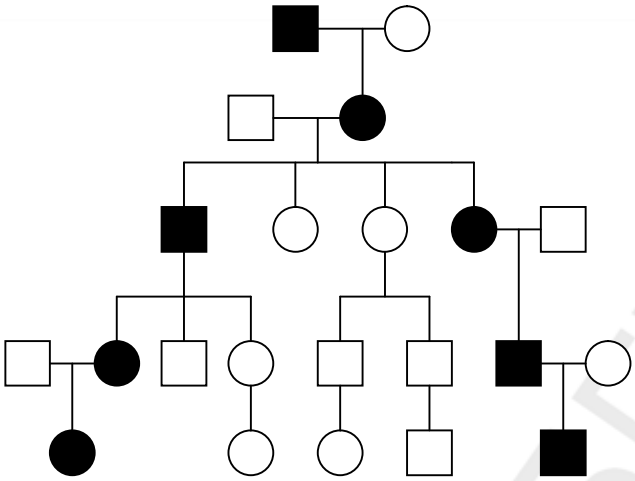
Appendix

EXAMPLES OF DISEASES AND DEVELOPMENTAL ABNORMALITIES WITH DIFFERENT TYPES OF INHERITANCE

Inheritance type	Pathology form
1. Autosomal-dominant (A-D)	Polydactylism Syndactylism Brachydactylism Dactylion Curvature of fingers, nails Anonychia (underdevelopment of nails) Absence of lateral incisors Short-sightedness Far-sightedness Astigmatism Otosclerosis Achondroplasia Family hypercholesteremia Chorea of Huntington Polyposes of the large intestine Neurofibromatosis
2. Autosomal-recessive (A-R)	Crescent-cellular anemia (by incomplete domination) Galactosemia Phenylketonuria Alcaptonuria Albinism Glycogenoses Mucoviscidosis Wilson–Konovalov disease (hepato-cerebral dystrophy) Adrenogenital syndrome Congenital deaf-muteness Microcephaly
3.Dominant X-linked (D-X)	Frontal-nasal dysplasia Hypoplasia of dental enamel Cataract Rickets, resistant to vitamin D
4. Recessive X-linked (R-X)	Hemophilia A and B Daltonism Hypogammaglobulinemia Duchenne's muscular dystrophy Hemeralopia
5.Hollandric Y-linked (H-Y)	Escessive hairiness of auricles Azospermia
6. Mitochondrial (M)	Leber's optic atrophy Mitochondrial encephalopathy Myoclonal epilepsy Cardiomyopathy

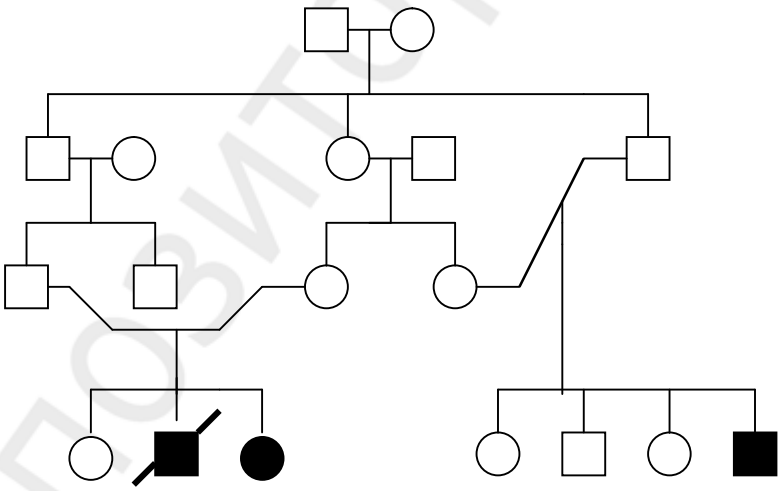
Autosomal-dominant type of inheritance



Inheritance characters on A-D type:

1. Identical pathology incidence both in males and females.
2. The presence of sick persons in every generation (vertical distribution character of the disease).
3. Birth probability of a sick child is 50 % (irrespectively of the child's sex and the number of deliveries).
4. Healthy members of the family have as a rule healthy descendant.

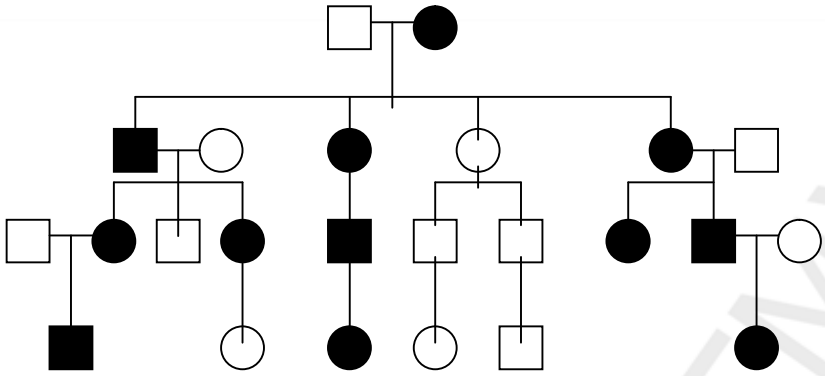
Autosomal-recessive type of inheritance



Inheritance characters on A-R type:

1. Identical pathology incidence both in males and females.
2. Manifestation of pathology in the genealogical tree along the horizontal line, often in siblings.
3. The patient's parents are healthy as a rule.
4. The disease may be revealed in other relatives, for example, y cousins and second cousins of the patient.

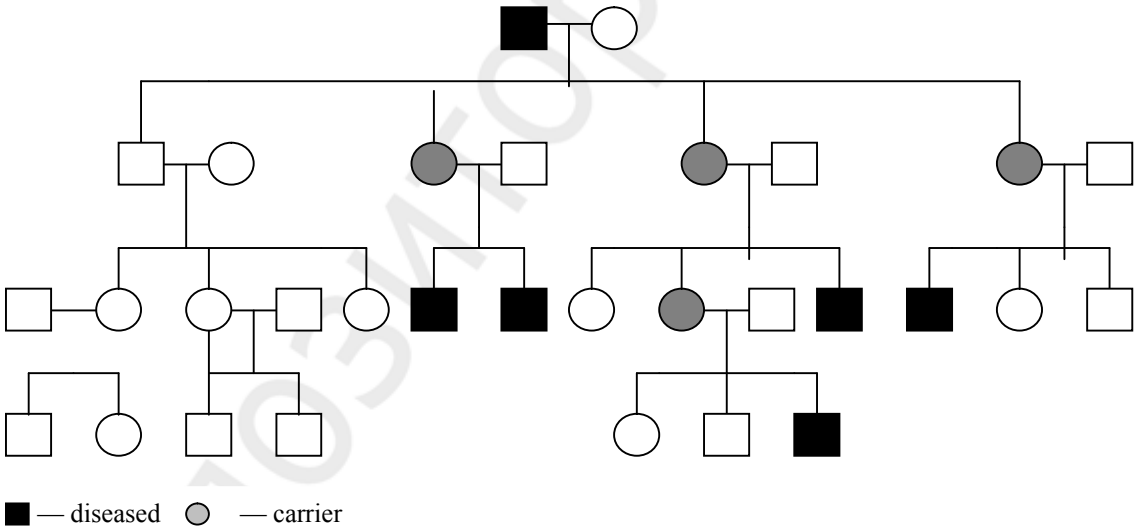
Dominant linked with X-chromosome type of inheritance



Inheritance characters on D-X type:

1. Fall ill both males and females, but females twice as often.
2. The disease is transmitted from a sick man to all daughters, but not sons (sons get an У-chromosome from the father).
3. The disease is transmitted from a sick woman both to sons and daughters with an equal probability.
4. A more severe course of the disease is observed in males than in females.

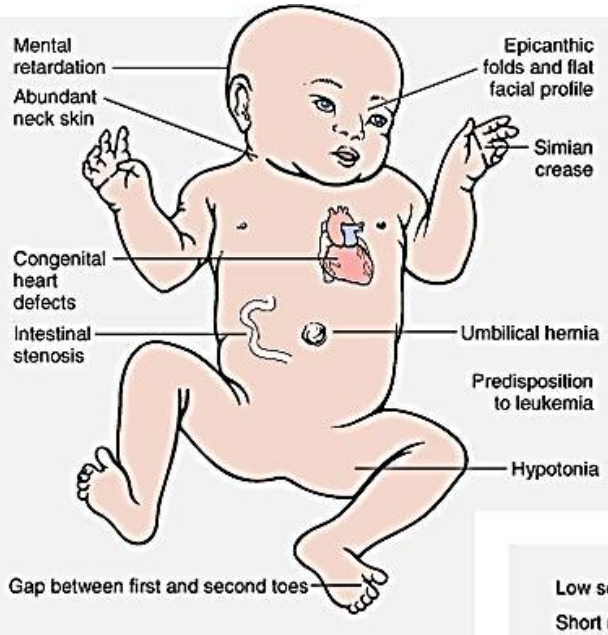
Recessive linked with X-chromosome type of inheritance



Inheritance characters on R-X type:

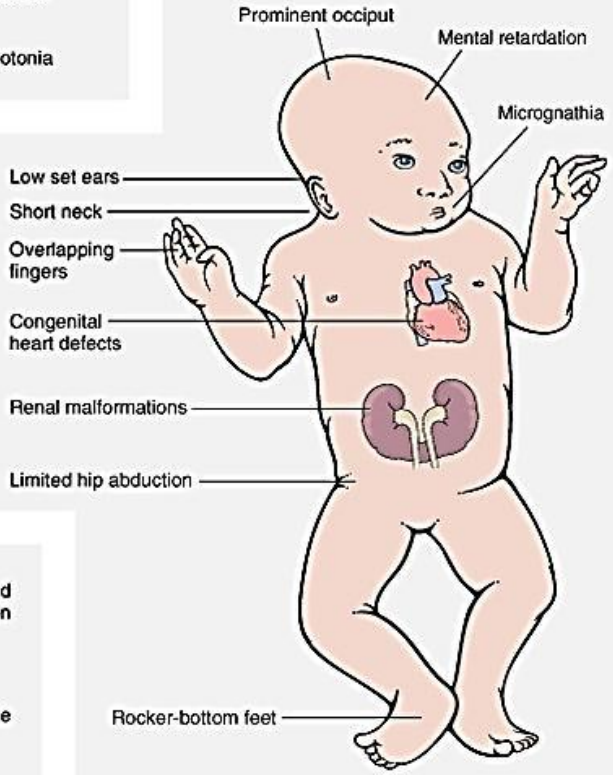
1. Sick children are born in phenotypically healthy parents.
2. The disease is observed mainly in males (mothers of patients are obligate carriers of a pathologic gene).
3. A son never inherits his father's disease.
4. A carrier of a mutation gene has the birth probability of a sick child of 25 % (irrespectively of sex of the neonate), the birth probability of a sick boy is equal to 50 %.

Clinical-cytogenetic characterization of some syndromes associated with numerical abnormalities of autosomes



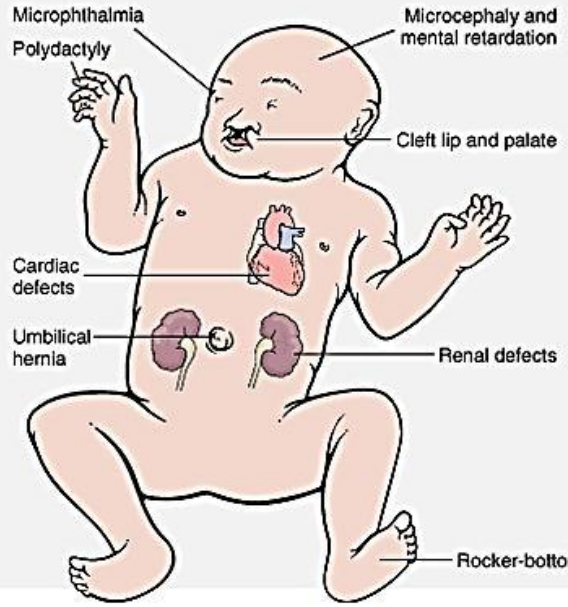
TRISOMY 21: DOWN SYNDROME

Incidence: 1 in 700 births
Karyotypes:
Trisomy 21 type: 47,XX, +21
Translocation type: 46,XX,der(14;21)(q10;q10),+21
Mosaic type: 46,XX/47,XX, +21



TRISOMY 18: EDWARDS SYNDROME

Incidence: 1 in 8000 births
Karyotypes:
Trisomy 18 type: 47,XX, +18
Mosaic type: 46,XX/47,XX, +18



TRISOMY 13: PATAU SYNDROME

Incidence: 1 in 15,000 births
Karyotypes:
Trisomy 13 type: 47,XX, +13
Translocation type: 46,XX,+13,der(13;14)(q10;q10)
Mosaic type: 46,XX/47,XX, +13

CONTENT