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ISCHEMIC HEART DISEASE: MOLECULAR AND GENETIC BASIS

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Annotation: Coronary heart disease (CHD) remains one of the leading causes of death and disability worldwide. Despite significant progress in diagnosis and treatment, the prevalence of the disease remains high, which necessitates an in-depth study of its pathogenesis. In recent years, special attention has been paid to the molecular and genetic mechanisms of CHD development. Genetic factors play a key role in the regulation of lipid metabolism, inflammatory processes, endothelial function and hemostasis, forming an individual predisposition to atherosclerosis and coronary ischemia. The article discusses current concepts of the genetic basis of CHD, the main candidate genes and polymorphisms, as well as the prospects for applying molecular genetic research in clinical practice and personalized medicine.

Key words: coronary heart disease, molecular genetics, atherosclerosis, gene polymorphism, genetic predisposition, personalized medicine.

Introduction. Coronary heart disease (CHD) is a group of clinical conditions that occur due to a mismatch between the myocardial oxygen demand and its delivery through the coronary arteries. The main morphological basis of coronary artery disease is atherosclerosis of the coronary vessels, leading to their stenosis or occlusion. The disease includes such clinical forms as stable and unstable angina, myocardial infarction, post-infarction cardiosclerosis, and sudden coronary death [14,16].

Traditionally, the development of CHD is associated with exposure to modifiable risk factors-smoking, dyslipidemia, arterial hypertension, diabetes mellitus, and obesity. However, numerous clinical and epidemiological studies have shown that the presence of CHD in the next of kin significantly increases the risk of the disease, especially in the early onset of the pathology. This indicates an important role of hereditary factors in the formation of coronary heart disease [1,8].

The development of molecular genetics and genomic technologies has made it possible to identify a large number of genes and genetic variations associated with CHD. Their study opens up new opportunities for understanding the pathogenesis of the disease and introducing personalized approaches to prevention and treatment [6,11,18].

Genetic nature of coronary heart disease.

CHD is a multi-factorial disease characterized by a complex interaction of genetic and external factors. Unlike monogenic diseases, hereditary predisposition to CHD is formed due to the combined influence of many genes, each of which makes a small contribution to the overall risk.

Genetic factors can determine:

- features of lipid metabolism;
- intensity of the inflammatory response;
- functional state of the endothelium;
- activity of the blood coagulation system;
- the body's response to medications.

Hereditary predisposition is especially significant in the early development of CHD, as well as in patients without pronounced traditional risk factors [12, 17].

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Lipid metabolism genes and atherosclerosis

Lipid metabolism disorders are a key mechanism for the formation of atherosclerotic plaques. Among the most studied genes are:

The APOE gene **APOE**encodes apolipoprotein E, which is involved in the transport of cholesterol and lipoproteins. The e4 allele is associated with increased levels of total cholesterol and low-density lipoproteins, as well as an increased risk of CHD.

The low-density lipoprotein receptor (**LDLR**) gene plays a key role in removing cholesterol from the bloodstream. Mutations in this gene lead to familial hypercholesterolemia and early development of coronary atherosclerosis.

The PCSK9 protein regulates the degradation of LDL receptors. Genetic variants that increase PCSK9 activity are associated with increased cholesterol levels and the risk of CHD, which served as the basis for the development of PCSK9 inhibitors.

Genes of inflammation and immune response

Atherosclerosis is currently considered as a chronic inflammatory disease of the vascular wall. Genetic variations affecting inflammatory responses play an important role in the development of CHD [3, 5, 7].

The main genes of inflammation include:

- **IL6**-encodes interleukin-6, which is involved in the systemic inflammatory response.
- **TNF-alpha** is a tumor necrosis factor that increases inflammation and endothelial dysfunction.
- **CRP** is a C — reactive protein gene, the level of which correlates with the risk of cardiovascular complications.

Polymorphisms of these genes can contribute to the accelerated growth of atherosclerotic plaques and their instability.

Endothelial function genes

The vascular endothelium plays a central role in regulating vascular tone, platelet aggregation, and inflammatory processes. Violation of its function is one of the earliest stages of the development of CHD [2, 4, 9].

Of particular importance is **the NOS3 gene** encoding endothelial NO synthase. Nitric oxide has a pronounced vasodilating and antiatherogenic effect. NOS3 genetic polymorphisms are associated with reduced NO production, increased vascular tone, and a risk of coronary ischemia.

Genes of the hemostatic system

Acute coronary events are most often associated with coronary artery thrombosis. Genetic changes in the hemostatic system increase the risk of blood clots:

- **F5 (factor V)** - Leyden mutation leads to resistance to activated protein C;
- **F2 (prothrombin)** — individual polymorphisms increase blood clotting.
- **PAI-1**-affects fibrinolysis and blood clot resistance.

The presence of such genetic variants increases the likelihood of a myocardial infarction, especially when combined with traditional risk factors.

Genome-wide Association Studies (GWAS)

Genome-wide association studies have identified dozens of genetic loci associated with CHD risk. The most significant part of chromosome **9p21** is associated with the development of atherosclerosis, regardless of cholesterol levels and other risk factors.

GWAS confirmed the polygenic nature of CHD and allowed the development **of polygenic risk scores** used to assess individual predisposition [4, 15].

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Molecular genetics and personalized medicine

The use of molecular genetic methods in clinical practice opens up new opportunities:

- early detection of people at high risk of coronary heart disease;
- individual selection of lipid-lowering and antithrombotic therapy;
- predicting the effectiveness and safety of medicines.

Of particular importance is pharmacogenetics, which allows us to take into account the genetic features of drug metabolism and reduce the risk of side effects.

Conclusion. Ischemic heart disease is a multi-factorial disease, in the development of which molecular and genetic mechanisms play an important role. Genetic variations affect lipid metabolism, inflammation, endothelial function, and the hemostatic system, forming an individual predisposition to the disease. Studying the genetic basis of coronary heart disease contributes to the development of personalized medicine and can significantly improve the effectiveness of prevention and treatment of coronary pathology.

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