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Molecular Genetic Aspects of Renin-Angiotensin-Aldosterone Systems in Chronic Heart Failure

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Abstract **Background.** Heart failure (HF) is a widespread disease with significantly elevated mortality, morbidity, and hospitalization rates. Dysregulation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) are both postulated to be significant regulators of cardiovascular function, thereby playing a pivotal role in its pathophysiology. The RAAS is a sophisticated hormonal system that controls electrolyte homeostasis, fluid balance, and blood pressure. It is well appreciated that several neurohormones and signaling cascades are activated that promote long-term deterioration of cardiac function and structure. Activation of the renin-angiotensin-aldosterone system (RAAS) and the adrenergic system is closely related to heart failure. Common gene variants that encode neurohormonal, adrenergic and intracellular proteins have been demonstrated to modulate the course and consequences of heart failure. **Objectives of study.** However, the literature is replete with conflicting results and it remains uncertain as to whether particular gene variants predispose heart failure. Therefore, the main purpose of this review presents a review of the literature on the molecular genetic aspects of the renin-angiotensin-aldosterone system in chronic heart failure.

Keywords Chronic heart failure, Renin-angiotensin-aldosterone system, Molecular genetic cardiology

1. Introduction

Cardiovascular genetics is a rapidly evolving subspecialty within cardiovascular medicine, and its growth is attributed to advances in genome sequencing and genetic testing and the expanding understanding of the genetic basis of multiple cardiac conditions, including arrhythmias (channelopathies), heart failure (cardiomyopathies), lipid disorders, cardiac complications of neuromuscular conditions, and vascular disease, including aortopathies. There have also been great advances in clinical diagnostic methods, as well as in therapies to ameliorate symptoms, slow progression of disease, and mitigate the risk of adverse outcomes. Emerging challenges include interpretation of genetic test results and the evaluation, counseling, and management of genetically at-risk family members who have inherited pathogenic variants but do not yet manifest disease. With these advances and challenges, there is a need for specialized programs combining both cardiovascular medicine and genetics expertise. The integration of clinical cardiovascular findings, including those obtained from physical examination, imaging, and functional assessment, with genetic information allows for improved diagnosis, prognostication, and cascade family testing to identify and to manage risk, and in some cases to provide genotype-specific therapy. This emerging subspecialty may ultimately require a new cardiovascular subspecialist, the genetic cardiologist, equipped with these combined skills, to permit interpretation of genetic variation within the context of phenotype and to extend the utility of genetic testing. This scientific statement outlines current best practices for delivering cardiovascular genetic evaluation and care in both the pediatric and the adult settings, with a focus on team member expertise and conditions that most benefit from genetic evaluation.

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2. Literature Review

The prognosis of patients with CHF remains extremely unfavorable: their risk of death is four times higher compared to individuals without CHF [1,20,22]. Recently, a new direction has been formed in the field of medicine - genetic cardiology, integrating the concepts and technologies of molecular genetics to understand the etiology and pathogenesis of clinical polymorphism of cardiovascular diseases (CVD) in humans. In recent years, there has been active development of medical genetics aimed at studying the prevalence of gene polymorphism that contribute to

the pathogenesis, development and progression of CHF. Given the important role of neuroendocrine systems in the pathogenesis of CHF, a relevant approach is the study of gene polymorphism, the expression products of which play a leading role in the initiation and progression of this process [2,13]. When studying genes involved in the development of CHF, of primary interest is the study of polymorphism of genes of components of the SAS and RAAS, which play a leading role in its pathogenesis, i.e. genes encoding proteins of the main neurohumoral systems. In particular, a number of studies have previously been conducted to study the role of genetic factors - genes of the renin-angiotensin-aldosterone (ACE, AGT, AGTR1 aldosterone synthase, REN), sympathoadrenal (ADRB1, ADRB2), endothelial (MTHFR, NOS3) systems, etc. in the development and prognosis of CHF [15,21,24,27]. Studies have shown that the activity of RAAS is to a certain extent controlled at the genetic level and the functional significance of RAAS in the processes of changing the geometry of the heart from the standpoint of molecular genetics is probably due to the level of AT II production, which in turn partially depends on the expression of the genes of renin, angiotensinogen and ACE, aldosterone, as well as the density and functional activity of receptors present in the myocardium and vessels, since their activation has an antiproliferative effect and induces apoptosis [14,16,18,30]. One of the key links in RAAS is ACE. The ACE gene, the size of which is 22 kb, is mapped on chromosome 17 (17g23) and consists of 26 exons and 25 introns. The size of the mRNA of the somatic form of the enzyme is 4.5 kb, the testicular - 2.6 kb. The ACE gene polymorphism type I / D (insertion / deletion) in the 16th intron is known, which is associated with ACE activity in the blood: carriers of the II genotype have the lowest level of the enzyme, while in people with the D/D genotype it is maximum. In the 16th intron, an insertion-deletion polymorphism was identified, associated with an insertion (I) or deletion (D) of the Alu repeat of 287 bp. The presence of the D allele is associated with a higher level of circulating (from 14 to 50%) and tissue ACE [9,15]. According to a number of studies, individuals with the D/D genotype of ACE have an increased risk of developing myocardial infarction and ischemic cardiomyopathy. A meta-analysis of 145 studies with a total of 49,959 observations devoted to the study of polymorphism of various genes encoding RAAS proteins showed that in patients with the D/D genotype, the risk of developing CHF was 45% higher [14]. However, other authors describe a high frequency of the D allele only among patients suffering from severe forms of CHF, and some did not establish statistically significant differences in the frequency of ACE gene alleles in patients with CHF. However, according to a number of other studies, no differences were found between the control groups and groups of patients suffering from CHF. Also, no reliable relationship was established between the presence of the D allele and the severity of CHF [15]. The study of the role of ACE gene polymorphism is of great interest in connection with the widespread use of inhibitors of this enzyme in modern cardiology. Thus, a number of studies have established that the presence of the D allele of the ACE gene is associated with a more pronounced decrease in the expression of type 1 AT receptors and a decrease in endothelial dysfunction during ACE inhibitor therapy, compared with patients carrying the I allele. Another study showed that when treating patients with hypertension with fosinopril at a daily dose of 20 mg for 6 months, patients with the D/D genotype showed a more significant decrease in systolic and diastolic blood pressure, compared with patients with the I/D and I/I genotypes. No less interesting is the fact that a connection was found between polymorphic variants of the ACE gene and the side effects of ACE inhibitors. For example, a decrease in renal function in patients with CHF during ACE inhibitor treatment was noted to a greater extent in individuals with the I/I genotype. In addition, the I/I genotype was also associated with a more frequent development of cough during ACE inhibitor therapy [19]. With the D/D genotype, there is a tendency for the glomerular filtration rate (GFR) to decrease in cardiovascular pathology than with other genotypes, but no convincing data on the effect of ACE genetic polymorphism on the survival of patients with CHF and the effect of ACE inhibitors in them have been obtained. Individuals with the D/D ACE genotype have an increased risk of developing MI and ischemic cardiomyopathy, and possibly dilated cardiomyopathy (DCM). Structural and functional parameters of the LV (LVEDV, LV myocardial mass index (LVMI), total peripheral resistance (TPR), EF, and other contractility parameters) in patients who had MI and suffer from CHF were somewhat worse (to varying degrees for different parameters) in the presence of the D/D genotype compared to other genotypes (D/I, I/I). With long-term (one year) treatment of these patients with ACE inhibitors (ACEI) perindopril, patients with the D/D genotype, compared with other genotypes, were found to have a more pronounced increase in EF and a decrease in TPR [4,17,31]. Teplyakov A.T. et al. (2015) studied the effect of ACE gene polymorphism as a dominant risk factor for the development of CHF and a target for effective therapy with ACE inhibitor - enalapril in patients with coronary heart disease [10]. The observation group included 226 patients with CHF receiving continuous basic therapy, which includes a beta-blocker (BB), a diuretic, an aldosterone antagonist, digoxin, and an ACE inhibitor; 78 patients received enalapril (at an initial dose of 2.5 mg 2 times a day with subsequent dose titration to 10-20 mg 2 times a day). The control group consisted of 136 people without signs of cardiovascular disorders. The D allele of the I/D polymorphic locus of the ACE gene in the homozygous state is associated with a high risk of development and severity of clinical manifestations of CHF. In patients with the D/D genotype of the ACE gene, a more pronounced decrease in the functional class of CHF and an increase in LVEF were noted during enalapril therapy compared to patients with the I/I and I/D genotypes. Associative relationships were revealed between the ACE gene polymorphism (I/D polymorphic locus) and the development and severity of CHF, as well as with the effectiveness of ACE inhibitor therapy - enalapril. A study of ACE (D/I), ADRB1 (Ser49Gly) and

other gene polymorphisms on 12-month prognosis in 145 patients who had ST-segment elevation MI (STEMI) found that the genotype of the ACE (I/D) polymorphic gene is a predictor of a favorable 12-month outcome of STEMI. The researchers concluded that genetic analysis to determine the I/I polymorphism of the ACE gene and the gene encoding the β1-adrenergic receptor (ADRB1) (Ser49Gly) is advisable to improve the 12-month prognosis and optimize therapy for patients with ST-segment elevation MI through a personalized approach to the choice of drugs, in particular ACE inhibitors and beta-blockers [34]. Taking into account the association of the D/D genotype of ACE with high levels of circulating and tissue ACE, it is possible to assume the effectiveness of ACE inhibitor and ARB therapy in these patients [9,23]. An equally important component of RAAS is the AGT gene (AGT – from English angiotensinogen), which is located in locus 42.2 of chromosome 1 and codes for the amino acid sequence of the protein molecule angiotensinogen. Polymorphisms are point mutations of the AGT gene. Point mutations, i.e. gene polymorphisms, are the most common cause of their differences and can occur both in exons and introns, promoter regions of genes with different frequencies, which is largely due to the pressure of natural selection. Currently, several structural polymorphisms of this gene have been described, among which the physiologically significant mutation in the 235th codon leads to the replacement of the encoded amino acid methionine with threonine (M235T). The international code of the polymorphism is rs699. Available foreign literature contains a wide range of data on the relationship between the AGT gene polymorphism and the development of CVD [5,18,33]. Several polymorphic states of the gene encoding AGT have been described, but the most significant are the polymorphic variants M235T and T174M, associated with the level of AGT activity in blood plasma, the content of ATII and, consequently, with the risk of CVD. Thus, when studying the M235T polymorphism, it was found that the presence of one or two T alleles leads to a significant increase in the content of ATII. According to the literature, the presence of the 174M risk allele of the AGT gene is much more common in patients with coronary heart disease, previous MI and LV hypertrophy (LVH). When studying the M235T polymorphism, it was found that the 235T variant is an independent risk factor for the development of cardiovascular disease [6,10,23]. There is also an opinion about the lack of influence of one or another variant of the AGT gene on the course and prognosis of patients with this pathology. Krasnova O.A. et al. (2012) did not reveal an association of the M235T polymorphism with a risk factor for the development of CHF in the Russian population [6]. However, it was noted that in patients with the T allele, MI developed at a younger age. In the group of patients with the M allele, a higher degree of LVH was recorded, and a correlation between mortality and the presence of the M allele was revealed. et al., studying the polymorphism of the ACE genes, the aldosterone synthase gene, and the AGT gene, noted that in patients with coronary heart disease with an unfavorable course of CHF, the T allele and the C/T genotype of the aldosterone synthase gene (C–344T), the T allele of the AGT gene (M235T), and the D allele and the D/D genotype of the ACE gene (I/D) are associated. The favorable course of CHF is associated with the carriage of the C allele and the C/C genotype of the aldosterone synthase gene (C–344T), the M allele and the M/M genotype of the AGT gene (M235T), and the I allele of the ACE gene (I/D) [7]. In patients with coronary artery disease with manifested CHF in carriers of the D/D genotype of the I/D polymorphic marker of the ACE gene, a 12-month course of therapy for CHF with fosinopril and enalapril was more effective than in carriers of the I/I genotype. No associations were found between AGT polymorphisms and the effectiveness of treatment with fosinopril and enalapril [12]. A study of the morphofunctional features of LV myocardial remodeling in patients with CHF in association with RAAS gene polymorphism revealed the prevalence of the eccentric type of LVH in patients with CHF in the hospital registry. A high frequency of the D allele of the ACE gene was revealed in patients with eccentric remodeling, and there were no patients with the TT genotype of the AGT gene in the group of patients with the concentric type of remodeling. These researchers also studied the M235T polymorphism of the AGT gene in patients with CHF in the comparison group of the Kazan region [8,11,33]. The distribution of allele and genotype frequencies was analyzed depending on the value of the Na + / Li ± countertransport rate through the erythrocyte membrane. A high frequency of the M allele and MM genotype of the AGT gene was revealed in patients with CHF in comparison with the comparison group. The AGT gene polymorphism type II 1 (CC genotype) in combination with the D / D genotype of ACE had an adverse effect on the survival of patients with CHF for 7 years. However, a number of studies have not revealed any association between genetic polymorphism of the RAAS (ACE, AGT, and ATP receptor genes) and the development of LVH, but have found an association between the D/D ACE genotype and impaired diastolic function [9,14,26]. ATII receptor type 1. The ATII receptor type 1 gene (AT2R1 – angiotensin II type 1 receptor) is localized on chromosome 3 (3q24). More than 16 structural polymorphisms of this gene are known, of which three have been most frequently used to study the association with polygenic hereditary diseases: a dinucleotide microsatellite in the 3'-untranslated region of the gene and single nucleotide polymorphisms T/C at position 573 (T573C) and A/C at position 1166 (A1166C) of the nucleotide sequence of the AT2R1 gene. The A1166C polymorphism, which results in the substitution of adenine for cytosine at position 1166 n.p., is associated with the functional activity of the ATII receptor and the implementation of ATII effects in the cell [28]. The ATII receptor type 2 gene. In recent years, the interest of many researchers has focused on the function of type 2 ATII receptors, which are localized not only in the reproductive system, as previously believed, but are also present in virtually all tissues, especially in the vascular endothelium. The gene of this receptor is located on the X chromosome and is characterized by a G/A polymorphism at codon 1675

and a substitution of adenine for cytosine at position 3123 n.p. (A3123C polymorphism) [27]. Aldosterone is a mineralocorticoid that is primarily synthesized in the zona glomerulosa of the adrenal cortex from deoxycorticosterone by the mitochondrial cytochrome p450 enzyme aldosterone synthetase, increases the number of ATII type 1 receptors in the cardiovascular system and potentiates the effects of RAAS. Aldosterone synthesized by the adrenal cortex primarily affects receptors located in the distal renal tubules and collecting ducts of the nephrons. By binding to intracellular mineralocorticoid receptors (corticoid receptors type 1), aldosterone interacts with hormone-sensitive elements of DNA and modulates the transcription of specific proteins. At the same time, in recent years the idea has been formed that aldosterone is synthesized not only in the adrenal cortex, but also in the myocardium, vascular endothelium, brain tissue and exerts its effect directly at the site of synthesis. It has been shown that aldosterone receptors are expressed on cardiomyocytes, endothelial cells, and human cardiac fibroblasts. By activating these receptors and, possibly, by other, so far hypothetical, mechanisms, aldosterone increases collagen synthesis and causes fibroblast proliferation. Experiments on rats have shown that myocardial fibrosis, especially around the coronary arteries, is caused by increased production of collagen types I and III, stimulated by the combined action of aldosterone and angiotensin II. In a culture of adult cardiac fibroblasts, aldosterone stimulates collagen synthesis through type 1 corticoid receptors. In addition, aldosterone induces local inflammation in the endothelium of medium and small coronary vessels and perivascular zones of the myocardium, increases the expression of ACE messenger RNA in myocardiocytes, determining local formation of ATII in the myocardium. Aldosterone synthetase is a human enzyme encoded by the CYP11B2 gene (cytochromeP450, family 11, subfamilyB, polypeptide 2) on chromosome 8. Aldosterone synthase belongs to the cytochrome P450 superfamily and provides the synthesis of the hormone aldosterone. The aldosterone synthetase gene is mapped to chromosome 8, location q24.3. It is located next to the 11beta-hydroxylase gene (CYP11B1). The CYP11B2 gene is highly homologous to the CYP11B1 gene encoding 11-beta-hydroxylase. Despite considerable research efforts, it remains unclear how the C-344T polymorphism affects steroid biosynthesis at the molecular level. On chromosome 8q24, the genes encoding aldosterone synthase CYP11B2 and 11B-hydroxylase CYP11B1 are located in close proximity. CYP11B1 catalyzes the final step in cortisol synthesis. The proximity of these genes means that uneven crossover at this locus may result in glucocorticoid-induced aldosteronism, a rare inherited form of hypertension. The close proximity of CYP11B2 and CYP11B1 provides a possible explanation for why the CYP11B2 polymorphism is associated with changes that may result from processes occurring in CYP11B1. Several polymorphic markers have been described in the aldosterone synthetase gene [3,25]. The most thoroughly studied polymorphism is the substitution of cytosine for thymine at position 344 of the nucleotide sequence, in the regulatory region of the gene. This region is the binding site of the steroidogenic transcription factor SF-1, a regulator of aldosterone synthase gene expression. According to recent studies, the T allele leads to increased aldosterone production, which in turn is associated with hypertension, as well as with myocardial fibrosis and hypertrophy and the risk of hypertensive complications of pregnancy. An association was found between aldosterone synthase gene polymorphism and LV size, mass, and diastolic function in young people. The aldosterone synthase gene is classified as a candidate gene for the development of remodeling and adverse prognosis of the cardiovascular system [31,36]. Sun X. et al. found that CYP11B2 T–344C gene polymorphism is not associated with AF, but may be associated with atrial remodeling due to hypertension in the Chinese population. Other studies have found a significant association between CYP11B2 T–344C gene polymorphism and the risk of AF, which was observed in individuals with the CYP11B2 T–344C C-allele, who had a higher risk of AF [30,35]. In patients with CHF, the aldosterone synthase gene (C-344T) was found to be associated with the severity of inotropic cardiac dysfunction and LV remodeling [3,29]. The studies showed that the frequency distribution of genotypes of the polymorphic locus C-344T of the aldosterone synthase gene in groups of patients with coronary heart disease in combination with hypertension corresponded to that in Caucasians [17,30]. The study of the relationship between CVD and the CYP11B2 T-344C gene polymorphism is still ongoing in large-scale studies. A review of domestic and foreign literature shows that the results of studies of RAAS gene polymorphism in patients with various cardiovascular pathologies are quite contradictory, so their determination has not yet been included in the diagnostic algorithms for cardiac patients. This is largely due to the small number and clinical heterogeneity of the studied patient samples. In addition, to date, it has not been possible to identify all the genes (the "gene network" of the disease) involved in the formation of hereditary predisposition for any CVD, and the study of individual genes does not solve the problem of "missing" ("disappearing") heredity. It is also worth noting that more and more facts are accumulating indicating a significant role in the formation of hereditary predisposition of epigenetic variability, which determines not only the activity, but also the interaction of genes with each other. Nevertheless, the compilation of the "gene network", the identification of central genes and modifier genes in it, the study of intergenic and gene-environmental interactions, the development on this basis of a set of preventive and therapeutic measures individual for each patient, undoubtedly constitute the strategic basis for a new, rapidly developing direction called predictive medicine [31,32]. Summarizing the studied data, it should be especially emphasized that the practical implementation of the results of genomic projects makes a broader assessment of genetic polymorphism in individual patients available [29]. Polymorphism of thousands of genes has already been identified. The map of such genes can be used to detect alleles important for the development of various

diseases and the response of patients to certain treatment. Genetic factors undoubtedly play an important role in the pathogenesis of CHF, but information on the mechanisms of genetic control of predisposition to cardiovascular pathology is clearly insufficient.

3. Conclusions

All this indicates that research in this area is very relevant and promising. The study of molecular genetic mechanisms of CHF development, determining the role of genetic markers for assessing the risk of CHF development is an urgent scientific and practical task. Gene determinants, indicating the probable prognosis of the risk of occurrence, severity, and nature of the course of CHF of various etiologies, allow us to identify groups at increased risk of CHF development and determine effective tactics for the prevention and treatment of this pathology, which ultimately helps improve the quality of life and survival of patients with CHF.

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