Molecular genetic markers of atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the supraventricular form of tachyarrhythmia characterized by uncoordinated atrial stimulation and manifested in the increased frequency of their contraction. The frequency of this pathology directly correlates with the patients’ age and reaches 50% in an older age group. This fact determines the need for search of any markers of individual AF risk, which may contribute to an increase in the effectiveness of preventive actions. Among such markers, polymorphic variants of genes involved in the pathogenesis of AF are the most promising markers. This review discusses the results of studying the genetic markers of the AF development, as well as the possibility of their use as predictors of this pathology.

Key words: atrial fibrillation, genetic polymorphism, cardiovascular diseases.

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Молекулярно-генетические маркеры фибрилляции предсердий

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РЕЗЮМЕ

Фибрилляция предсердий (ФП) – наджелудочковая форма тахиаритмии, характеризующаяся несокоренспондированным возбуждением предсердий, проявляющимся в увеличении частоты их сокращения. Частота возникновения данной патологии напрямую коррелирует с возрастом пациентов и достигает 50% в старшей возрастной группе. Необходимость увеличения эффективности профилактиче-
INTRODUCTION

Atrial fibrillation (AF) is a subtype of supraventricular tachyarrhythmia, characterized by disorganized atrial activation with the atria’s contractions occurring up to 350 times per minute. It significantly weakens the heart’s pump function [1]. The prevalence of AF in the general population is constantly growing. It is estimated to affect 33.5 million people globally [2]. The relationship between AF and age has been well described in the medical literature. AF occurs in 0.5% of young adults aged less than 40 years and increases up to 25% in adults aged 40 to 70 years. Among the elderly, its incidence increases up to 50% [3–5]. AF is commonly considered as a severe risk factor contributing to the development of adverse cardiovascular events. Almost 12.5% of adverse events among elderly patients are associated with the presence of AF [6–8]. Long-term survival of patients undergoing mitral valve repair depends on the presence of concomitant AF that is commonly diagnosed in 40–60% of patients with mitral valve insufficiency. Oda-renko et al. have reported a 17-fold increased risk of thromboembolism in patients with rheumatic mitral valve disease and concomitant AF in comparison with sinus rhythm patients. AF persisting after mitral valve repair was associated with atriomegaly and a long history of heart rhythm disturbances [9].

Myocardial pathology or alterations in the neurohumoral activation are generally considered as the main mechanisms contributing to the pathogenesis of AF [10, 11]. AF is secondary to arterial hypertension, coronary artery disease (CAD), hypertrophic and dilated cardiomyopathy, and congenital and acquired heart disease in almost 70% of cases. But in some cases, its etiology remains unknown and AF is considered as idiopathic or primary [12] and commonly referred to as familial AF [13]. Moreover, the genetic contribution should not be excluded from the list of the factors leading to the onset of secondary AF. The probability of its onset varies even if the underlying diseases are of similar severity.

There are two groups of risk factors contributing to the development of AF: traditional risk factors (age, ischemia, diabetes mellitus, metabolic syndrome, binge alcohol consumption, etc.) and genetic risk factors (gene polymorphisms involved in the pathogenesis of AF). Genetic risk factors are currently on the rise as they may provide novel insights into drug targets for therapy and give clues how to improve the prognosis. Over 30 genetic loci have been recently determined that are involved in the pathogenesis of AF [14]. Today, molecular genetic studies of AF are focused either on identifying mutations in the genes linked to the onset of AF or determining gene polymorphisms that indirectly affect myocardial function (the renin-angiotensin-aldosterone system gene, inflammatory response, etc.).

Thus, the identification of candidate genes associated with an increased risk of AF is the most important direction of modern genetics.
studies are aimed at defining the triggers that are responsible for the onset of various forms of AF, and the factors relevant to the chronicity of this pathology [5, 14].

MOLECULAR GENETIC MARKERS ASSOCIATED WITH AN INCREASED RISK OF AF

While the role of traditional risk factors in the development of AF has been studied well, the genetic contribution to its onset has recently received recognition worldwide. In 2004, Lubitz et al. showed that the presence of AF in parents increased the risk of AF developing in their children by 40% [15]. Investigators from Iceland found that the risk of AF reduced with increased genetic distance between relatives [16]. In addition, the risk of developing AF in both monozygotic twins was higher than in dizygotic twins [17]. All these studies have confirmed the significance of genetics in the development of AF, giving the green light to molecular genetic studies. Over 3,800 studies have been performed examining the associations of genetic polymorphisms and phenotypic traits (genome-wide association studies, GWAS) by the end of December 2018 [18]. In 2007, investigators from Iceland reported that two independent single nucleotide polymorphisms (SNP) on chromosome 4q25 were associated with AF [19]. Other studies in the independent samples from Caucasian [20], Chinese [21] and African American [22] populations confirmed the role of this locus in the development of AF. Since 2006, genome-wide association studies (GWAS) allowed defining additional 23 loci related to AF. What is more, the role of most of them in the pathogenesis of AF has been described for the first time [14, 23–27].

ION CHANNEL GENES

GWAS have indicated that the development of familial AF is caused by the KCN (KCNA5, KCND3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNN2, KCNN3 and KCNQ1), SCN (SCN5A and SCN10A), J1A, G1, JAA, G1, J1A, G1, and G (CAV1 and CAV2) gene mutations [5, 14]. These genes encode proteins of potassium and sodium channels, connexin and calveolin that are involved in the membrane transport. They play an important role in the function of the myocardium. Mutations in these genes have been shown to affect the function of ion channels and the conformation of proteins, which affects the state of the myocardium. In 2012, Danish researchers examined the relationship of the KCNE1 gene mutation, encoding the potassium channel beta subunit protein, with AF. They bidirectionally sequenced the entire coding sequence of the KCNE1 gene in 209 patients with early-onset AF (aged under 40 years) and in 216 healthy individuals. Patients with AF were heterozygous carriers of the KCNE1 c.74 G> T and KCNE1 c.179 G> A. In addition, functional analysis of polymorphic variants showed that mutations in c.74 G> T and c.179 G> A were associated with an increase in the flow of potassium ions across the membrane, thereby confirming the role of this process in the pathogenesis of AF [23].

In 2014, the coding regions of KCNE2 and KCNE3 were bidirectionally sequenced in 192 patients with early-onset AF. Two missense mutations, M23L (c.67A>T) and I57T (c.170T>C), were identified in KCNE2. These mutations were absent in the control group without AF. There were no AF-specific mutations in KCNE3. Thus, researchers reported two mutations in KCNE2, encoding potassium channel β-subunit protein, as possible genetic substrates for early-onset AF [24].

Li et al. assessed the associations of polymorphisms on KCNE1, KCNQ1, KCNH2 gene with the risk of AF in Chinese population. The study included 438 AF patients and 450 healthy subjects, ensuring high reliability of the results. Among the nine SNPs, only three SNPs were associated with an increased risk of AF. Polymorphism of rs1805127*G allele in KCNE1 was significantly associated with the risk of AF as compared to A allele (A/G vs. A/A, OR 1.56, \( p = 0.049 \); G/G vs. A/A, OR 1.59, \( p = 0.044 \); dominant G/G + A/G vs. A/A, OR 1.57, \( p = 0.036 \)) as well as rs2283228*C allele (A/C vs. A/A, OR 1.62, \( p = 0.036 \); C/C vs. A/A, OR 1.73, \( p = 0.012 \); C/C + A/C vs. A/A, OR 1.64, \( p < 0.001 \) and rs1057128*A allele on KCNQ1 (A/A vs. G/G, OR 1.92, \( p = 0.013 \); A/A + A/G vs. G/G, OR 1.78, \( p < 0.025 \)). The polymorphism of rs1805120*T allele on KCNH2 was associated with a lower risk of AF. Five other SNPs (rs2237892, rs2237895, rs2237897, rs2070357 and rs2070356) showed no significant association with the risk of AF (\( p > 0.05 \) [25]).

The role of mutations in the KCNQ1 gene has also been studied in vitro. In induced atrial repolarization, the S140G mutation was associated with an almost four-fold increase
in positive repolarization currents and peak potential during membrane repolarization, compared with carriers of the major allele. In induced ventricular repolarization, the peak potential in mutant cells was three times higher than that of carriers of the major alleles. In general, the total peak potential was higher compared to that in the experiments with atrial repolarization, regardless of allelic carriage. The change in potential, in turn, led to a shortening of the QT interval, which in patients with AF with the S140G mutation of the KCNQ1 gene can be a predictive factor [26]. Similar results were obtained using in silico modelling [27].

Several studies have shown the effects of nonsense mutations in the KCNQ1 gene, encoding the Kv1.5 transmembrane protein. This protein forms sodium channels that are activated by changing the membrane potential in the region near the channel. This mutation leads to the synthesis of a defective protein and is associated with an increased risk of AF [19–30].

KCNQ3 gene encoding the Kv4.3 transmembrane protein is another well-studied gene associated with AF. In 2000, German researchers found that patients with AF showed a 61% decrease in mRNA expression of the gene compared with sinus rhythm patients ($p < 0.001$), despite similar expression of mRNA of KCNA4 and KCNA5 genes in both groups [31]. A similar trend has been reported by Brundel et al. The expression of KCND3 and KCNJ5 genes was 35% and 47% lower in patients with chronic AF compared with those in the control group. Significant differences in mRNA expression were obtained only for the KCND3 gene among patients with paroxysmal AF. Likely to the previous study, similar expression of KCNA5 gene was observed in both groups. Interestingly, the expression of KCND3 and KCNJ5 proteins was significantly reduced in chronic and paroxysmal AF [32]. In 2013, the role of KCND3 c.1633G>C [33] and g.112392360 G>T [34] in the development of early-onset AF was described in 209 young adults with AF (aged under 40 years).

Recently, Danish investigators have examined 14 genes encoding the proteins that make up the ion channels. One substitution in GJA5, KCND3, KCNE5 genes, two substitutions in KCNE1, KCNE2, SCN2B genes, three substitutions in KCNA5, KCNQ1, SCN3B genes and eight substitutions in SCN5A gene were associated with early-onset AF [35].

ADRENERGIC RECEPTOR GENES

Adrenergic receptors are a class of receptors that are localized on the outer cell membrane. They are responsible for the recognition and binding of epinephrine, norepinephrine and synthetic analogues of catecholamines and mediating their physiological and pharmacological effects. Adrenergic receptors are divided into several classes based on their location and function: 1) $\alpha_1A$ are expressed in the bladder neck, urethra and prostate; 2) $\alpha_2\beta$ are expressed in arterioles (their stimulation and narrowing leads to an immediate increase in arterial blood pressure); 3) $\alpha_2$ are expressed in neuromuscular synapses; 4) $\beta_1$ are expressed in the myocardium and kidneys (their stimulation increases both the heart rate and the strength of the heart muscle, followed by an increase in conduction velocity of the nerve impulse); 5) $\beta_2$ are expressed in bronchioles and liver; and 6) $\beta_3$ are expressed in adipose tissue. Based on their biological function, the genes encoding B1- and $\alpha_2\beta$-adrenergic receptors (ADRB1 and ADRA2B, respectively) are of the greatest interest to researchers examining genetic predictors of AF.

The $ADRB1$ gene is located on the long arm of chromosome 10 (11q23-q25) and encodes a protein consisting of 477 amino acid residues. The available data on its role in the development of AF are contradictory. In 2014, a large prospective study in 947 adult Americans who underwent cardiac surgery (coronary artery bypass grafting, heart valve replacement, congenital heart surgery) was performed in the period from 1999 to 2005. The associations of two major SNPs, Arg389Gly (rs1801253) and Ser49Gly (rs1801252) in the $ADRB1$ gene with a risk of AF in the postoperative period (14 days after the indexed surgery) were examined. Atrial fibrillation was recorded in 239 (25.2%) patients. Carriers of the Gly389Gly genotype (rs1801253) showed a two-fold increased risk of AF (OR 2.63, $p = 0.008$), compared with carriers of the Arg389Arg genotype. Patients who did not receive $\beta$-blocker therapy demonstrated further risk increase (OR 7.00, $p = 0.005$). Ser49Gly polymorphism was not associated with the risk of developing AF [36], as opposed to the results of the study in the Russian population. The latter reported that the heterozygous genotype of the rs1801252 (Ser-49Gly) of the $ADRB1$ gene was associated with an increased risk of both primary and secondary AF [37]. However, carriers of the Arg389Arg genotype (rs1801253) of the $ADRB1$ gene with a
confirmed diagnosis of AF were less sensitive to the therapy for heart rate control and required higher dosages of drugs (atenolol, carvedilol, metoprolol, diltiazem, verapamil) compared to heterozygous carriers [38]. Importantly, a 40% decrease in mortality was observed among patients with this genotype who received bucindolol compared with carriers of the Gly allele [39].

The ADRA2B gene is located on the long arm of chromosome 2 (2q11.2) and encodes the α2β-adrenergic receptor. The relationship between the inheritance of certain genetic variants of the ADRA2B gene and the risk of familial AF was examined in the Russian population [100 probands with diagnosed AF and three siblings (n = 144)]. Three types of genotypes were identified: homozygous I/I genotype, heterozygous I/D genotype, and homozygous D/D genotype. Homozygous I/I genotype prevailed among AF patients compared with the control group (43.7% vs. 25.2%, respectively, p = 0.034). Patients were then subdivided into the primary AF group and secondary AF group. Homozygous I/I genotype was commonly found in patients with primary AF (42.2%) compared with the control group (25.2%). However, there were no significant differences found in the frequencies of genotypes in AF patients and their relatives as well as healthy volunteers. Researchers concluded that the I/I genotype of the ADRA2B gene could be a risk factor for primary AF [40].

GENES OF THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAAS) is a hormone system that regulates blood pressure through the effects on vascular tone. The peptide hormone angiotensin II plays the key role in this process. Angiotensinogen is a precursor to angiotensin II. Angiotensinogen is cleaved to angiotensin II. Angiotensinogen is a precursor to hormone angiotensin II plays the key role in through the effects on vascular tone. The peptide hormone system that regulates blood pressure

In 2004, Taiwanese researchers examined the insertion/deletion (I/D) polymorphism of the ACE gene, 6 allelic variants of the AGT gene (T174M, M235T, G-6A, A-20C, G-152A, G-217A), and AGTR1 A1166C gene polymorphism in 250 AF patients. The AGT gene haplotypes significantly differed between the groups of patients with AF and the control group (250 people). In addition, reliable associations of multiple AGT gene polymorphisms, M235T, G-6A, and G-217A, with a risk of AF were reported [42]. Later, these findings were confirmed by Topal et al., Zhao et al. The T allele and the T/T genotype of M235T polymorphism, the G allele and the G/G genotype of G-6A polymorphism were associated with an increased risk of AF [43, 44]. In 2008, the same research group recruited 1,236 patients to identify associations between individual polymorphic variants of the studied genes and the risk of AF. While none associations were determined, the differences in haplotypes between AF patients and healthy subjects were confirmed. Moreover, intergenic interactions were found between the I/D polymorphism of the ACE gene, A1166C polymorphism of the AGTR1 gene, and AGT haplotypes [45].

Danish researchers examined the AGT gene polymorphism (A-20C, G-6A, T174M and M235T) and the I/D ACE gene polymorphism in 9,253 patients. Out of them, 968 patients suffered from AF. They found that carriers of the A/C and C/C genotypes of the AGT gene had a higher risk of AF compared with carriers of the A/A genotype (OR 1.1 and 1.5, respectively). Moreover, the combination of the I/D and D/D genotypes of the ACE gene synergized to increase the overall risk of AF (OR 1.2 and 2.4, respectively) [46].

In 2011, a meta-analysis examining the I/D polymorphism of the ACE gene, covering 18 studies (a total of 7,577 AF patients) was published. Researchers concluded that there were no evidences to confirm the presence of the relationship between this polymorphism and the risk of AF. But they hypothesized that the ACE gene and AF in patients with arterial hypertension were linked [47]. Then, a number of studies of the I/D polymorphism of the ACE gene were performed. The results of most studies confirmed previous data on the association of the ACE gene I/D and D/D genotypes with an increased risk of AF [48, 49]. However, one of the recent studies in the Russian population has reported that carriage of the homozygous D/D genotype may have a relatively protective effect on the development of AF [50].

Feng et al. have recently showed the associations of rs1492099 polymorphism in the AGTR1, gene encoding the angiotensinogen receptor, (the frequency of the minor allele in the patient group was 14.2% vs. 8.8% in

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the control group, OR 1.727) and rs6632677 polymorphism of the ACE2 gene (the frequency of the minor allele was 16.3% in male patients vs. 9.1% in healthy men, OR 1.954) with AF in Chinese population [51].

NITRIC OXIDE SYNTHASE GENE

Various vasodilation factors that regulate vascular tone can modulate contractile activity of the myocardium, thus participating in the pathogenesis of AF. These factors include nitric oxide (NO), which prevents the tonic contraction of blood vessels originated by endocrine, neuronal or local sources followed by NO synthase (NOS) formation. A decrease in the production of NO synthase can cause oxidative stress and provoke changes in the myocardial conduction system, leading to the development of AF [52]. NO synthase is encoded by the \( eNOS \) gene located on chromosome 7. Russian investigators examined 100 probands and their three siblings and compared the findings with those obtained for 91 healthy subjects recruited in the control group [53]. The homozygous G/G genotype (G894T) prevailed in AF patients (58.5%) compared with the control group (39.6%; \( p = 0.039 \)). Patients with AF were further subdivided into the groups with primary and secondary AF. The homozygous G/G genotype was found only in patients with primary AF compared with the control group. Patients with secondary AF did not report any statistically significant differences in the frequencies of alleles and genotypes. Thus, the G allele has been shown to serve as a predisposing factor for atrial fibrillation.

The relationship of G894T, T786C, and 4b/a in the \( eNOS \) gene and AF in patients with heart failure was also studied. The G allele (G894T polymorphism) was more common in the group of patients with AF. Carriers of the G/G genotype demonstrated almost a three-fold increased risk of AF [54, 55]. Other polymorphic variants were not associated with AF [54, 57]. Nevertheless, recent evidences have suggested the protective effects of T786C polymorphism on the risk of AF [56].

G PROTEIN-COUPLED RECEPTOR GENES

G protein-coupled receptor kinases (GRKs) are a family of protein kinases that phosphorylate the intracellular domains of G-protein coupled receptors (GPCRs) and regulate their activity. Phosphorylation occurs after ligand receptor binding and G-protein dissociation. In addition, GRK kinases regulate the cellular response independently of their kinase activity. The \( GRK5 \) gene is an important regulator of GPCR function that maps on chromosome 10 at the region of q24 (10q24). Recent studies have shown that the polymorphism of this gene is associated with a decrease in mortality among African Americans with heart failure and coronary artery disease [58].

In 2014, a study in 563 patients undergoing coronary artery bypass grafting, of whom 111 patients developed postoperative AF, was performed. A total of 492 SNPs in 10 genes were analyzed. Four polymorphic variants of the \( GRK5 \) gene were associated with an increased risk of postoperative AF (rs3740563, OR = 2.75; rs4752292, OR = 2.21; rs11198893, OR = 2.51; rs10787959, OR = 1, 72). The meta-analysis showed that the polymorphic variant rs3740563 played a key role in the formation of individual sensitivity to AF. Thus, the genetic variation of the \( GRK5 \) gene was associated with postoperative AF in patients who underwent coronary artery bypass grafting, despite preoperative therapy with \( \beta \)-blockers [59].

A similar study was conducted in Chinese population in 2015. The study included 1,348 patients. Nine SNPs were examined. Of them, six SNPs were assessed in another group of 2,000 patients to validate the results. Only two variants of the \( GRK5 \) gene (rs4752292 and rs11198893) were associated with an increased risk of AF (OR for the minor allele was 1.32 and 1.47, respectively) [60].

CONCLUSION

Our review confirms the genetic contribution of various systems in the pathogenesis of AF (ion channels, adrenergic receptors, the renin-angiotensin system, NO synthase, and GRK kinase receptors) and formation of increased individual risks of its onset. The available data have indicated a fairly extensive panel of genes that can serve as potential molecular genetic markers of AF development, as well as stated the need to study intergenic interactions between potential candidate genes. The presented inconsistencies on the association of some genes with AF as well as interpretative variations depending on the studied population have set the rationale for further studies in different ethnic groups.
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