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MOLECULAR GENETIC BASIS OF DIAGNOSTICS AND TREATMENT OF ISCHEMIC HEART DISEASE (LITERATURE REVIEW)

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Abstract

In the Republic of Uzbekistan, diseases of the circulatory system are one of the most pressing health problems and occupy one of the leading places in the structure of mortality of the population. The development of multifactorial diseases, including cardiovascular diseases (CVD) are based on genetic disorders, both hereditary and acquired, causing an individual predisposition to the development of the disease and acquired by an individual as a result of exposure to external environmental factors. Most of such genetic disorders are represented by point mutations (single-nucleotide polymorphisms) or short deletions. Also, the development of coronary heart disease and ischemic brain disease is based on the interaction of various genetic factors of the external environment. In this regard, the problem of studying the genetic mechanisms of CVD is quite complex and is associated with the development of adequate approaches and methods of analysis, which is noted by many authors. One of the effective approaches to studying the role of genetic mechanisms in the development of CVD is associated with the identification of a group of genes with the potentially greatest contribution to the pathogenesis of the disease – these are the so-called candidate genes.

Keywords: molecular genetics, genotype, single nucleotide polymorphism (SNPI), ischemic heart disease, genetic thrombophilia, genes IIGB3, GP1B/IIIA, NOS3, P2RV12, ITGA2.

YURAK ISHEMIK KASALLIKLARINI DAVOLASH VA DIAGNOSTIKASINING MOLEKULAR GENETIK ASOSLARI (ADBIYOTLAR SHARXI)

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Annotatsiya

O‘zbekiston Respublikasida qon aylanish tizimi kasalliklari, sog‘liqni saqlashning eng dolzarb muammolaridan biri bo‘lib, aholi o‘limida yetakchi o‘rinlardan birini egallaydi. Ko'p faktorli kasalliklarning, shu jumladan yurak-qon tomir kasalliklarining (YuQTK) rivojlanishi irsiy va orttirilgan, kasallikning rivojlanishiga individual moyillikni keltirib chiqaradigan va tashqi muhit omillari ta'siri natijasida shaxs tomonidan orttirilgan genetik kasalliklarga asoslanadi. Ushbu

genetik kasalliklarning aksariyati mutatsiyalari (yagona nukleoid polimorfizmlari) yoki qisqa deletsiyalar bilan ifodalanadi. Shuningdek, IHD va koroner miya kasalliklarining rivojlanishi turli genetik muhit omillarining o'zaro ta'siriga asoslanadi. Shu munosabat bilan, YuQTKning genetik mexanizmlarini o'rganish muammosi juda murakkab va ko'plab mualliflar tomonidan ta'kidlangan adekvat yondashuvlar va tahlil usullarini ishlab chiqish bilan bog'liq. YuQTK rivojlanishidagi genetik mexanizmlarning rolini o'rganishning samarali usullaridan biri kasallikning patogeneziga eng katta hissa qo'shadigan genlar guruhini aniqlash bilan bog'liq - bular nomzod genlar deb ataladi.

Kalit so'zlar: molekulyar genetika, genotip, yagona nukleotid polimorfizmi (SNPI), yurak tomirlari kasalligi, genetik trombofiliya, IIGB3, GP1B/IIIA, NOS3, P2RV12, ITGA2 genlari.

МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ ОСНОВЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА (ОБЗОР ЛИТЕРАТУРЫ)

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Аннотация

В Республике Узбекистане болезни системы кровообращения представляют одну из самых актуальных проблем здравоохранения и занимают одно из ведущих мест в структуре смертности населени. В основе развития мультифакториальных заболеваний, в том числе и сердечно-сосудистых заболеваний (ССЗ) лежат генетические нарушения, как наследственно-приобретенные, обусловливающие индивидуальную предрасположенность к развитию заболевания и приобретенные индивидуумом в результате воздействия внешних факторов среды. Большая часть таких генетических нарушений представлена точечными мутациями (однонуклеоидными полиморфизмами) или непротяженными делециями. Также в основе развития ИБС и ишемической болезни мозга лежит взаимодействие различных генетических факторов внешней среды. В связи с этим проблема исследования генетических механизмов ССЗ является достаточно сложной и связана с разработкой адекватных подходов и методов анализа, что отмечается многими авторами. Один из эффективных подходов к изучению роли генетических механизмов развития ССЗ связан с выделением группы генов с потенциально наибольшим вкладом в патогенез заболевания – это так называемые гены-кандидаты.

Ключевые слова: молекулярная генетика, генотип, однонуклеотидный полиморфизм (SNPI), ишемическая болезнь сердца, генетические тромбофилии, гены IIGB3, GP1B/IIIA, NOS3, P2RV12, ITGA2.

Achievements of modern molecular genetics in decoding the human genome contributed to the birth of a new science – medical genomics, one of the central places in which is occupied by research into the influence of genetic factors on the formation of pathological conditions in humans. A special place in this research is

occupied by cardiovascular diseases, since they are widespread, characterized by a severe course leading to disability, and a high mortality rate in developed countries and in Kazakhstan [1, 2, 3]. At the same time, much attention is paid to such diseases as coronary heart disease (CHD) and ischemic brain disease. In the structure of mortality from CVD, these diseases account for about 85-90% [1, 5]. The social significance of the problem is enhanced by the tendency observed in recent years for the occurrence of heart attacks and strokes in young people. In this regard, research devoted to the study of these diseases is becoming especially relevant.

1. Genetic risk factors for cardiovascular diseases. Identification of genetic factors and assessment of their contribution to the development of CVD are the main tasks of modern molecular cardiology. Polymorphisms in several hundred genes have been studied as genetic risk factors for atherosclerosis, hypertension, coronary heart disease, myocardial infarction, stroke, thrombotic and other diseases [1, 6, 7].

Many similar studies conducted in different populations, on clinically heterogeneous patient samples, are characterized by direct associations with a relatively small number of candidate genes [6, 7]. Most often, connections between genetic risk factors and predisposition to disease are found in groups of patients exposed to some additional unfavorable external influences, such as smoking or other bad habits, unhealthy lifestyle, physical inactivity, unbalanced diet, poor environmental conditions, etc. In many cases, the additive nature of the action of various genetic and environmental risk factors is shown. To date, dozens of polymorphic genes have been identified that affect the occurrence and clinical course of various pathologies. A tendency to thrombosis is more often observed in people with "unfavorable" alleles of proteins participating in the hemostatic cascade [8, 9, 10]. The risk of atherosclerosis and its complications can be modified by polymorphism of apolipoprotein genes [11]. The diversity of metabolic genes also explains the phenomenon of individual intolerance to some drugs. It is very important to emphasize that information about the medical aspects of gene polymorphism is only beginning to acquire a form suitable for the practical application of diagnostic tests, and new knowledge about predisposition genes is appearing with astonishing speed [12, 13].

2. The role of molecular genes in the hemostasis system and the formation of atherosclerosis. The most common cause of cardiovascular complications is atherothrombosis: the process of thrombus formation on atherosclerotically altered vessels, which leads to complications such as myocardial infarction and stroke. The share of atherothrombosis in the structure of overall mortality is about 28% [14]. The establishment of the leading role of the platelet link of hemostasis in the pathogenesis of atherothrombosis contributed to the development of a large number of drugs that have demonstrated their effectiveness in large multicenter studies in patients with

acute coronary syndromes (ACS) and chronic forms of ischemic heart disease, including percutaneous revascularization procedures [15, 16]. The development of ischemic heart disease is based on the interaction of various genetic factors with environmental factors. The complexity of pathogenesis creates great difficulties in studying the nature of these diseases. In this regard, the problem of studying the genetic mechanisms of CVD is quite complex and is associated with the development of adequate approaches and methods of analysis [17]. One of the effective approaches to studying the role of genetic mechanisms of CVD development is associated with the identification of a group of genes with the potentially greatest contribution to the pathogenesis of the disease - these are the so-called candidate genes [6, 7]. One of the main triggers of the pathogenesis of coronary heart disease is a violation of the functional properties of the endothelium, which subsequently leads to a change in the tone of the vascular wall and the further development and progression of the pathological process. In this regard, genes whose products are involved in the regulation of vascular tone are of great interest.

3. Recommendations for the use of pharmacogenetic testing in clinical practice. Clinical pharmacogenetics studies the role of genetic factors in the formation of the human body's response to drugs. The patterns revealed by pharmacogenetics allow the doctor to individually approach the choice of both the drugs themselves and their doses for each specific patient, ensuring the most effective and safe pharmacotherapy. Genetic factors are polymorphic regions of genes, the products of which are involved in the implementation of various pharmacokinetic and pharmacodynamic processes. Genetic characteristics of patients associated with changes in the pharmacological response are revealed during pharmacogenetic testing, i.e. this is the identification of specific genotypes. Such tests are based on the polymerase chain reaction (PCR). The results of the pharmacogenetic test represent the identified genotypes of the patient for one or another marker. As a rule, a clinical pharmacologist interprets the results of a pharmacogenetic test – formulates recommendations for the choice of a drug and its dosage regimen. The use of such tests allows for an early prediction of the pharmacological response to a drug and a personalized approach to the choice of a drug, as well as patient management tactics. It is assumed that the introduction of new testing technologies based on “microarrays” (microarray technology, DNA chips) will allow for the determination of polymorphisms of specific genes and the total screening of allelic variants in the human genome [18].

4. Mechanisms of resistance to antiplatelet drugs and how to overcome it. In recent years, the problem of resistance to ASA therapy has been actively discussed. This is understood as the inability of ASA in some patients to adequately suppress platelet function, reduce the synthesis of thromboxane A 2 and/or prolong bleeding time [21, 22]. The prevalence of resistance to ASA therapy, according to various

studies, ranges from 10 to 45% [23, 24]. The following are among the possible causes of this phenomenon: pharmacodynamic interactions of ASA with non-steroidal anti-inflammatory drugs; the presence of non-platelet sources of thromboxane A2 synthesis; COX-2 expression in newly formed platelets; aspirin hydrolysis by esterases of the gastrointestinal mucosa; increased synthesis of thromboxane A2; hyperlipidemia; genetic features. There is reason to believe that resistance to ASA therapy may be associated with polymorphism of the cyclooxygenase gene affecting the active center of the enzyme (Ser529), polymorphism of genes encoding other enzymes involved in the mobilization and metabolism of arachidonic acid (phospholipase, thromboxane synthetase) and polymorphism of genes encoding other platelet GP receptors [25, 26].

Possible causes of resistance to ASA may be non-compliance with the ASA regimen by the patient - low patient commitment to treatment, as well as low absorption when prescribing an inadequate dose or when using enteric-coated forms of ASA. There are reports that ASA produced in the form of tablets with a protective coating has weaker antiplatelet properties than the usual, soluble form, and this, according to Dr. Soh, may be one of the reasons for resistance to ASA, observed in approximately one third of patients taking small (up to 75 mg / day) doses of the drug [27, 28, 29]. This is especially common in obese individuals, for whom the likelihood of ineffectiveness of taking low doses of ASA in the form of film-coated tablets reaches 40%. The advantage of soluble forms of ASA at a dose of 75 mg/day. Is that they suppress the activity of serum thromboxane B 2 (TXB2) by more than 95% and more actively prevent platelet aggregation. At the same time, ASA in the form of tablets with a protective coating, which is used more and more often, is absorbed not in the stomach, but in the large intestine. In this case, the presence of a protective coating can weaken the antiplatelet effect of ASA [30, 31, 32]. Another reason for the ineffectiveness of therapy may be interaction with other drugs. Ibuprofen, for example, can bind to the active center of COX-1, thus changing its spatial configuration and thereby preventing the antiplatelet effect of ASA. It is known that ACS and congestive heart failure are associated with increased platelet reactivity compared to stable coronary heart disease [33, 34]. There is evidence that the highest frequency of ASA-resistant is observed among patients with ST-segment elevation myocardial infarction, which correlates with a high level of ADP in the blood [34, 35]. This is probably due to generalized activation of platelets and the release of large amounts of ADP, thromboxane, and an increased level of von Willebrand factor due to damage to endothelial cells [36]. In addition, during ischemia, ADP can be released by other cells: myocytes, endothelial cells, erythrocytes, and sympathetic nerve endings [37]. The presence of hyperglycemia also leads to a decrease in the effectiveness of antiplatelet therapy due to the reactivation of free radicals [37, 38],

and hypercholesterolemia can weaken the effect of ASA on thrombin. Physical exertion and stress lead to an increase in catecholamines, which also reduces the antiplatelet effect. Cellular factors that affect the effectiveness of ASA include insufficient suppression of platelet COX-1 function, as well as increased expression of platelet and endothelial cell COX-2 mRNA. The formation of 8-iso-PGF2a, which is a product of arachidonic acid conversion in the body, can also reduce the effectiveness of ASA by binding to thromboxane receptors [39, 40]. Resolvins, metabolites of omega-3 polyunsaturated fatty acids formed as a result of COX-2 acetylation under the influence of ASA, have an anti-inflammatory effect [41]. Deficiency of these substances can also weaken the therapeutic effect of ASA (Fig. 1). Resistance to ASA may be associated with genetic factors - polymorphism of the platelet receptor genes PL(A1A2) [42, 43]. For example, the presence of polymorphism of the PLA2 allele of glycoprotein III a (subunit b) in most (but not all) studies was associated with an increased risk of thrombotic complications, such as early development of myocardial infarction and stent thrombosis during ASA therapy [43].

The presence of the PLA2 allele is associated with a higher affinity of glycoprotein IIb/IIIa receptors to fibrinogen, which can lead to more pronounced thrombus formation as a reaction to vessel wall damage. A certain significance in increasing thrombotic readiness and resistance to ASA may be due to platelet reactivation through the thromboxane A 2 system or the ADP-dependent pathway, and is also due to the presence of polymorphism of the genes of platelet receptors for collagen and von Willebrand factor [44], single nucleotide polymorphism of the P2Y1 gene (Fig. 2) [45]. Thrombin, which is formed in high quantities during ACS, can serve as a stimulator.

4. The role of genes Len33ro; Thr145Met; C786T; HI/H2; C807T in the pathogenesis and development of cardiovascular diseases.

4.1. Leu 33Pro polymorphism of the gene encoding GP IIIa (ITGB3). Characteristics of the beta-3 integrin (GPIIIa, platelet fibrinogen receptor) mutation ITGB3 Leu33Pro. The gene encodes the beta-3 subunit of the integrin complex of the platelet surface receptor GPIIb/IIIa, also known as glycoprotein-3a (GPIIIa). ITGB3 is involved in intercellular adhesion and signaling, provides interaction of platelets with plasma fibrinogen, which leads to rapid platelet aggregation and subsequent healing of the damaged epithelial surface.

The 33P mutation results in an increased tendency of platelets to aggregate, which increases the risk of cardiovascular diseases. Patients with this mutation often have low efficacy of aspirin as an antiplatelet agent. The prevalence of the ITGB3: 1565 T>C (Leu33Pro) mutation in the European population ranges from 8 to 15% [46]. Indications for use: family history of early coronary heart disease, myocardial

infarction, history of thromboembolic conditions, postangioplastic thrombosis, neonatal thrombocytopenia, antithrombotic therapy with aspirin. The L33P polymorphism is associated with atherothrombosis and coronary heart disease [47]. Glycoprotein IIb/IIIa is the main platelet receptor involved in the aggregation process and is a typical representative of the integrin family. Its a-subunit or glycoprotein IIb (molecular weight - MM - 136 kDa) consists of heavy and light chains. The light chain has a short cytoplasmic tail, a transmembrane portion and a short extracellular domain. The heavy chain is located outside the cell. b-subunit or glycoprotein IIIa (MM 92 kDa) consists of a single polypeptide with a short cytoplasmic tail, a transmembrane portion and a large extracellular domain. The subunits are non-covalently linked to each other; calcium is required to maintain the heterodimeric structure. GP IIb/IIIa are the most common platelet receptors; there are 50,000 to 80,000 receptors on the surface of a single platelet. The ligands of GP IIb/IIIa platelet receptors are fibrinogen, von Willebrand factor, fibronectin and vitronectin. The frequency of detection of the PL(A2) allele among representatives of the white race, according to various studies [46, 47], ranges from 15 to 30%, homozygous carriage is observed in 2% of cases. According to some authors [48, 49], carriage of the PL(A2) allele of the PL(A1)/PL(A2) polymorphic marker of the ITGB3 gene is a risk factor for coronary heart disease. In a number of studies [46, 50], an association of the PL (A2) allele with the development of acute coronary syndrome was found. Thus, E. Weiss et al. showed that the frequency of detection of the PL (A2) allele in patients hospitalized due to myocardial infarction or unstable angina exceeds that in the control group by 2.1 times, and in individuals with the onset of the disease at the age of up to 60 years - by 3.6 times [51, 52]. D. Walter et al. showed that carriers of the PL (A2) allele have a 5-fold increase in the risk of developing coronary stent thrombosis, independent of clinical and angiographic parameters. The association of the PL (A2) allele with an increased risk of thrombosis after interventions on the coronary arteries was also discovered by other researchers [52, 53].

4.2. Polymorphism of the gene encoding GP Ia (ITGA2) polymorphic marker C807T. Characteristic of the ITGA2 gene - platelet alpha 2 integrin (glycoprotein IIa) is the main platelet collagen receptor. Polymorphism names: C807T (rs1126643) (substitution of the nucleotide cytosine for thymine in the coding region of the gene, but does not lead to an amino acid substitution in the protein). ITGA2 polymorphisms are associated with coronary heart disease and, in particular, with myocardial infarction [54]. The frequency of occurrence of the mutant variant of the gene: 35-44%. The type of inheritance of the mutation: autosomal dominant (occurs in men and women with equal frequency, for the development of the disease it is enough to inherit 1 mutant variant of the gene from one of the parents, the probability of the disease in children is 50%). Gene function: codes for glycoprotein Ia, a component of

the blood coagulation system (thrombotic component of hemostasis). This protein, together with glycoprotein IIa, forms a receptor complex responsible for the interaction of platelets, on the surface of which it is located, with the collagen of the vessel wall, which leads to platelet aggregation and thrombus formation. Molecular effects of the mutation: with a rarer variant C807T, the receptor density on the platelet surface increases, which leads to increased platelet aggregation activity and a tendency to thrombus formation. Characteristic manifestations of the mutation: atherosclerosis (against the background of high blood cholesterol levels), thrombosis, thromboembolism, myocardial infarction, ischemia, pregnancy pathologies (fetal loss syndrome , preeclampsia). Indications for the study : thrombosis, infarction in the patient's history or in close relatives; preparation for surgery, pregnancy, oral contraceptives, HRT. Polymorphic marker C807T in 1997 T. Kunicki identified and described the mononucleotide polymorphic marker C807T in the coding region of the ITGA2 gene. The T allele of the polymorphic marker C807T of the ITGA2 gene is associated with increased expression of platelet GP Ia receptors and increased platelet adhesion to collagen [46]. A number of studies [47, 48, 50] have shown that carriage of the T allele is a risk factor for myocardial infarction and stroke. Thus, in a case-control study conducted by K. Moshfegh et al., it was found that in homozygous carriers of the T allele of the C807T polymorphic marker of the ITGA2 gene, the relative risk of developing myocardial infarction was 3.3 times higher than in the control group. Of particular interest is the fact that in carriers of the T allele of the C807T polymorphic marker of the ITGA2 gene, as well as in carriers of the PL(A2) allele of the PL(A1)/PL(A2) polymorphic marker of the ITGB3 gene, the risk of developing myocardial infarction was expressed to a greater extent in young patients. Angiolillo et al. studied platelet reactivity in patients with different genotypes of the PL(A) polymorphic marker of the ITGB331 gene who underwent coronary angioplasty with stenting (n=38) and found an association of the PL(A2) allele with increased activation of GP IIb/IIIa platelet receptors and P-selectin expression. The study also showed that PL(A2) allele carriers had a less pronounced antiplatelet effect of a loading dose of clopidogrel (300 mg). An association was shown between the PL(A2) allele of the PL(A) polymorphic marker of the ITGB3 gene and an unfavorable outcome in patients who received therapy with oral GP IIb/IIIa platelet receptor blockers. There is reason to believe that resistance to therapy with drugs of this group in carriers of the PL(A2) allele is one of the reasons for their ineffectiveness [59, 60]. Unlike previous researchers, A. Weber et al. did not identify an association of the PL(A1)/PL(A2) polymorphic marker of the ITGB3 gene with the suppression of ADP-induced fibrinogen binding by platelet GP IIb/IIIa receptor blockers: abciximab, tirofiban, and eptifibatide.

Thus, literature data on the relationship between various polymorphic markers of candidate genes and the effectiveness of therapy with the main classes of antiplatelet drugs are few. In this regard, it is currently not possible to identify genetic predictors of the effectiveness of using a particular antiplatelet agent and requires further study.

4.3. Nitric oxide synthase 3 (NOS3) mutation-1, C786T. Study of one of the possible mutations of the gene of the enzyme responsible for the synthesis of nitric oxide (NO) in the body - one of the most important biologically active substances - regulator of many physiological processes. One of its functions is the regulation of vascular tone. NOS3 polymorphism is important in predicting the risk of cardiovascular diseases [48]. Characteristics of the NOS3 gene - endothelial nitric oxide synthetase. Levels of divalent nitric oxide (NO) affect the walls of blood vessels, platelet aggregation. Polymorphisms of the NOS3 gene are associated with the risk of vascular diseases. Determination of the C 786T polymorphism of the endothelial NO synthase gene promoter is associated with the effectiveness of thrombolytic therapy in patients with acute myocardial infarction, since coronary heart disease, in particular acute myocardial infarction (AMI), is the object of intensive genetic research. The gene encoding endothelial NO synthase (eNOS) is one of the studied genes. This enzyme is involved in the synthesis of NO by the endothelium and, consequently, in the regulation of vascular tone, blood flow, and arterial pressure. NO may also be important in the pathogenesis of coronary heart disease, since it inhibits the proliferation of smooth muscle cells, has a protective effect on platelet aggregation, and inhibits leukocyte adhesion to the endothelium [52, 56]. Suppression or reduction of eNOS activity leads to a deficiency of nitric oxide, an endothelial dysfunction that, according to the classical “response to injury” theory, plays a major role in the initiation of atherogenesis and the development of atherothrombosis [57]. The gene encoding eNOS is located on chromosome 7q35–36 and consists of 26 exons [58, 59]. The eNOS gene promoter contains several domains, i.e. it can be regulated by a number of transcription factors [60]. To date, polymorphism of the eNOS gene has been described in 11 places, 8 of which have been studied as possible risk factors for cardiovascular diseases. The most studied are the 4a/b polymorphism of the 4th intron, the G894T (Glu298Asp) polymorphism of the 7th exon and the T-786C polymorphism of the eNOS gene promoter [61]. There are results of the study “T-786C polymorphism of the endothelial NO synthase gene promoter: relationship with the effectiveness of thrombolytic therapy in patients with acute myocardial infarction”, which indicate that Corvitin significantly increases the frequency of restoration of coronary blood flow, and this is mainly achieved due to patients with a normal TT genotype of the eNOS gene promoter. This fact is of interest due to a number of aspects. Thus, we have demonstrated for the first time the

possibility of improving the results of TLT not by using a new antithrombotic agent, but a metabolically active agent that is safe enough in terms of the absence of the risk of bleeding. The results obtained indicate that the bioavailability of nitric oxide is of great importance for increasing the effectiveness of reperfusion therapy - it is in patients with normal homozygote TT (i.e. with preserved ability to increase nitric oxide synthesis) that treatment results can be improved by using Corvitin. In patients with heterozygote TS and pathological homozygote CC, initial disturbances in enzyme synthesis and an initial deficiency in nitric oxide formation are noted. Under such conditions, Corvitin could not realize its potential. These results confirm that the mechanism of the positive effect of Corvitin in TLT in patients with AMI is its ability to influence nitric oxide metabolism.

The obtained data can serve as a basis for the development of a new approach to the treatment of patients with AMI who have undergone myocardial revascularization in order to improve the restoration of tissue blood flow.

4.4. Polymorphism, Thr145 Met encoding GPIBA. Characterization of the GPIBA gene (OMIM 138720). Glycoprotein Ib is the main platelet receptor that interacts with the von Willebrand coagulation factor. Glycoprotein Ib is also involved in platelet aggregation and cell adhesion. This glycoprotein consists of 4 globules: GPIba, GPIbb, GPIX and GPV. Polymorphisms T145M and 5 T>C in the GP1BA gene (alpha-globule) were associated with CVD [62].

4.5. Mutation of the platelet ADP receptor P2RY12 H1/H2. The gene encodes the synthesis of the purinergic platelet receptor; gene mutation is associated with increased platelet reactivity, coronary heart disease (especially in non-smokers), and poor response to clopidogrel and aspirin [63]. Indications for use: coronary heart disease, myocardial infarction, history of thromboembolic conditions, postangioplastic thrombosis and restenosis, antithrombotic therapy with aspirin and clopidogrel. The thienopyridine derivatives ticlopidine and clopidogrel suppress platelet function by irreversibly blocking the binding of ADP to its P2Y12 (P2Yac) platelet receptor. Both drugs, being prodrugs, undergo in vivo conversion to active metabolites with the participation of the hepatic cytochrome P450 system: CYP3A4 and CYP1A2. At present, there are no convincing data on genetic predictors of resistance to thienopyridine therapy. Polymorphism of the gene encoding P2RY12 ADP-receptor of platelets (HORK3, P2Y12, ADPG-R, SP1999, P2T(AC), P2Y(AC), P2Y(ADP), P2Y(cyc)) is a G(i)-associated receptor that plays a key role in suppressing irreversible platelet aggregation. Binding of ADP to this receptor leads to inhibition of adenylate cyclase, concomitant decrease in intracellular cAMP content, and to phosphoinositide-3-kinase-dependent activation of GP IIb/IIIa receptors of platelets. P. Fontana et al. identified and described four polymorphic markers of the P2RY12 gene, two of which are a mononucleotide substitution in intron 5 (i-C139T,

i-T744C), one is a mononucleotide substitution in exon 2 (G52T), and one is a mononucleotide insertion in intron 5 (i-ins801A) of the P2RY12 gene. The researchers identified two haplotypes: the main haplotype H1 (C at position 139, T at position 744) and haplotype H2 (T at position 139, C at position 744) [64]. It was shown that haplotype H2 is associated with increased ADP aggregation of platelets, which, according to the researchers, may be due to an increase in the expression of platelet ADP receptors. There is reason to believe that the carriage of the H2 haplotype is associated with an increased risk of atherothrombosis and resistance to thienopyridine therapy. The list of candidate genes studied can be significantly expanded. The information obtained as a result of these studies on the presence of genetic defects leading to dyslipidemia, endothelial dysfunction, and an increased risk of coronary vessel restenosis after cardioinvasive interventions already now makes it possible to choose an adequate patient management tactic and conduct pathogenetically substantiated treatment using drugs that modulate the identified metabolic disorders.

Thus, polymorphic alleles, unlike mutant ones, do not determine a fatal predisposition to pathology, but have the ability to potentiate the action of other harmful influences. On the other hand, unfavorable environmental influences can lead to the development of a disease without the participation of the genotype, that is, in the absence of any features of the genetic constitution.

In conclusion, it should be recalled that the presence of an “unfavorable” polymorphic allele is a probabilistic indicator, the importance of which cannot be overestimated - knowledge of the genotype in this case does not play an independent role, but is a component of a comprehensive study of the patient.

Based on the above, it becomes obvious that genetic testing of predisposition to aspirin resistance in patients with coronary heart disease will allow us to approach the format of personalized medicine, based on the use of treatment regimens taking into account the individual genetically determined characteristics of the patient, personalized selection of antiplatelet agents, and prediction of the development of resistance to aspirin.

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