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GENETIC PREDICTORS OF THE CHRONIC HEART FAILURE DEVELOPMENT AND PROGRESSION: THE ROLE OF POLYMORPHIC GENES

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Abstract:

According to the results of epidemiological studies conducted in the last decade, achievements in the treatment of cardiovascular diseases are noted, but despite this there is a continuous increase in chronic heart failure (CHF), primarily due to the prevalence of etiological causes, a significant increase in the average life expectancy of patients, "escape phenomena" with the prescribing of β-blockers (BB) and blockers of the renin-angiotensin-aldosterone system (RAAS) at the outpatient stage. Studying the contribution of various genes to predicting the risk of occurrence, the nature of the course, and choosing the optimal therapy for a stable course of CHF is an relevant scientific and clinical task. The article provides an overview of the most ambitious clinical studies available to date, both foreign and domestic, which allow us to conclude about the role of genetic factors in the development and progression of CHF. The main gene polymorphisms that are components of the sympathoadrenal (CAS) and renin-angiotensin-aldesterone systems (RAAS) are considered, which is associated with their leading role in the pathogenesis of not only basic diseases, but also CHF itself. The studies presented in the article confirm the multifactorial nature of CHF, and demonstrate a certain relationship between gene polymorphism with clinical manifestations, response to therapy, mortality, and confirm the need for further study of the genetic mechanisms of development and the clinical course of CHF.

Key words: *CHF, polymorphic genes, RAAS, CAS, AGT gene, ADRB gene polymorphism.*

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INTRODUCTION:

Chronic heart failure (CHF) is one of the most significant public health problems. Despite the fact that there are relevant achievements in the treatment of cardiovascular diseases, the number of patients with heart failure is steadily growing. According to epidemiological studies (EPOHA-CHF, EPOHA-O-CHF, EPOHA-Hospital-CHF and EPOHA-Decompensation-CHF) in the Russian Federation from 1998 to 2014, the prevalence of CHF significantly increased from 4.9% to 10.2 % (p = 0.01), and is more than 22 million people [1-3]. The number of patients with chronic heart failure III-IV FC also significantly increased: from 1.2% (1998) to 4.1% (2014) (p = 0.002), which is explained by a significant increase in the average life expectancy of patients from 64.0 ± 11, 9 years of 69.9 ± 12.2 years (p = 0.02) and the prevalence of etiological causes of heart failure, including arterial hypertension, coronary heart disease and myocardial infarction. This is largely due to the low frequency of β-blockers (BB) and blockers of the renin-angiotensin-aldosterone system (RAAS) prescribing at the outpatient stage, the use of these groups in low doses (according to the EPOHA-CHF study, the syndrome of the effect of therapy on the outpatient stage was noted), which does not allow to achieve target levels of blood pressure and heart rate [4-7]. Most often, cessation of drug admission was noted among patients who took mineralocorticoid receptor antagonists (54.7%) and β-blockers (26.6%). In 92.6% of cases after discharge, there was no tactic for titration of RAAS blockers or β-blockers to optimal doses.

All this indicates that the development of decompensations prevention and the creation of a basis for optimal therapy for a stable course of heart failure is one of the priorities of the cardiological medical community. Currently, there is a rapid growth in medical science and the introduction into practice of a large number of new dosage forms, but still the cornerstone is the effectiveness of pharmacotherapy in patients with heart failure. Undoubtedly, the introduction into practice of personalized medicine, which is based on the selection of drug therapy, the dosage regimen taking into account the characteristics of the patient is one of the ways to increase it [8-11].

The study of the human genome, on the one hand, led to the emergence of molecular medicine and made it possible to determine the genetic predisposition of people to the development of various diseases, to carry out pre-symptomatic diagnosis of multifactorial diseases, on the other hand, laid the foundation for new areas in science, for example, predictive medicine, which can be considered as one from the early stages of the correction of possible diseases [12].

Predicting the risk of occurrence, the nature of the course and the effectiveness of drug therapy for heart failure, today is a relevant scientific and clinical task, the solution of which is aimed at studying the molecular genetic mechanisms of development, determining the role of genetic markers of heart failure.
Reviews of scientific literature, both foreign and domestic, allow us to conclude that genetic factors play an important role in the development and progression of cardiovascular diseases, including heart failure, however, the available clinical trial data on gene polymorphisms are contradictory. The prognostic value of the revealed polymorphic markers of structural protein genes in patients with CHF, which developed against the background of ischemic and post-infarction myocardial remodeling, has not been adequately studied.

The aim of the study: to summarize the current data on the possibility of using genetic markers as predictors of clinically significant outcomes in patients with heart failure, including survival, the risk of exacerbations and hospitalization, and predicting the response to drug therapy.

The greatest interest in the development and progression of heart failure is the study of genomic polymorphism of the components of the sympathoadrenal (CAS) and renin-angiotensin-aldesterone systems (RAAS). Due to the fact that they play a leading role in the pathogenesis of not only basic diseases, such as coronary heart disease (CHD), arterial

hypertension (AH), but also heart failure itself. Studying the polymorphism of genes encoding proteins that are part of enzymes, hormones, and receptors of neurohumoral systems will help to identify high-risk groups for the development of heart failure, as well as choose the most effective tactics for the prevention and treatment of heart failure, which ultimately will improve the quality of life of patients.

In studying the molecular genetic aspects of chronic heart failure, the polymorphism of the gene of angiotensin-converting enzyme (ACE), whose locus is located on the 17th chromosome (17q23), is of greatest interest. The mechanism of polymorphism is the absence (deletion) or presence (insertion) of a DNA fragment consisting of 287 nucleotide pairs in the 16th intron of the ACE gene. Therefore, there are alleles I and D, and genotypes II, ID, DD. The concentration of the angiotensin-converting enzyme correlates with the presence of the D allele and in healthy people homozygous for the D allele is almost two times higher than for homozygous for the allele I [13-17].

Polymorphism of the ACE gene as a predictor of clinically significant outcomes in patients with heart failure was studied in several prospective studies, so it was shown that in people with the DD genotype, the risk of developing atherosclerosis, essential hypertension, coronary heart disease, left ventricular hypertrophy and insulin resistance is higher [13-17], which is essential in the progression of chronic heart failure.

Over the past twenty years, a number of studies have been conducted to identify the association of ACE gene polymorphism with the development of left ventricular hypertrophy (LVH). So V.A. Almazov et al. found the association of the DD genotype with a violation of the diastolic function of the left ventricular myocardium, but no genetic polymorphism was found. [18]

M.D. Smirnova et al. identified the association of ACE I / D polymorphism with the thickness of the interventricular septum in patients with hypertension and LVH, genotype II was extremely rare in patients with hypertension and was not associated with LVH [19].

In connection with the widespread use of drugs of angiotensin-converting enzyme inhibitors (ACE inhibitors), the problem of studying the ACE gene polymorphism in patients while taking drugs of this group is becoming particularly relevant. The results of research in this area are few and contradictory.

Thus, in a study conducted by the National Institute of Heart, Lung, and Blood of the USA, including 56 patients with atherosclerosis, it was shown that the presence of the ACE gene D allele is associated with a decrease in the expression of angiotensin receptors of the first type and a decrease in endothelial dysfunction during treatment with ACE inhibitors, in comparison with patients carrying the allele I [20, 21].

According to the results of a study of the Greek population, which was attended by 104 patients with AH who had not previously received therapy, it was found that treating with fosinopril for six months in a daily dose of 20 mg, the most significant decrease in blood pressure was observed in patients with the DD genotype, compared with patients with genotypes DI and II [22], these studies led to the conclusion that the ACE gene polymorphism affects the therapeutic effect of ACE inhibitors.

Also interesting is the relationship of ACE gene polymorphism with side effects of ACE inhibitors. Thus, when conducting a double-blind, randomized study, it was found that carriers of the ACE gene allele II have a more pronounced change in the level of tissue bradykinin during therapy with ACE inhibitors, which subsequently led to the appearance of cough when using drugs of this group [23].

ACE inhibitors have been shown to lower blood pressure and slow the progression of kidney damage, however, in a double-blind cross-sectional study in 34 patients with hypertension receiving ACE for 6 weeks, there was a decrease in renal function during treatment with patients with genotype II to a greater extent than in individuals with genotypes DD and ID [24].

Unfortunately, clinical studies performed to date do not allow certain conclusions. However, the rapidly developing field of pharmacogenomics will soon also affect therapeutic decisions in this direction.

The available literature presents data on the relationship of the polymorphism of the angiotensinogen gene (AT, AGT) with the development of cardiovascular diseases. The AGT gene is located at the q42-43 locus of chromosome 1 and encodes the amino acid sequence of the angiotensinogen molecule. Several structural polymorphisms are described, among which the most significant is the M235T polymorphism, which leads to the replacement of methionine (M) at the 235th locus of the AGT gene with threonine (T). The international polymorphism code is ge699. So, M235T polymorphism is associated with the level of blood plasma AT activity and the content of angiotensin II (A II), therefore, with a risk of CVD [25, 26]. However, the research results are contradictory and depend on racial and population characteristics. Thus, a connection between the M235T polymorphism of the AGT gene and the development of AH in A. Sethi et al. studies was noted, while Glavnic N., in his studies, does not confirm the association of the M235T polymorphism with damage to target organs in hypertension in representatives of the European ethnic groups [27].

The results of a meta-analysis, including 45,267 Caucasian people, showed higher plasma angiotensinogen content in carriers of the T allele, in the homozygous state was 11% higher, and 5% in the heterozygous state, in contrast to people with M235M polymorphism. Representatives of the Mongoloid and Negroid races did not reveal such a pattern [28].

Several large studies have examined the role of the M235T polymorphism of the AGT gene as an independent risk factor for CHD. So Cong N.D. et al. showed a negative correlation between the M235M genotype and the risk of coronary heart disease, T. Katsuya et al. noted a high risk of coronary heart disease in patients with TT genotype, however, in the European PROCAGENE study, with the participation of 619 people, fewer cases of coronary artery atherosclerosis were found in patients with TT genotype [29, 30, 31].

Of interest are the results of a study conducted in southern Germany on 396 patients, where the relationship of AGT and ACE gene polymorphism with the level of AT and ACE in plasma was revealed. Thus, the T235 allele of the AGT gene is associated with a lower plasma renin and prorenin content [26]. Another study found that the T235 allele is an independent parameter of the best response to monotherapy with ACE inhibitors. The latest study was conducted on 125 patients suffering from hypertension, but who had not previously received antihypertensive therapy [32].

An analysis of the literature on the polymorphism of the RAAS genes and its effect on clinically significant outcomes in patients with CHF suggests that DD genotypes associated with increased ACE activity and M235T-with an increased concentration of angiotensin II prevail in patients with CHF [33].

As you know, in the pathogenesis of heart failure, an important role belongs to a change in the ratio and sensitivity of β-adrenoreceptors, which may be due to polymorphism of the genes of the sympathoadrenal system (SAS). The most studied polymorphisms of genes encoding β1-adrenergic receptors (ADRB1) and β2-adrenergic receptors (ADRB2) [34].

Two polymorphisms of the ADRB1 gene with single nucleotide substitutions are known: substitution in the nucleotide sequence at position 145 of adenine with guanine, which leads to a replacement in the amino acid sequence of the β1-adrenergic receptor of glycine by serine at position 49 (polymorphic marker Gly49Ser), and also the replacement of guanine by cytosine at position 1165 , leading to the replacement in the amino acid sequence of glycine by arginine at position 389 (polymorphic marker Gly389Arg). These polymorphic β1-AR variants appear to play an important role in the phenotypic features of heart failure. For example, Ranade et al. found an association of Ser49Gly polymorphism with heart rate. The study showed that individuals homozygous for Gly49 have the lowest heart rate, and each Ser allele increases the basal heart rate [26].

The β2-adrenoreceptor gene polymorphism (ADRB2) is represented by many polymorphic variants, the most studied of which are non-synonymous nucleotide substitutions: Arg16Gly, Thr164Ile, Gln27Glu, these polymorphisms play an important role in the functioning of the receptor. [35-38]. The association of AH with the polymorphic marker Arg16Gly was revealed (replacement of the amino acid sequence at the 16th position of arginine with glycine), carriers of the Gly16 allele have

a higher risk of hypertension. A number of researchers have identified a relationship between Arg16Glu polymorphism and a higher threshold level of SAS activation, lower concentrations of adrenaline and norepinephrine than with the polymorphic version of Arg16Arg [39–41].

Among the polymorphic variants of the β2-adrenergic receptor gene, the marker Thr164Ile deserves special attention. This polymorphism was studied by S.B. Liggett et al. [42, 43] with the participation of 259 patients with heart failure of different genesis. As a result of which it was revealed that carriers of the 164Ile allele have a more severe form of heart failure, the mortality rate and the number of hospitalizations of these patients were higher than those of carriers of the 164Thr allele.

The effect of carriage of polymorphic markers on the action of β-adrenergic blockers is being actively studied, the results of the studies are ambiguous and contradictory, so in a study conducted in the USA that included 1094 patients with heart failure II-IV FC and a LV ejection fraction of less than 35%, it was shown that the best response to carvedilol therapy was found in individuals carrying the Glu27 allele of the ADRB2 gene, which was expressed in an increase in the ejection fraction of the left ventricle compared with patients with the Gln27 allele in their genotype [35].

A striking example of the ambiguous conclusions of researchers can be the results of the association of the β-blockers action (carvedilol, bisoprolol and metoprolol) with the carriage of certain polymorphic markers. So F. Rochais et al. concluded that carriers of the Arg389 allele of the ADRB1 gene have an EF 1.5 times higher than the carrier variant of the polymorphic marker Glu389, and the use of carvediol reduces cardiac contractility in patients carriers of the Arg389 allele [36]. At the same time, while conducting another study using carvedilol, among the 224 patients with heart failure, the most pronounced improvements were observed in Arg389 homozygotes [36], and in a study by Mialet Perez J et al, involving 61 patients with heart failure, treated with metoprolol, a pronounced increase in LV pumping function was revealed in carriers of the Arg389 allele of the ADRB1 gene, in comparison with Glu389 homozygotes [37].

CONCLUSION:

Thus, the published results of numerous studies over the past decade demonstrate a definite relationship between gene polymorphism and clinical manifestations, important endpoints of heart failure, response to therapy, and mortality. However, the presence of an adverse allele does not allow us to judge the severity and time of onset of the disease. At the moment, there are difficulties in predicting the clinical manifestations characteristic of a particular genotype. The presence of clinical and genetic diversity, as well as pleiotropism of the results of gene studies lead to a probabilistic approach in the medical interpretation of the "genetic passport". In the preasymptomatic period, genetics will only reveal a predisposition to the development of heart failure in the genome and outline the path of early prevention. In conclusion, we would like to note that the above studies confirm the multifactorial nature of heart failure, while the genetic aspect is only one of the components of its development, and confirm the need for further study of the genetic mechanisms of development and regulation of heart failure.

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