The role of polymorphisms in genes that regulate neurohumoral systems in patients with atrial fibrillation

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Key words: genetic polymorphism, atrial fibrillation, renin-angiotensin-aldosterone system, catecholamines, NO synthase.

The aim of the study is to analyze the modern literary sources related to the role of gene polymorphisms regulating some neurohumoral systems in group of patients with atrial fibrillation.

A combination of certain genes polymorphisms can contribute to AF risk. Especially important are gene studies of the renin-angiotensin-aldosterone system (RAAS) role in the pathogenesis of AF which are currently being studied with a particular intensity. Recent data show that activation of RAAS plays an important role in the development and recurrence of AF. These studies are of great practical interest as the associative effect of angiotensin converting enzyme (ACE) inhibitors in the prevention of AF has been identified.

AGT gene encodes a plasma protein known as angiotensinogen. This protein is expressed in the liver and is cleaved by the enzymatic active enzyme angiotensin II. Defects in this gene may also be associated with non-hereditary AF. More than 16 spot mutations in the AGT gene were discovered, most of which resulted in amino acid substitutions.

Conclusions. The analysis of the literature allows to conclude that, first, genetic polymorphisms may influence both the severity of pathological changes in the body and the efficacy of pharmacotherapy, and second, the study of RAAS gene polymorphisms may allow early detection of persons with increased risk of persistent AF recurrence and its prevention.

One of the important medical and social present-day problems is atrial fibrillation (AF) which prevalence in the adult population is 2 % for persons under 65 and 9 % for those over 65 years of age and it is a common cause of ischemic stroke. The embolic complications incidence is 2.1 % per year in patients with paroxysmal AF, and 3.0 % per year in patients with persistent AF.

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UDC: 616.125-008.318-036.11:575.24/.25:616.8

Review

Висновки. Аналіз сучасної фахової літератури, в якій описано роль поліморфізмів генів, що регулюють деякі нейрогуморальні системи, в пацієнтів із фібриляцією передсердь, показав, що генетичні поліморфізми впливають на виникнення, тяжіння, та ефективність лікування цих захворювань. Особливо важливі є зміни гену AGT, який кодує ангиотензиноген, а також гену RAAS, який кодує реніну-ангиотензин-альдостеронову систему.

Ключові слова: поліморфізм генів, фібриляція передсердь, ренін-ангиотензин-альдостеронова система, катехоламіні, NO-синтаза.


DOI: 10.14739/2310-1210.2019.3.169201
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Роль поліморфізмів у генах, що регулюють нейрогуморальні системи, у пацієнтів із фібриляцією передсердь

I. М. Фуштей, С. Г. Подлужний, Е. В. Сідь

Одно з важливих медико-соціальних проблем сучасного життя є фібриляція передсердь (ФП), поширеність якої в дорослого населення становить 2 % серед осіб віком до 65 років і 9 % серед старших за 65 років та є причиною ішемічного високого ускладнення. Частота емболічних ускладнень становить 2.1 % на рік у пацієнтів із пароксизмальною ФП та 3.0 % на рік у пацієнтів із персистентною ФП.

Висновки. Аналіз сучасної фахової літератури, в якій описано роль поліморфізмів генів, що регулюють деякі нейрогуморальні системи, в пацієнтів із фібриляцією передсердь, показав, що генетичні поліморфізми впливають на виникнення, тяжіння, та ефективність лікування цих захворювань. Особливо важливі є зміни гену AGT, який кодує ангиотензиноген, а також гену RAAS, який кодує реніну-ангиотензин-альдостеронову систему.

Ключові слова: поліморфізм генів, фібриляція передсердь, ренін-ангиотензин-альдостеронова система, катехоламіні, NO-синтаза.
Цель работы — анализ современной научной литературы, описывающей роль полиморфизмов генов, регулирующих некоторые нейрогуморальные системы, у пациентов с фибрилляцией предсердий. Появлению ФП может способствовать сочетание полиморфизмов некоторых генов. Особенно актуально изучение генов ренин-ангиотензин-альдостероновой системы (РААС), так как ее роль в патогенезе ФП изучают особенно интенсивно. Последние данные показывают, что активация РААС играет важную роль в развитии и сохранении ФП. Эти исследования имеют большой практический интерес, поскольку установлен ассоциативный эффект ингибиторов ангиотензин-превращающего фермента (АПФ) в профилактике ФП.

Ген AGT кодирует белок ангиотензиноген. Этот белок экспрессируется в печени и расщепляется под действием фермента ренина в ответ на снижение артериального давления. Полученный продукт, ангиотензин I, затем расщепляется АПФ до физиологически активного фермента ангиотензина II. Дефекты в этом гене могут быть также связаны с ненаследственной фибрилляцией предсердий.

Выводы. Анализ научной литературы позволяет сделать выводы: во-первых, генетические полиморфизмы могут влиять как на выраженность патологических изменений в организме, так и на эффективность фармакотерапии; во-вторых, изучение полиморфизмов генов РААС может способствовать раннему выявлению лиц с повышенным риском рецидива персистирующей ФП и проведение ее профилактики.

Actuality. One of the important medical and social present-day problems is atrial fibrillation (AF) which prevalence in the adult population is 2 % for persons under 65 and 9 % for those over 65 years of age and it is a common cause of ischemic stroke. The embolic complications incidence is 2.1 % per year in patients with paroxysmal AF, and 3.0 % per year in patients with persistent AF. At present, AF is considered to be a potentially lethal arrhythmia, given the wide range of its negative consequences associated not only with a significant deterioration in the quality of life, but also a significant increase in the frequency of serious complications [1,2].

AF is a multifactorial disease in the development of which such factors as senile age, arterial hypertension, environmental factors and genetic predisposition are important. The risk of AF development increases for persons, who have at least one of the parents with this arrhythmia in the anamnesis [3,4].

Genetic predisposition to AF has a strong hereditary component that is independent of concomitant cardiovascular disease. Up to a third of patients with this arrhythmia have general genetic variants that lead to AF, albeit with relatively low additional risk. Although currently genetic testing is not used in routine clinical practice, in the future, genomic analysis may provide an opportunity to improve the diagnosis and management of patients with AF [5].

Aim

The aim of the study is to analyze the modern literary sources related to the role of gene polymorphisms regulating some neurohumoral systems in group of patients with atrial fibrillation.

A combination of certain genes polymorphisms can contribute to AF risk. Especially important are gene studies of the renin-angiotensin-aldosteron system (RAAS) role in the pathogenesis of AF which are currently being studied with a particular intensity. Recent data show that activation of RAAS plays an important role in the development and recurrence of AF. These studies are of great practical interest as the associative effect of angiotensin converting enzyme (ACE) inhibitors in the prevention of AF has been identified [6,7].

AGT gene encodes a plasma protein known as angiotensinogen. This protein is expressed in the liver and is cleaved by the enzymatic renin action in response to lower blood pressure. The resulting product, angiotensin I, is then cleaved by ACE to the physiologically active enzyme angiotensin II. Defects in this gene may also be associated with non-hereditary AF. More than 16 spot mutations in the AGT gene were discovered, most of which resulted in amino acid substitutions. Allelic variants of the Met235RThr and Thr174Met mutations are the most studied [8].

In the study of N. P. Topal et al., the relationship between polymorphisms of RAAS genes and AF development was investigated. Several polymorphisms including Met235RThr were genotyped. The study concluded that patients with mutations in the RAAS genes may be susceptible to AF. In their view, it is the genetic predisposition that can be the basis of acquired AF [9].

A group of scientists led by Q. Wang et al. investigated Met235RThr polymorphism in the AGT gene in patients suffered AF, who had undergone catheter ablation, and concluded that this polymorphism could be associated with AF recurrence. The authors argue that genotyping is useful in identifying patients with a high risk of AF recurrence after catheter ablation, and it is necessary to develop an individual strategy for further action based on genotyping results [10].

The effects of angiotensin II are mediated by type 1 and type 2 receptors (AT1 and AT2). A group of scientists led by BoldtA. et al. found that AF is associated with an up-regulation of AT1 in the left atrium, but not in the right atrium [11].

The interaction between angiotensin II and AT1 receptors located on the fibroblasts of the heart leads to induction of fibroblast hyperplasia, activation of collagen biosynthesis and inhibition of its degradation pathways, as well as decrease in collagenase activity. The AGTR1 gene encoding the angiotensin II receptor was mapped to chromosome 3 [12].

Currently, the most actively studied is AGTR1 A1166C polymorphism. So Bonnardeaux A. et al. have proved that the mutation of the A1166C nucleotide sequence in the AGTR1 gene affects functional activity of the receptor and angiotensin II [13].

In a research work of Y. N. Beleinov et al. there was studied the relationship between A1166C genetic polymorphism of the AGTR1 gene, which is also a key gene in the RAAS, and the risk for AF. According to the results of the work, it has been established that the presence of this polymorphism is associated with an increased risk of AF, having a cumulative effect on the disease phenotype, as well as with the development of severe myocardial hypertrophy [14].
AGTR1 gene A1166C polymorphism is also associated with essential hypertension [13] and arterial vasoconstriction [15]. Increased cardiovascular risk associated with this polymorphism was explained by P. P. van Geel et al. by the increased arterial response to angiotensin II. So, it can be assumed that A1166C polymorphism promotes an individual response to various antihypertensive drugs [16].

It is known that RAAS blockers are able not only to reduce the risk of developing first-detected episode of AF in patients with hypertension, but also to prevent AF recurrence in patients without it. In addition, experimental studies have shown that RAAS blockers prevent the remodeling of not only the left ventricle, but also the left atrium, which also indicates the pathogenesis of AF [17–19].

Regulation of the sympathoadrenal system (SAS) activity is important for favorable course of persistent AF. SAS plays an important role in the pathogenesis of heart rhythm disturbances. The negative effect of catecholamines is mediated mainly by β1-adrenergic receptors which functioning is facilitated by G protein. The activation of G-protein starts when the agonist binds to the receptor. It is followed by a series of biochemical reactions launch with cardiomyocytes contraction as the final point. However, β1-adrenergic receptors activity may also depend on the genetic features of a patient [20].

β1-adrenergic receptor is encoded by the ADRB1 gene located on chromosome 10 ( locus 10q25.3). This gene is polymorphic, and to date, more than ten polymorphisms have been described, two of which are the most clinically significant, namely Gly49Ser and Gly389Arg [21].

In a study of B. Parvez et al., the doses of drugs required for control AF were documented. The authors examined the association of polymorphisms in the gene variants ADRB1 Arg389Gly and Ser49Gly with AF. It has been found that the Gly389Arg variant was significantly associated with the difference in response to therapy, while the Ser49Gly did not influence outcome of rate control therapy in patients with AF [22].

In a research work of A. M. Nia et al., the impact of different ADRB1 genotypes on antiarrhythmic action of flecainide in patients with AF was studied. It has been found that Arg389Gly and Ser49Gly polymorphisms might be of predictive value for AF [23].

Association of the ADRB1 gene polymorphisms with AF was studied by S. Niculita et al. The purpose of their research was to determine the probability and patterns of AF inheritance in families, and to find an association of primary and secondary AF with polymorphism Ser49Gly of the gene encoding ADRB1. According to the results, the authors concluded that the Gly49Gly genotype of ADRB1 gene can be considered as one of the genetic predictors for development of primary or secondary AF. Relatives of probands with primary AF and Ser49Gly genotype should be included in the risk group for developing this arrhythmia [24].

Hyperactivation of RAAS and SAS promotes the development of endothelial dysfunction. The main vasoconstrictor in the vascular wall is endothelin-1, which suppresses the expression of endothelial nitric oxide synthase (eNOS), resulting in a decrease in nitric oxide (NO) production, which stimulates the production of superoxide radicals that directly or through proinflammatory cytokines activation damage myocardium. NO production is associated with an impact on blood vessel walls, platelet aggregation [25].

Endothelial cells have their own enzyme activity, influence the smooth muscle cells regulating their growth and protecting from vasoconstrictors. Some authors consider that endothelial function violation is one of the central components of cardiovascular diseases pathogenesis [26].

The gene that encodes eNOS is localized to chromosome 7q35–36 and consists of 26 exons. 11 polymorphisms of the eNOS gene have been described, 8 of which have been studied as possible risk factors for cardiovascular disease. To date, the most studied are the G894T and C786T polymorphisms of the eNOS gene [27].

Data on the role of C786T polymorphism in predicting the risk of cardiovascular disease are quite controversial. According to the study of G. K. Pal et al., the NOS gene polymorphisms were found to be associated with the risk of vascular disease [28].

Then, in the work of M. Hasanzad et al., which was devoted to study the eNOS C786T polymorphism, there was no significant association with the risk for coronary artery disease. However, the authors noted the importance of further study on single nucleotide polymorphisms (SNPs) and development of SNP panel that can be used as a genetic marker of risk for cardiovascular disease [29].

A modern scientific research is aimed at the problem of nitric oxide, new data on its role in various cardiovascular diseases continue to attract the interest of the scientific community. The importance of nitric oxide and the necessity of its metabolism correction in AF patients seems to be a major challenge. Further study of this issue will give the opportunity to assess and understand in detail the whole complexity and significance of the nitrogen oxide system function in the body.

Thus, nowadays a paradigm shift in the treatment of patients with cardiac pathology is taking place. Genomics is becoming more common in cardiovascular medicine. In the coming years, we expect that genomic testing implementation and complex genomic and environmental risk analysis will contribute to further improving the individual approaches to AF patients management.

Conclusions

The analysis of the literature allows to conclude that:

– first, genetic polymorphisms may influence both the severity of pathological changes in the body and the efficacy of pharmacotherapy;

– second, the study of RAAS and SAS gene polymorphisms may allow early detection of persons with increased risk of persistent AF recurrence and its prevention.

Prospects for further research. It is increasingly clear that there is a need for detailed study in this area to develop a personalized approach to the selection of drugs that improve the prognosis for patients with persistent AF, aiming to ensure correction of pathogenetic processes based on the genotypic characteristics of a patient. Creating individual complex therapeutic and preventive measures is the foundation of personalized medicine as a relatively new, but successfully developing direction.
Обзоры

Conflicts of interest: authors have no conflict of interest to declare.

Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 21.11.2018
Після доопрацювання / Revised: 10.12.2018
Прийнято до друку / Accepted: 26.12.2018

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400 ISSN 2306-4145 http://zmj.zsmu.edu.ua Запорожский медицинский журнал. Том 21, № 3(114), май – июнь 2019 г.