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Х А Б А Р Ш Ы С Ы

ВЕСТНИК

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН

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NAS RK is pleased to announce that Bulletin of NAS RK scientific journal has been accepted for indexing in the Emerging Sources Citation Index, a new edition of Web of Science. Content in this index is under consideration by Clarivate Analytics to be accepted in the Science Citation Index Expanded, the Social Sciences Citation Index, and the Arts & Humanities Citation Index. The quality and depth of content Web of Science offers to researchers, authors, publishers, and institutions sets it apart from other research databases. The inclusion of Bulletin of NAS RK in the Emerging Sources Citation Index demonstrates our dedication to providing the most relevant and influential multidiscipline content to our community.

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НАН РК сообщает, что научный журнал «Вестник НАН РК» был принят для индексирования в Emerging Sources Citation Index, обновленной версии Web of Science. Содержание в этом индексировании находится в стадии рассмотрения компанией Clarivate Analytics для дальнейшего принятия журнала в the Science Citation Index Expanded, the Social Sciences Citation Index и the Arts & Humanities Citation Index. Web of Science предлагает качество и глубину контента для исследователей, авторов, издателей и учреждений. Включение Вестника НАН РК в Emerging Sources Citation Index демонстрирует нашу приверженность к наиболее актуальному и влиятельному мультидисциплинарному контенту для нашего сообщества.

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POLYMORPHISMS OF SOME GENES, ASSOCIATED WITH HYPERTENSION: A REVIEW OF RELEVANT PUBLICATIONS

Abstract. Purpose of the review: To review relevant publications on the study results of gene polymorphisms in hypertension.

Methodology: A search of relevant publications was conducted in electronic databases including Embase, PubMed/Medline, Science Direct, Ebscohost, Springer Link, The Cochrane Library, Web of Knowledge (Thomson Reuters), and eLibrary. The depth of search for publications was 16 years (2002-2018). More than 30 publications were selected and reviewed as analytical material for this article. The inclusion criteria were meta-analyzes, systematic reviews, full-text articles published earlier in 2002, the results of randomized studies, research reports with evidence base.

Results and conclusion. An analysis of relevant publications indicated that despite the many ongoing studies on the polymorphisms of genes involved in the renin-angiotensin-aldosterone system in hypertension, the results of these studies are contradictory. Sample size, the specific population and other external factors influence study results. Each population has its own characteristics that affect the result of the study. When assessing the association between gene polymorphisms and the risk of hypertension, it is necessary to take into account changes in the genes with the geographical features of the studied population. In addition, an example of such a study would be the Kazakh population.

Keywords: hypertension, gene polymorphisms, single nucleotide polymorphism, renin-angiotensin-aldosterone system.

Introduction. Hypertension is a widespread chronically occurring multifactorial disease that is associated with the interaction between the genetic background and environmental factors [1]. The prevalence of hypertension throughout the world is constantly growing, and medical costs associated with treating its complications are increasing exponentially in all countries. According to the World Health Organization, hypertension is globally one of the risk factors for a number of non-communicable diseases.

One of the proven risk factors for the development of hypertension is a genetic predisposition in which the signs of this disease are transmitted to offspring. Identification of genetic factors to predict the formation and progression of hypertension and its complications is an important task for the Republic of Kazakhstan due to the high prevalence and epidemiological, medico-social and economic significance of hypertension for society and the health system [2, 3].

Genetic factors largely determine the risk of developing hypertension and target organ damage, are constant throughout the life of the individual and can be diagnosed at any time, including well before the onset of the clinical symptoms of the disease. However, most of the identified genetic factors were obtained in studies of people of European descent, whereas there are significant differences in the association of polymorphisms in genes with diseases between representatives of the Asian and European populations.

To date, there are many studies that are devoted to the study of gene polymorphisms in various diseases including hypertension.

The purpose of this article is to review relevant publications on the study results of gene polymorphisms in hypertension.

Materials and methods. A search of relevant publications was conducted in electronic databases including Embase, PubMed/Medline, Science Direct, Ebscohost, Springer Link, The Cocrane Library, Web of Knowledge (Thomson Reuters), and eLibrary. The depth of search for publications was 16 years (2002-2018). The following search terms were used for the search: "hypertension" OR "essential hypertension" OR "high blood pressure", "gene polymorphisms" OR "single nucleotide polymorphisms" OR "polymorphism", "genetic association" OR "genetic variant" OR "genetic association study". More than 30 publications were selected and reviewed as analytical material for this article. The inclusion criteria were meta-analyzes, systematic reviews, full-text articles published earlier in 2002, the results of randomized studies, research reports with evidence base. All selected publications were in English and Russian, and included studies in individuals with hypertension and metabolic syndrome.

Results and discussion. To date, there have been identified a polymorphism of dozens of genes claiming to be hereditary markers of hypertension and other cardiovascular diseases.

In large-scale studies (GWAS), international consortia (Global Blood pressure gen Consortium, CHARGE, International Consortium for Blood Pressure, Asian genetic epidemiological network) evaluated associations between genomic variants and phenotypic traits in different ethnic groups and identified 147 single-nucleotide polymorphisms associated with hypertension and the risks of target organ damage [4-8].

The search for candidate genes in hypertension should be based on existing ideas about the mechanisms of their development. Therefore, special attention was paid to the study of genes involved in the renin-angiotensin-aldosterone system (RAAS), since the RAAS affects the homeostasis of the vascular volume and vascular tone [9, 10]. We analyzed various genes - candidates for hypertension to determine their association with each other.

Angiotensin-converting enzyme (ACE). Among numerous studies, considerable attention was paid to the study of the polymorphisms of the angiotensin-converting enzyme gene, which catalyzes the splitting of inactive angiotensin I to active angiotensin II. There are a number of polymorphisms in the ACE gene. One of them is associated with the insertion (I) or deletion (D) of the Alu element with a size of 287 base pairs in the 16th intron and 3 genotypes are distinguished: I/I homozygotes, D/D deletion homozygotes, I/D heterozygotes [11]. Genotype II carriers have the lowest enzyme level, while in people with DD genotype, it is maximal. Therefore, the presence of allelic variant D leads to an increased content of angiotensin II, a decrease in the level of bradykinin and may be a risk factor for cardiovascular disease.

Currently, there are many studies on insertion-deletion (ID) polymorphism of the ACE gene in patients with hypertension. In the world as we know the ethnic origin affects the gene polymorphism of ACE I/D [12]. Some studies conducted in the African, Australian, Mongolian, and Pakistani populations revealed a link between the polymorphism of the ACE DD gene and the development of hypertension.

Tchelougou D. et al. (2015) investigated the association between the three polymorphisms of the renin-angiotensin system and hypertension in the African population. The study results showed a strong link between the polymorphism of the ACE I/D genes and the development of hypertension. Therefore, they indicate that the DD genotype is a predictor of the risk of hypertension, regardless of other environmental factors [13].

In addition, other studies have demonstrated a link between allele I and hypertension [14]. The limited number of individuals studied and the presence of high levels of inbreeding [15] explained the association between allele I and hypertension in the Pakistani population.

However, some studies conducted in the Belgian, Dutch, Indian and Bangladeshi populations did not reveal any connection between the polymorphisms of the ACE gene and hypertension [16].

Sumeet G. et al. (2009) in their study have seen that the polymorphism of the ACE I/D genes is not a risk factor for the development of hypertension in the study of rural population from India.

The inability to find a link between the polymorphism of the ACE I/D genes and hypertension in this study strongly suggests that the ACE gene does not play a dominant role in the pathophysiology of hypertension in the Indian population and it is not a good predictor of hypertension [17].

Thus, ethnic and geographical differences may affect the ACE I/D polymorphisms, but their association with the development of hypertension remains controversial.

Type I angiotensin II receptor (AGTR1). The gene encoding angiotensin II receptor type I (AGTR1) is located on chromosome 3 (3q24). Activation of the renin-angiotensin-aldosterone system and the subsequent generation of angiotensin II play an important role in normal physiology and in the progression of heart and kidney diseases. According to G. Nickenig and D. Harrison (2002) study, type I angiotensin II receptor is regulated by different mechanisms.

Glucocorticoids, aldosterone, insulin, LDL, estrogen, progesterone, sodium influence the expression of the angiotensin II receptor of type I. Increased serum LDL levels play a fundamental role in the pathogenesis of hypertension. An increased level of LDL enhances angiotensin II type I receptor mRNA and protein expression, thereby increasing angiotensin II sensitivity [18].

Fung M. and a group of researchers (2011) in their work showed that polymorphisms of the AGTR1 gene can contribute to the development of hypertension in patients with highly normal blood pressure indicators [19]. In this study, insulin resistance was observed in patients with highly normal blood pressure, and this was associated with the metabolic syndrome. Moreover, the less studied A/G polymorphism was associated with HDL and apolipoprotein A1.

Palatini P. et al. (2009) investigated the effects of A1166C gene polymorphism for AGTR1 and -1332G/A for AGTR2 on the incidence of stable hypertension and metabolic syndrome in a cohort of young patients who had screening test for stage I hypertension. They showed that SS genotype carriers increased the risk of developing metabolic syndrome, which was due to an increased tendency to gain weight and the presence of hypertension. According to the results of this study, the polymorphism of the AGTR1 gene is a significant predictor of the development of hypertension and metabolic syndrome [20].

Sean O. Henderson et al. (2004) showed that the T allele (-535) of the AGTR1 gene and the T allele (-344) of the CYP11B2 gene may increase the risk of hypertension among African Americans, but not among Hispanics [21].

S. Mehri et al. (2011) studied the association between the genes AGTR1 and ACE with the risk of developing cardiovascular diseases. The study indicated that the A1166C polymorphisms of the AGTR1 gene are genetic risk factors for the development of cardiovascular disease [22].

According to Behravan J. et al. (2006), the frequency of the C allele of the AGTR1 gene was higher in women with hypertension than in women without hypertension, and in men, this frequency was not observed [23]. The authors explain that the A/CC genotype is associated with higher blood pressure numbers than the AA genotype in women. In addition, the results of the study showed that some components of the RAAS in women are regulated by estrogen.

Abdollahi M. and a group of researchers conducted a new approach to quantifying the haplotypes of the AGTR1 gene transcript [24]. The authors studied the association of homozygous and heterozygous haplotypes with the metabolic syndrome and, as a result, the metabolic syndrome was associated with the C allele rs5186 of the AGTR1 gene.

Shatskaya E. et al. (2011) conducted a study to identify the association between the genes - candidates of the RAAS, lipid metabolism, hemostasis factors responsible for the function of the endothelium and hypertension [25]. The results of the study showed that the A1166C polymorphism of the AGTR1 gene was more common in patients with hypertension and was associated with parameters of hemodynamics and metabolic status, determining the risk of developing cardiovascular complications in patients with hypertension.

Aldosterone synthase (CYP11B2). The CYP11B2 gene encodes a second cytochrome P450 polypeptide of family 11, subfamily B (cytochrome P450, subfamily XIB, polypeptide 2; CYP11B2), catalyses the last step in the synthesis of the hormone aldosterone from deoxycorticosterone. Several single nucleotide polymorphisms are known in the CYP11B2 gene. The most fully studied polymorphism, which is manifested in the replacement of cytosine by thymine in the -344th position of the nucleotide sequence, in the regulatory region of the gene. This site is the binding site of steroidogenic transcription factor SF-1, an expression regulator for aldosterone synthase gene. According to research, the allele T leads to increased production of aldosterone, which in turn is associated with hypertension.

Many researchers have studied and analyzed single nucleotide polymorphisms of the gene that affect the function of aldosterone synthase activity. As a result, they created a database on the polymorphisms of this gene [26].

Y.R. Kim et al. (2014) examined the association of the polymorphisms -344C/T, K173R and IC of the CYP11B2 gene with hypertension in Korean patients. The study authors found that the genotype RR polymorphism K173R was associated with the development of hypertension [27].

Chandra et al. (2015) in their study determined the correlation between increased expression of the CYP11B2 gene and hypertension [28]. They consider these results as a factor in the progression of increased blood pressure in patients with hypertension.

E. Androulakis (2012) and other scientists studied the effect of aldosterone synthase gene polymorphism on vascular dysfunction and inflammation in hypertension. As a result, they concluded that the homogeneous T allele of the polymorphism –344C/T of the CYP11B2 gene is a marker of the risk of developing hypertension, but it was not associated with vascular changes in hypertension [29].

Many scientists use large-scale studies of the association of genomic diseases (GWAS) and candidate genes to study the genetic basis of hypertension and among these scientists were K. Miyaki (2012) et al. who studied 12 independent gene variants [30].

Sh. Niu et al. (2016) studied the effect of polymorphisms of RAAS genes on hypertension in the Kazakh population living in northwestern China [31]. As a result, the authors found that a strong synergistic effect between polymorphisms of ACE I/D and CY11B2 T-344C genes and a moderate effect between polymorphisms of ACE I/D and CY11B2 T-344C genes increases the risk of developing hypertension among Kazakhs.

F. Takeuchi et al. (2012) in their large study on the Japanese population evaluated the association of blood pressure with seven candidate genes [32]. The researchers found a link between the rs1799998 polymorphism of the CYP11B2 gene and the rs699 of the AGT gene with hypertension.

However, there have been some studies, the results of which did not reveal the association of CYP11B2 gene polymorphisms with the development of cardiovascular diseases [33-37].

Conclusion. An analysis of relevant publications indicated that despite the many ongoing studies on polymorphisms of genes involved in the RAAS in hypertension, the results of these studies are contradictory. Sample size, the specific population and other external factors influence study results. Each population has its own characteristics that affect the result of the study.

Thus, to assess the association between gene polymorphisms and the risk of hypertension, it is necessary to take into account changes in the genes with the geographical features of the studied population. The Kazakh population study of polymorphisms associated with hypertension could significantly complement global studies and accelerate the acquisition of specific data for the development of personalized approaches in the prevention and treatment of hypertension.

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АРТЕРИЯЛЫҚ ГИПЕРТЕНЗИЯМЕН АССОЦИАЦИЯЛАНҒАН КЕЙБІР ГЕНДЕРДІҢ ПОЛИМОРФИЗМДЕРІ: БЕЙІНДІ ЖАРИЯЛАНЫМДАРҒА ШОЛУ

Аннотация. Мақсаты: Артериялық гипертензия кезінде гендер полиморфизмдерін зерттеу нәтижелері бойынша бейінді жарияланымдарға шолу жасау.

Әдістеме: Embase, PubMed/Medline, Science Direct, Ebscohost, Springer Link, Кокран кітапханасы, Web of Knowledge (Thomson Reuters), eLibrary кіретін электрондық дерекқорларында бейінді жарияланымдарға іздеу жүргізілді. Жарияланымдарды іздеу тереңдігі 16 жыл (2002-2018 жж.) болды. Осы мақаланың талдамалық материалы ретінде 30-дан астам жарияланымдар қарастырылып іріктелді. Жарияланымдарды қосу критерийлері болып 2002 жылдан бастап жарияланған толық мәтінді мақалалар, мета-анализдер, жүйелі шолулар, рандомизацияланған зерттеулердің нәтижелері, дәлелденген негізі бар зерттеу есептері табылды.

Нәтижелер мен қорытындылар: бейінді жарияланымдарды талдау артериялық гипертензиядағы ренин-ангиотензин-альдостерон жүйесінде қатысатын гендердің полиморфизмдеріне қатысты көптеген зерттеу-

лерге қарамастан осы зерттеулердің нәтижелері қарама-қайшылықты көрсетті. Зерттеу нәтижелеріне іріктеу өлшемі, нақты популяция және сыртқы факторлар әсер етеді. Гендердің полиморфизмдері мен артериялық гипертензияның даму қаупінің өзара байланысын бағалау кезінде әртүрлі географиялық ерекшеліктерге әсер ететін халықтың гендеріндегі өзгерістерді ескеру қажет. Осындай зерттеудің мысалы ретінде қазақ популяциясы бола алады.

Түйін сөздер: артериялық гипертензия, гендер полиморфизмдері, бір нуклеотидті полиморфизм, ренин-ангиотензин-альдостерон жүйесі.

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ПОЛИМОРФИЗМЫ НЕКОТОРЫХ ГЕНОВ, АССОЦИИРОВАННЫЕ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ: ОБЗОР ПРОФИЛЬНЫХ ПУБЛИКАЦИЙ

Аннотация. Цель: провести обзор профильных публикаций по результатам изучения полиморфизмов генов при артериальной гипертензии.

Методология: проведен поиск профильных публикаций в электронных базах данных, вошедших в Embase, PubMed/Medline, Science Direct, Ebscohost, Springer Link, The Cochrane Library, Web of Knowledge (Thomson Reuters), eLibrary. Глубина поиска публикаций составляла 16 лет (2002-2018 гг.). Были рассмотрены и отобраны более 30 публикаций в качестве аналитического материала для данной статьи. Критериями включения являлись мета-анализы, систематические обзоры, полнотекстовые статьи, опубликованные не ранее 2002 года, результаты рандомизированных исследований, отчеты исследований, имеющие доказательную базу.

Результаты и заключение. Анализ профильных публикаций показал, что несмотря на множество проводимых исследований по полиморфизмам генов, участвующих в ренин-ангиотензин-альдостероновой системе при артериальной гипертензии, результаты этих исследований очень противоречивы. На результаты исследования влияет размер выборки, конкретная популяция и внешние факторы. При оценке взаимосвязи полиморфизмов генов и риска развития артериальной гипертензии необходимо учитывать изменения в генах популяции, испытывающей влияние различающихся географических особенностей. И примером такого исследования могла бы стать казахстанская популяция.

Ключевые слова: артериальная гипертензия, полиморфизмы генов, однонуклеотидный полиморфизм, ренин-ангиотензин-альдостероновая система.

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