DNA-TECHNOLOGY

REPRODUCTION

REPRODUCTIVE GENETICS:

MONOGENSCREEN, ANEUSCREEN ILM, ANEU QF-PCR, NEOSCREEN SMA/TREC/KREC

Prevention of hereditary and congenital diseases in children and prevention of childhood disability is one of the important tasks of the genetic counseling. It can be carried out as part of preconception care, prenatal and neonatal screenings and enables doctors to identify possible diseases at different stages of family planning.

At the stage of preconception preparation, it is possible to identify the carriage of mutations in future parents, prenatal screening allows to evaluate the risks of fetal malformations in early pregnancy, and neonatal screening can help to take measures to minimize the symptoms of the possible disease as early as possible.

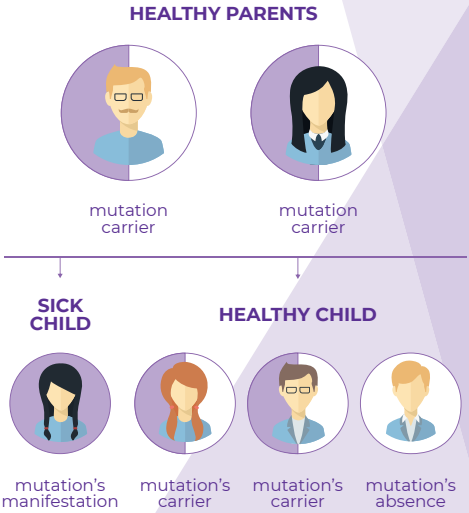
PREGNANCY PLANNING —

TEST «MONOGENSCREEN»

Monogenic diseases are hereditary disorders that develop as a result of mutations in one gene, leading to a change in the functionality of the protein. Among them, a group of autosomal recessive disorders stands out, which are inherited according to the laws of classical Mendelian genetics and manifest themselves in the recessive homozygotes.

Two healthy parents who are heterozygotes for the same mutation have a 25% chance of having a child homozygous for a recessive trait.

In Russia, neonatal screening for monogenic diseases — cystic fibrosis, phenylketonuria, galactosemia, and sensorineural non-syndromic hearing loss — is mandatory for all newborns [1-2]. At present, biochemical and audiological screenings are used, which bring out the phenotypic manifestations of the disorder and allow physicians to prescribe treatment to minimize the symptoms of the disease.



Genetic screening is an alternative approach to the problem of monogenic diseases. Carriers of recessive mutations have no manifestations of disease and have been considered outside the medical field, only genetic testing can detect them. So, healthy heterozygous carriers planning a pregnancy can be made aware of the possible risks and have the opportunity to use assisted reproductive technologies [3].

Genetic testing of prospective parents makes it possible to assess the risk of having a child with monogenic disorders and may become the basis for their primary prevention.

The MonogenScreen test

is designed to detect mutations in the genes that lead to cystic fibrosis, phenylketonuria, galactosemia, and sensorineural non-syndromic hearing loss.

Genes included in the **MonogenScreen** test and related diseases:

Gene	Disease	Prevalence in Russia
CFTR	cystic fibrosis	1:10 000
GJB2	sensorineural non-syndromic hearing loss	1:1 000
GALT	galactosemia	1:20 000
PAH	phenylketonuria	1:10 000

Cystic fibrosis is an autosomal recessive monogenic disease characterized by lesions of all exocrine glands, as well as vital organs and systems [4, 5]. In cystic fibrosis, electrolyte transport in the epithelial cells lining the excretory ducts of the exocrine glands is disrupted. As a result of a change in the electrolyte composition and dehydration, the excreted secret becomes excessively thick and viscous. In this case, the lungs, gastrointestinal tract, liver, pancreas, and genitourinary system suffer [4, 6]. The progression of pulmonary and heart failure is the cause of death in 95% of cases of cystic fibrosis.

The HGMD-base (The Human Gene Mutation Database) describes about 2,000 mutations in the CFTR gene responsible for the development of symptoms of cystic fibrosis [7]. In patients with cystic fibrosis from the Russian Federation, the following mutations are most common [8]:

F508del	52,8%	G542X	1,3%
CFTRdele2,3	6,2%	394delTT	0,9%
E92K	3%	R334W	0,8%
2143delT	2,1%	W1282X	0,6%
3849+10kbC>T	2%	3821delT	0,5%
2184insA	1,8%	S466X	0,5%
1677delTA	1,8%	3944delGT	0,3%
N1303K	1,5%		

All mutations from the above list can be determined using the **MonogenScreen** RT PCR kit.

Sensorineural non-syndromic hearing loss is a hereditary disease associated with congenital bilateral hearing loss. The reason is mutations in the GJB2 gene, the most common of which is the 35delG deletion [9]. In a healthy population, the frequency of its heterozygous carriage is 2-6%. In the Russian Federation, this form of congenital hearing loss occurs in more than 50% of children with persistent bilateral hearing loss.

In children with two recessive mutations in the GJB2 gene, in the absence of inflammatory changes in the middle ear, hearing thresholds are usually stable. Early initiation of rehabilitation can slow or prevent the progression of the disease and avoid the development of total deafness.

Galactosemia is a group of hereditary disorders of carbohydrate metabolism, in which an excess of galactose and its metabolites accumulate in the body [10]. Galactose is a source of energy for the cell, plays an important prebiotic role, and also serves as an essential building material for the synthesis of glycoproteins, glycolipids as well as other complex compounds used by the body to form cell membranes, including in nervous tissue. Violation of the metabolism of galactose inevitably leads to disruption of the functioning of many organs and systems of the body.

The most common form is type I galactosemia. It arises due to mutations in the *GALT* gene, which leads to a deficiency of galactose-1-phosphate uridyltransferase. The most common mutations are Q188R and K285N. Type II and III galactosemias are caused by mutations in the GALK1 and GALE genes, respectively [10]. At the same time, type II galactosemia occurs in 1:100,000 newborns, and type III is very rare [11].

As a result of insufficiency of any of the three enzymes encoded by these genes, the concentration of galactose in the blood increases. In type I galactosemia, galactose-1-phosphate also accumulates in the patient's body, which causes most of the clinical manifestations of the disease and the formation of delayed complications. Excessive galactose in the body can also be converted to galactitol, which contributes to the formation of cataracts. There is evidence that a high content of galactitol in brain tissues contributes to the swelling of nerve cells and the formation of a brain pseudotumor in some patients [10].

Detecting the disease at an early stage allows timely exclusion of sources of galactose from the child's diet and prevents the development of symptoms of the disease.

Phenylketonuria is an autosomal recessive disease conditioned by a metabolic disorder of the amino acid phenylalanine (FA), that enters into the human body with protein foods. The cause of the disease is the insufficiency of phenylalanine hydroxylase activity, which leads to the accumulation of FA and its metabolic products in the body [12-14]. At high FA concentrations, alternative metabolic pathways are activated with the formation of phenylpyruvate, phenylacetate, and phenyllactate, which have a toxic effect on various organs and tissues [12, 13]. The central nervous system suffers the most. Brain damage results from an imbalance of amino acids in the brain tissues, impaired myelination of neurons, and a decrease in the synthesis of norepinephrine and serotonin, which play an extremely important role in the maturation and functioning of the CNS [12, 13, 15].

Regardless of the diagnostic concentration of FA, the most common (98%) cause of FA metabolism disorders are mutations in the PAH gene. The carrier frequency of pathogenic mutations in the PAH gene in the Russian Federation is 1:50 [16]. The most common mutations are IVS12+1G>A, R261Q, R252W, R158Q, P281L, IVS10nt546, which can be detected using the MonogenScreen RT PCR kit [17].

TEST IS RECOMMENDED FOR

- pregnancy planning
- suspected carriage of mutant alleles of the CTFR, GJB2, GALT, PAH genes

MATERIAL SUITABLE FOR TESTING:

- Dry blood spots
- Whole peripheral blood

DURING PREGNANCY —

ANEUSCREEN ILM and ANEU QF-PCR

Chromosomal aneuploidies are among the most common causes of reproductive losses, neonatal mortality and childhood disability. These are genetic disorders in which chromosome number in cells is not a multiple of the main set. Miscarriages in the 1st trimester of pregnancy in 41-50% of cases are caused by aneuploidy, most often by autosomal trisomies [18].

In newborns, chromosomal aneuploidies occur with a frequency of up to 1:300. The most common in newborns are trisomies on chromosomes 21, 18 and 13, leading to manifestations of Down, Edwards and Patau syndromes. Aneuploidies for other autosomes are extremely rare in newborns, because lead to early termination of pregnancy [19].

DIAGNOSTICS

In order to prevent hereditary and congenital diseases in children and limit childhood disability, it is introduced a mandatory prenatal examination of pregnant women in Russia, which includes two stages: screening and clarifying the nature of the pathology [20].

As a part of the mass combined screening of pregnant patients at 11-14 weeks (I trimester) of pregnancy, they are sent for ultrasound of the thickness of the collar space and for studies of the blood levels of β-hCG (human chorionic gonadotropin) and PAPP-A (protein A associated with pregnancy) with subsequent software calculation of the individual risk of having a child with a chromosomal pathology [20]. In the case of a high (1/100 and above) risk, the patient is referred for a second ultrasound examination with a recalculation of the individual risk indicator.

If a high risk is confirmed, the patient is recommended to undergo an invasive examination (up to 14 weeks — aspiration/biopsy of the chorionic villi, after 14 weeks — placentocentesis, amniocentesis or cordocentesis) with further use of the cytogenetic method or molecular karyotyping [20].

Mass combined screening is based on indirect markers and has limited sensitivity and specificity. Thus, during mass screening in order to detect chromosomal disorders, many women bearing a healthy fetus fall into the risk group. The high probability of a false positive screening result leads to a decrease in confidence in it and, consequently, to a significant number of refusals from its verification by invasive diagnostic methods. It is abandoned by about half of women from the high-risk group for giving birth to a child with a chromosomal pathology, who do carry a fetus with trisomy on the 21st chromosome.

Important tasks in the development of prenatal diagnostics are to increase the accuracy of screening and minimize invasive interventions.

The most promising in this direction is a non-invasive method of prenatal aneuploidy screening (NIPT), based on the analysis of fetal extracellular DNA in the mother's blood. It is recommended to be carried out from the 11th week of pregnancy [21].

The DNA-Technology company offers 2 sets of reagents for the detection of aneuploidy in the fetus: AneuScreen ILM and QF-PCR Aneu.
Studies are recommended to assess the risk of aneuploidy and chromosomal abnormalities in the fetus.

Reagent kit

AneuScreen ILM study

The AneuScreen ILM reagent kit is intended for non-invasive DNA screening of pregnant women in order to detect fetal chromosomal abnormalities — aneuploidies for autosomes 13, 18, 21, sex chromosomes X and Y, as well as partial duplications and deletions using the study of extracellular fetal DNA by high-throughput sequencing (NGS) on the Illumina platform using the AneuScreen software.

After sequencing, AneuScreen software determines the proportion of fetal DNA and the risk of aneuploidy (low/high). If a high risk of trisomy for other chromosomes is detected, the software indicates this in the report based on the results of the study. It is also possible to obtain information about the presence of partial duplications and deletions with the participation of a bioinformatician.

BIOMATERIAL FOR RESEARCH:

mother's blood

The study is possible with multiple pregnancy, the use of a donor egg and surrogate motherhood.

If it is necessary to carry out an invasive test for the aneuploidy, the **Aneu QF-PCR** study can be performed.

Reagent kit

Aneu QF-PCR

Aneu QF-PCR reagent kit is intended for prenatal and postnatal diagnosis of fetal chromosomal abnormalities: trisomies for autosomes 13, 18, 21 and aneuploidies for sex chromosomes X and Y by PCR followed by fragment analysis of amplification products using genetic analyzers.

BIOMATERIAL FOR RESEARCH:

For prenatal diagnosis — epithelial cells of the amniotic fluid, biopsies of chorionic villi

For postnatal diagnosis — whole blood, sectional material

NEWBORN SCREENING — NEOSCREEN SMA/TREC/KREC

Neonatal screening is a diagnostic study that allows you to identify the most common genetic diseases that pose a threat to the life and health of a child. Neonatal screening allows doctors to detect the disease at the preclinical stage, start treatment in a timely manner and avoid serious complications.

Previously (until now), neonatal screening of five hereditary diseases was carried out in Russia: cystic fibrosis, galactosemia, adrenogenital syndrome, congenital hypothyroidism, and phenylketonuria. From 2023, an expanded neonatal screening program will be introduced. The list of studied hereditary diseases will expand to 36, including spinal muscular atrophy (SMA) and primary immunodeficiencies (PID) [22].

PRIMARY IMMUNODEFICIENCIES

Primary immunodeficiency states (PIDS) are a genetically heterogeneous group of congenital disorders of the immune system, which are clinically manifested by recurrent infectious and autoimmune diseases of varying severity, as well as malignant neoplasms [23]. Most primary immunodeficiencies appear in infancy and early childhood.

The most dangerous form of PIDS is severe combined immunodeficiency (or severe combined cellular and humoral immunity deficiency (SCID). SCID is characterized by an almost complete absence of mature T-lymphocytes with or without B- and NK-lymphocytes, which leads to early extremely severe infections caused by both obligate pathogens and opportunistic microorganisms.

In the absence of pathogenetic therapy, SCID leads to death in the first two years of life [24].

Until recently, it was almost impossible to identify children with primary immunodeficiency before the onset of the disease. Over the past decade, the determination of universal markers of T-cell immunodeficiencies — TREC (T-cell receptor excision circle) and B-cell immunodeficiencies — KREC (kappa-deleting recombination excision circle) for screening congenital pathologies of the immune system has been actively introduced into the practice of healthcare in many countries [25, 26].

TREC and KREC are extrachromosomal circular DNA structures that are formed during the rearrangement of genes encoding T- (TCR) and B- (BCR) cell receptors of lymphocytes and serve as markers of naive T- and B-cell populations [27, 28]. TREC and KREC molecules are stable and do not replicate during mitosis, allowing

TREC to be used as a marker of the normal proliferation of T-lymphocytes in the thymus, and KREC as a marker of the normal development of the B-cell link of the immune system.

Regardless of the genetic defect, low levels of TREC and KREC in the blood of newborns indicate T- and/or B-cell lymphopenia, which makes it possible to use the determination of TREC and KREC levels for early diagnosis of immunodeficiency states [24-28, 30].

Analysis of TREC level is effective for verification of severe combined immunodeficiency, combined immune disorders without an identifiable molecular cause, as well as syndromic immunodeficiency states [24, 27, 30]. KREC quantification is used to diagnose congenital agammaglobulinemias and other B-cell disorders [28, 30].

When analyzing the levels of TREC and KREC, it is important to take into account factors that can affect the decrease in the level of analytes in addition to PIDS. These include:

- Gestational age (prematurity);
- Hereditary diseases (often caused by chromosomal aneuploidies and microdeletion syndromes) [31];
- Secondary or idiopathic T-cell lymphopenia;
- Pathology of the development of the cardiovascular system, gastrointestinal tract;
- Hypo- or aplasia of the thymus [31-33].

Analysis of TREC and KREC levels in newborns is carried out using dried capillary blood spots plotted on neonatal screening cards by using real-time PCR [25-30] and meets all the requirements for inclusion in the neonatal screening program.

PROXIMAL SPINAL MUSCULAR ATROPHY 5Q

Proximal spinal muscular atrophy 5q (SMA) is a severe autosomal recessive neuromuscular disease characterized by progressive symptoms of flaccid paralysis and muscle atrophy due to degeneration of α-motor neurons of the anterior horns of the spinal cord [31]. The development of proximal spinal muscular atrophy 5q is caused by mutations in the SMN1 gene, which encodes the survival moto neuron (SMN) protein. The SMN1 gene is mapped to chromosome 5 and has a centromeric copy (SMN2) that differs by five nucleotides in the DNA sequence. Due to differences in the nucleotide sequence, the main transcript

of the SMN2 gene does not contain exon 7 and is functionally defective [34, 35]. Homozygous deletions of exons 7 or 7-8 represent the most common variant of SMN1 gene mutations and are detected in 95% of SMA patients [34, 35].

SMA is one of the most common hereditary diseases. The general population prevalence of proximal spinal muscular atrophy is 1 in 6,000 to 10,000 newborns [35, 36]. For the diagnosis of SMA, a set of examination methods is used, including genealogical analysis, neurological examination, electroneuromyography, and genetic testing [34-35].

All patients with suspected SMA 5q are recommended to undergo a molecular genetic study of mutations in the SMN1 gene; the diagnosis of SMA is confirmed when a deletion of exon 7 or exons 7–8 of the SMN1 gene is observed in the homozygous state (i.e., in both copies of the gene) [35]. Genetic screening of newborns for SMA makes it possible to detect the presence of a mutation in the SMN1 gene in the first weeks of a child's life, before the first symptoms appear, and to start treatment in a timely manner, to mitigate the course of the disease, and to avoid the patient's disability when using pathogenetic therapy.

RT PCR kit

NeoScreen SMA/TREC/KREC

The NeoScreen SMA/TREC/KREC RT PCR kit is designed to detect a homozygous deletion of the 7* exon of the SMN1 gene and a relative quantitative assessment of the content of T-cell receptor excision circles (TREC) and recombination excision circles of the kappa-deleting element (KREC) in order to screen for spinal muscle atrophy and primary immunodeficiencies by real-time PCR.

INDICATIONS FOR PERFORMING STUDIES:

screening of newborns for proximal spinal muscular atrophy 5q (SMA) and primary immunodeficiencies (PID) associated with disorders of the T- and B-cell components of the immune system.

MATERIAL SUITABLE FOR TESTING:

Dry blood spots

Whole peripheral blood samples

* determination of deletion of exon 7 and exon 7-8 of the SMN1 gene in the homozygous state

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