

UDC 616.12-008.331-056.257:575.174.015.3:577.112.386:546.172.6

Polymorphism of the renin-angiotensin system genes and endothelial no-synthase gene in obese patients with arterial hypertension

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The review is dedicated to relationships between the blood pressure and body mass. Endothelial dysfunction and imbalance of neurohumoral systems, namely, the pathological increase in the activity of the renin-angiotensin system, in combination with obesity are the main mechanisms of the of the hypertonic disease pathogenesis. Here we discuss the research on polymorphism of the renin angiotensinic system genes and the endothelial synthase nitric oxide gene. The difficulty lies in the correct assessment of associations of alleles which have clinical significance. It is essential to determine precisely the associations of gene polymorphisms in the hypertonic disease with obesity. This provides an opportunity to identify new personified approaches to the treatment of patients with this complex pathology.

Keywords: endothelial nitric oxide synthase, renin-angiotensin system, gene polymorphism, hypertonic disease, obesity.

Introduction

Genetic polymorphism is the presence of alleles, different variants of one gene, in a population. Herewith the allele can be considered as polymorphism, if the frequency of its occurrence in the population is not less than 1 %. Human genome polymorphisms are decisive for the development, progression and therapeutic intervention for various pathological conditions. Polymorphisms in different genes contribute to functional changes in the protein activity or expression. Therefore, it is important to clarify not only the effect of individual

polymorphisms on the function of genes, but also the relationship between polymorphisms in different genes, especially those that are functionally related [1]. The structure and activity of the protein products of the gene may depend on the variant of the allele.

It is generally believed that the environmental and genetic factors influence the formation of arterial hypertension (AH) phenotype and determine its progression. At present, a significant role in the pathogenesis of polygenic diseases, in particular, arterial hypertension (AH), is given to genetic polymorphisms. A number of studies have revealed the connec-

tion between numerous polymorphic markers of genes, coding the components of the renin-angiotensin-aldosterone system (RAAS), the sympathoadrenal system (SAS), endothelial and other factors with the AH development.

All over the world, hypertension (HD) occupies a leading place in the structure of cardiac pathology and, due to its spreading among people of working age and early development of complications that lead to prolonged disability and invalidization is an urgent medical and social problem. Arterial hypertension (AH) as a starting and modelling mechanism induces the development of pathological changes in the cardiovascular system and internal organs [1]. At present, AH goes beyond medical problems taking a multidisciplinary and socially significant character.

The risk of complications and death in the AH patients increases according to numerous concomitant risk factors. AH in isolated form occurs only in 8 % of cases, whereas in others it is combined with one or more factors of cardiovascular risk. In 20–22 % of cases AH is combined with hyperlipidemia, in 30 % with hyperlipidemia and obesity, whereas 32 % of patients suffered from dyslipidemia, obesity and various disorders of carbohydrate metabolism — glucose intolerance, insulin resistance, 2nd type diabetes mellitus (DM type 2) [2].

There are many researches on the genetic mechanisms of susceptibility to cardiovascular disease (CVD). Recently, it has been proved that genetic predisposition contributes to the inheritance of AH. The genetic factors can play a significant role in the development of AH confirming its polygenic nature. Therefore, the search for the genetic markers of the renin-

angiotensin system (RAS) responsible for the development of AH and related disorders, namely obesity, and carbohydrate metabolism is an urgent problem of great interest to many scientists. The genetic polymorphism [3] is proved to be a significant factor affecting a level of expression of endothelial nitric oxide synthase (eNOS). The level and activity of NO depend on the allelic variant of the NO synthesis genes. In this regard, the study on the genes involved in the synthesis of NO (primarily eNOS) has become an important step in identifying the genetic risk factors for CVD. Their study is complex because of the large number of genes that can participate in the formation of hereditary predisposition either independently or through interaction with each other. Recently, a huge amount of information has been accumulated regarding polymorphic regions of the human genome as a whole, as well as their correlation with various diseases.

Modern strategy for researching a genetic predisposition is based on the study of the polymorphic markers of candidate genes. These are genes, the expression products of which are involved in the pathogenesis of this disease. Importantly, the genetic predisposition to such multifactorial pathologies, as AH and obesity is also polygenic, which requires an assessment of the integrated genetic panel. To clarify the nature of the link between the gene and metabolic state of the organism, single nucleotide polymorphisms (SNPs) are investigated. SNPs are defined as loci with alleles that differ at a single base, with a frequency of at least 1 % in a random set of individuals in the population [4].

Nowadays, the polymorphism of dozens of genes has been found that claims the role of

hereditary markers of atherosclerosis, AH, coronary heart disease (CHD), myocardial infarction, chronic heart failure (CHF), and microvascular complications in type 2 diabetes, namely, diabetic retinopathy and nephropathy [5,6]. However, their clinical and prognostic values are not completely comprehensible; besides, the literature data are obviously contradictory.

The pathogenesis of hypertensive disease (HD) in obese persons is a multicomponent process, including an increase of circulating blood volume, vasoconstriction, and hyperactivity of sympathoadrenal, renin-angiotensin systems, and metabolic disorders. One of the early phases of the pathogenesis of this complex pathology is the development of endothelial dysfunction (ED).

Due to the fact that the leading mechanisms for the development of cardiovascular disease are ED and the imbalance of the neurohumoral systems of the body, in particular the pathological increase in the activity of the renin-angiotensin system (RAS), it is the search and study of the polymorphisms of the genes of these systems is the most relevant today.

The genome-wide association studies (GWASs) have identified thousands of genes and genetic variants (mainly SNPs) that contribute to the complex diseases in humans. At the heart of the GWAS-based approaches lies the “common variant–common disease” hypothesis. The arrival of Next-Generation Sequencing (NGS) technologies facilitated a shift in focus from common to rare variants and provided the opportunity to unravel the genomic architecture underlying a hypertension risk.

Neurohumoral system in regulation of vascular tone and endothelial-dependent vasodilation in patients with hypertensive disease with obesity

The main components of the renin-angiotensin system (RAS) are angiotensinogen (AGT), angiotensin converting enzyme (ACE) and angiotensin II (AT II) in patients with AH.

For many decades considerable attention has been paid to determining the role of RAS in the development of cardiovascular disorders, namely in the pathogenesis of AH. RAS plays a special role in vasoconstriction and vasodilation, regulating long-term blood pressure. Juxtaglomerular kidney cells secrete the enzyme renin. Renin proteolyzes the inactive peptide of angiotensinogen, converting it into angiotensin I (AT I). AT I is then transformed into AT II using ACE.

AT II is one of the strongest vasoconstrictors. In kidneys, AT II leads to the contraction of glomerular arterioles, thus changing the glomerular filtration rate. In the adrenal cortex, AT II causes the release of aldosterone, which in turn affects the renal tubules, which leads to reabsorption of the majority of sodium and water ions from the urine due to displacement of potassium ions in the renal tubules. Aldosterone also affects the central nervous system, increasing the appetite of humans to salt and causing a feeling of thirst. Besides, AT II is able to increase the inflammatory potential, to provoke oxidative stress and endothelium dysfunction, to activate atherogenesis [7].

Two types of receptors are involved in the implementation of AT II influence on the heart and blood vessels. The receptors of AT II type 1 (AT1 receptors) mediated the main physi-

ological and pathophysiological effects of AT II whereas the role of type 2 receptors (AT₂ receptors) remains controversial. Under normal conditions, they are present in a small amount in the vascular endothelium, but their expression significantly increases in various pathological conditions associated with inflammation and remodelling of the heart and vessels: AH, atherosclerosis, DM type 2, myocardial infarction [8].

It was determined that AT II participates in the regulation of growth and development of adipose tissue [9]. Today it is known that the formation of AT II is not limited to the system circulation, it can be synthesized in a variety of tissues. In recent years much attention has been paid to adipose tissue, which is no longer considered only as an energy depot.

The increased levels of adipocyte-secreted angiotensin are an important link between visceral obesity and ED, as evidenced by the correlation between the “waist circumference / hip circumference” and the level of RNA angiotensinogen (AGT) of visceral and subcutaneous adipose tissue. Further enhancement of the AT II production at the tissue level stimulates the secretion of superoxide — a leading factor in the etiology of ED. Thus, the activation of vascular RAS in subjects with abdominal obesity should be considered as a leading mechanism of ED [10].

At present, the leading role of endothelium and nitric oxide (NO) in the genesis of cardiovascular complications of HD has been proven. Endothelium is rightly called the largest endocrine gland of the body.

In physiological conditions, there is predominance of secretion of substances that cause relaxation, one of which, nitric oxide

(NO) controls the basal tone of arterial vessels and, as a consequence, the blood pressure level. NO is a universal regulator of physiological functions, in particular a powerful vasodilator. For HD, the main factor in the development of ED is the reduction of NO synthesis with preserved or increased secretion of vasoconstrictors (endothelin-1, angiotensin II), which aggravate endothelium-dependent relaxation, lead to the degradation and changes in the cytoarchitectonics of blood vessels. The main target of NO is soluble guanylate cyclase, the heme of which is a receptor for NO. The heme-linked NO induces soluble guanylate cyclase, which leads to the enhanced synthesis of cyclic guanosine monophosphate (cGMP). Nitric oxide is formed in endothelial cells from L-arginine under the action of enzymes of the NO-synthase system — constitutional neuronal (NO-synthase type 1, NOS 1 or nNOS), “inducible” (NO-synthase type 2, NOS 2 or iNOS) and constitutional endothelial (NO-synthase type 3, NOS 3 or eNOS). In the active form all three isoforms are homodimers having a molecular weight of 130 (iNOS), 135 (eNOS) and 160 (nNOS) kDa [11]. The formation of NO is regulated by altering the expression or activity of the eNOS enzyme itself, as a result, of changes in the activity of either cofactors, or endogenous inhibitors.

A number of studies have shown that a deficiency of NO in the blood leads to a number of CVDs. The risk of AH significantly increases with the excess body weight and obesity. Body mass closely correlated with BP. In some studies at the population level, it has been shown that overweight is an independent risk factor for hypertension. In recent years,

the term “obesity-induced hypertension” has appeared [12].

In connection with the study of mechanisms that regulate energy metabolism and provide neurohumoral homeostasis, new concepts have been rebuilt for the presence of pathogenetic links between excess body weight and increased levels of blood pressure (BP). The effect of excess body weight on the level of BP depends on the genetic and neurobiological mechanisms that underlie the development of obesity.

Obesity contributes to the development of AH, and AH can cause a decrease in the sensitivity of peripheral tissues to insulin and further obesity [13]. The probability of development of AH in persons with excess body weight is 50 % higher than in those with normal body mass (Framingham Study) [14]. About 75 % of cases of AH are associated with obesity, but the mechanism by which it promotes the development of AH is not yet fully studied. A rise in body weight by 5 % increases the risk of AH by 30 % over four years. The frequency of AH increases to 55 % in those who had BMI greater than 30 kg/m² regardless of gender and age [15]. In a number of observations, attention was drawn to the fact that along with the degree of obesity a significant factor in the cardiovascular disease is a mode of the distribution of adipose tissue. It is abdominal obesity [16], which is mainly located in the upper half of the body more often than the accumulation of fat in the lower half of the body (hyoid or peripheral), is combined with cardiovascular disease and mortality, accompanied more often by a violation of glucose tolerance, diabetes mellitus and dyslipidemia.

Polymorphism of the renin-angiotensin system genes and cardiometabolic risk

One of the key components of RAS is angiotensin converting enzyme (ACE). Normally, in different people, the ACE levels in blood plasma can vary up to 5 times. In a particular person, the ACE level is fairly stable. Such fluctuations in the level of ACE among people are caused by the polymorphism of the *ACE* gene. The *ACE* gene is charted in chromosome 17q23. In the 16th intron of the *ACE* gene, an insertion-deletion (*I/D*) polymorphism (rs1799752) was found, which is one of four SNPs representing perhaps the best studied *ACE* SNP. It is actually not a single nucleotide polymorphism at all; instead, it is an insertion/deletion of an Alu repetitive element of 287 pairs of nucleotides in intron of the *ACE* gene. Alleles containing the insertion are called “*I*” alleles, and “*D*” alleles lack the repetitive element. The Alu-repeat deletion results in an increase in the expression of the *ACE* gene. In this case, there was a correlation between *D* alleles and the level of ACE in blood, lymph and tissues. The level of ACE in serum in healthy people who are homozygous for *D* allele (*DD* genotype was observed in approximately 36 % of people) was almost twice as high as in homozygous for *I* allele (*II* - genotype, about 17 % of people) and had an average value in heterozygous — *ID* genotype (47 %). The gene polymorphism is also associated with ACE level in the human heart.

Thus, 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 the development of cardiovascular disease [16].

To date, a number of data on the association of the *ACE* gene polymorphism with myocardial infarction, sudden death, hypertension, left ventricular hypertrophy (LVH), hypertrophic cardiomyopathy, endothelial dysfunction, kidney disease and microvascular complications of diabetes mellitus have been accumulated [16, 17]. In particular, it was found that the presence of allele *D* in the genotype of patients was associated with higher levels of BP (both systolic and diastolic), predisposition to the crisis course of hypertension and a significantly higher severity of left ventricle myocardial hypertrophy. The presence of genotype II in patients with hypertension, on the contrary, was associated with its asymptomatic course and a significantly later age of manifestation [18]. Additionally, it has been shown that the genotype *DD* is more common in the patients with CHD, diabetes mellitus and other risk factors (hyperlipidemia, smoking, family history of CVD) [16,17,19]. The *DD* variant of the genotype was associated with any myocardial infarction, as well as a stroke and the development of AH [20].

The data of another study show that in the survey of a fairly large population (3145 people) in the framework of Framingham study, it was found that the presence of the *D*-allele of the *ACE* gene in men is associated with a higher level of BP, especially the marked association of *D*-allele was observed with the level of DBP. For women, such patterns were not found [21].

On the other hand, there is also evidence of the absence of association of the *ACE* polymorphism with hypertension. Later, the same author established that the connection is absent in the groups with a milder degree of hyperten-

sion, and in the persons with a malignant form of the *DD* genotype it occurs 3 times more often. The results of the initial studies were subsequently called into question in more extensive studies and through using randomized and well-organized groups. As a rule, many researchers do not take into account the population and ethnic features of clinical material. In multifactorial diseases, the genetic system of polygenes is represented by a huge polymorphism of alleles of genes, the effects of which may be separately not so significant or manifested in certain circumstances. And because of ethnic diversity and high migration of people with different forms of hypertension it is impossible to bring the results to a common denominator. Therefore, the choice of methods for detecting the connection between polymorphisms with AH, the features of the studied groups, as well as the effect of hidden causes that determine the levels of BP and diagnosis of AH may be decisive in the findings of the study.

The results showing the contingency of the allele *D* with the presence of abdominal obesity were obtained. The relationship between abdominal obesity and the diagnosis of AH was of linear symmetric and mean strength. Thus, one can judge common genetic component in the implementation of hypertensive disease and abdominal obesity [22].

Interesting data on the association of polymorphism of the *ACE* gene with endothelial dysfunction, as well as the processes of vascular wall remodeling and atherogenesis are available. An increase in the activity of the local endothelial ACE is associated with a disturbed endothelium-dependent vasodilatation on acetylcholine in the hereditary AH of

rats. This suggests that local hyperactivity of RAS can lead to the endothelial dysfunction.

On this basis, the attempts were made to link the endothelium dysfunction with the genotype of *ACE*. F.Perticone studied vasodilation of the brachial artery in the patients with HD and healthy individuals in response to infusion of acetylcholine (endothelial-dependent vasodilation) and sodium nitropruside (endothelial-independent stimulus). At the same time, in the group of people with AH endothelial-dependent vasodilation was significantly less in the patients with *DD* genotype compared with the patients with *II + ID* genotype. In this case, endothelial-independent vasodilation in these groups of patients did not differ significantly. Thus, the patients with *DD* genotype showed a greater degree of endothelial dysfunction, although they did not differ from the patients with *II* and *ID* genotypes in the level of BP, age, parameters of daily BP monitoring. In the group of healthy control such regularities were not revealed.

Among numerous candidate-genes, the type 1 receptor gene to angiotensin II (*AGTR1*) also attracts attention because it mediates not only the vasoconstrictive action of angiotensin II, but also the expression of growth factors, the proliferation of smooth muscles, the release of tissue activator inhibitor Plasminogen and a number of other important effects [23].

Thus, the changes in expression or structure of the angiotensin II receptor of type 1 due to the polymorphism of its gene may lead to the changes in the regulation of vascular tone or proliferation of the elements of the vascular wall, so the gene of the angiotensin II receptor type 1 is considered as one of the candidate-

genes, associated with the pathology of the cardiovascular system.

The gene encoding the 1st type angiotensin II receptor (*AGTR1*) is located on chromosome 3 (3q24). The most actively studied is polymorphism *A1166C* (rs5186, a SNP known as *+1166A/C* or *A1166C*, is located in the 3' untranslated region of the angiotensin II receptor type 1 gene *AGTR1*), which leads to the replacement of adenine (A) with cytosine (C) in the 1166 position of the *AGTR1* gene. B. Bonardeaux *et al.* have proved that the mutation precisely in the 1166th position of the nucleotide sequence of the *AGTR1* gene affects the functional activity of the receptor type 1 of angiotensin II. Polymorphism of *A1166C* in *AGTR1* was associated with CHD, as well as with myocardial infarction and the development of AH [24].

There are interesting results of the study on the pulse wave velocity propagation and evaluation of the stiffness of large arteries in people with AH and healthy people, depending on the genotype. The increased stiffness of the aorta with high probability was associated with the *1166CC* genotype in people with AH.

Such a connection was not observed in people with normal pressure. The multiple regression analysis showed that the genotype of the angiotensin II receptor type 1 is the second after SBP level most important determinant of aortic stiffness [25].

Equally important component of RAS is the protein — angiotensinogen (*AGT*).

The *AGT* gene is localized in the first chromosome (locus 1 q42-43). In 1992, H. Jeunemaitre *et al.* for the first time confirmed the correlation between the *AGT* gene polymorphism and AH among Europeans and

Americans. 15 variants of the *AGT* gene were identified, but the association with the plasma levels of AGT and hypertension was detected only for both point mutations with the replacement of threonine with methionine and methionine with threonine in 174 and 235 gene codons — *T174M* (rs 4762, which is commonly referred to in the literature as “T174M” or “Thr174Met”); however, databases now indicate that the amino acid that varies is #207 (not 174, as the protein is currently numbered) and *M235T* (rs699, that is a SNP in the angiotensin *AGT* gene that encodes a functional change ??). In most published works, the name for this SNP is *M235T*, or perhaps *Met235Thr*, however its amino acid 268 (not 235) that varies based on the numbering in today's databases. rs699 is also occasionally known as C4072T. In any case, the rs699(C) allele encodes the threonine variant, which is associated with higher plasma angiotensin levels, and ultimately higher blood pressure leading to an increased risk for the hypertension associated disorders [17]), respectively, associated with the AGT activity levels of blood plasma, with the content of AT II and, consequently, with the risk of CVD. According to the literature, the presence of a *174M* allele of the *AGT* gene is much more common in the patients with CHD, with myocardial infarction and LV hypertrophy [26]. In study on the *M235T* polymorphism, it was found that variant *235T* is an independent factor in the risk of developing a heart attack, a risk factor for CHD. At the same time, it was found that the presence of one or two *T*-alleles led to a substantial increase in the level of AGT in plasma, resulting in a higher content of angiotensin II. It is a reason by which many authors explain

the association of this polymorphism with AH. Sethi A. *et al.* conducted a meta-analysis, the purpose of which was to study the association of the *AGT* gene *M235T* polymorphism with the concentration of angiotensinogen in blood plasma, the level of systolic blood pressure (SBP) and diastolic blood pressure (DBP), AH and the risk of developing myocardial infarction and CHD. The study included three major ethnic groups: representatives of the Caucasian, Mongoloid and Negroid races. In representatives of Caucasian races an increase in the concentration of AGT in plasma by 5 % in *MT* heterozygotes and by 11 % in homozygotes in the *235T* allele was noted compared with the carriers of *MM* genotype. The *M235T* polymorphism of the *AGT* gene is associated with the risk of developing AH in Caucasians and indigenous people in Asia. However, in all three ethnic groups, this polymorphism was not associated with the risk of developing myocardial infarction and CHD [27].

Additionally, according to other studies, there is a correlation between the *TT* genotype of the *M235T* polymorphism of the *AGT* gene with a higher probability of development of AH, higher levels of BP and of concentration of ACE [28]. In another study of the *M235T* polymorphism it was demonstrated that the presence of one or two *T*-alleles is accompanied by a significant increase in the level of AT II, which in turn, is able to trigger a cascade of inflammatory reactions, leading to various disorders.

There is also an evidence of a correlation between the frequency of *T/M* allele of the *M235T* polymorphism of the *AGT* gene in hypertensive patients, which is 0.73/0.27. That is, the frequency of *T*-allele is almost twice higher in the patients suffering from AH [29].

The *M235T* polymorphism of the *AGT* gene can promote the activation of immune inflammation in the patients with AH. Thus, it was demonstrated that AH occurs and deepens in the individuals who are carriers of the gene of the *T*-allele of the *M235T* polymorphism of the *AGT* gene when the cytokine-interleukine-1 (IL-1) and TNF- α concentrations are elevated. A high level, in particular IL-1, can promote inflammation, higher expression of AGT, and vasoconstriction of vessels in the patients with AH. That is, the *M235T* polymorphism of the *AGT* gene is a significant risk factor and a hereditary marker of the AH development [30].

Characteristics of endothelial nitric oxide synthase gene polymorphisms of G894T, T-786C and 4th intron

At present, a significant amount of data on the association of polymorphisms of the *eNOS* gene with various diseases, including CVD, has been accumulated.

NO of endothelial origin is an important atheroprotector mediator, and the disorder of the regulation of its synthesis is associated with an increased risk of CVD. Hypertension develops in the NOS mouse line, and atherosclerosis develops in the line combining the absence of a functioning apolipoprotein E gene and the *NOS* gene (*NOS3* is also known as *eNOS*) in the genome. Therefore, the processes of regulation of the synthesis of NO and the gene encoding the NOS, are the first candidates in the study of endothelial dysfunction of blood vessels and a number of CVD [31]. Among the genes encoding NOS, the most likely candidate for the development of CVD is precisely the *NOS3* gene.

The eNOS enzyme and *NOS3* gene were described in 1992–1993. The gene encoding the *eNOS* is located on the chromosome 7q35-36 and consists of 26 exons [32]. The *eNOS* gene promoter contains several domains, i.e. it can be controlled by a number of transcription factors [33]. To date, the polymorphism of the *eNOS* gene in 11 locations has been described, 8 of which were studied as possible risk factors for CVD [34]. The most studied are the *4a/b* polymorphism of 4th intron (27-bp-VNTR), the *G894T* (*Glu298Asp*) (rs1799983) polymorphism of the 7th exon and the *T-786C* (rs2070744) polymorphism of the *eNOS* gene promoter [35,36]. Fig.1.

The DNA region of the *NOS3* gene, in which guanine (*G*) is replaced by thymine (*T*) in position 894, is called the genetic marker *G894T*. As a result of such a substitution, the properties of the protein are transformed, because in its amino acid sequence the glutamic amino acid at position 298 is replaced by asparaginic acid (*Glu298Asp*). The possible genotypes are *G/G*; *T/T*; *G/T*. A number of studies have shown that the people with genotype *T/T* have a higher risk of coronary heart disease (CHD), myocardial infarction and ischemic stroke. This is especially true in modern life, when the cardiovascular system of a person is constantly subjected to various stresses. On the background of the genetic predisposition to CVD (the presence of allele *T* on *SNP G894T* of the *NOS3* gene in the genotype) a probability of the pathology development increases. The *T*-allele carriers (*T/T* and *G/T* genotypes) are more common in pregnant women who suffer from hypertension and placental abruption, compared to the group of women without these complications of preg-

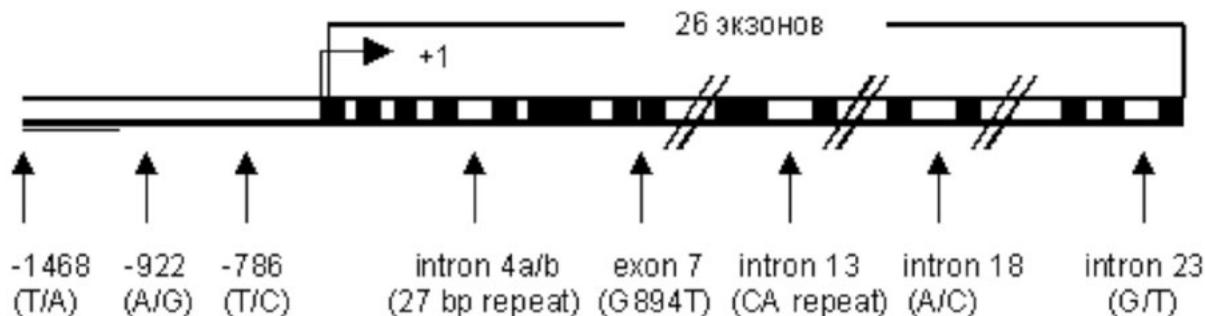


Fig. 1. Polymorphism of the endothelial *NO* gene of synthase (*eNOS*)

nancy. Thus, the presence of *T*-allele is a potential independent factor that increases the risk of developing hypertension in pregnancy [37].

The literature presents contradictory information on the relationship between the alleles of the polymorphism *G894T* and the content of NO in the blood. So, according to Dias R.G. *et al* [38], the *TT* genotype of *G894T* polymorphism causes an increase in the proteolytic activity in endothelial cells, leading to a decrease in the levels of functional eNOS and nitric oxide, and Sakar M. N. *et al.* [39] showed that the individuals with the *TT* genotype have statistically significantly lower NO level compared to the subjects with *GG* or *GT* genotypes ($p < 0.05$). At the same time, Mackawy A.M. *et al* [40] found that the allele *T* of *G894T* polymorphism is associated with elevated levels of nitrates in plasma: the content of plasma nitrates in the individuals with genotypes *GG*, *GT* and *TT* was 9.92 ± 1.65 ; 12.11 ± 1.04 ; 14.55 ± 2.18 mmol/ml, respectively. In this regard, additional studies with a large number of subjects are needed to clarify this issue.

It is proved that the modification of the *eNOS* gene polymorphism is associated with

the oxidative stress [41]. The role of gene polymorphism, in particular *NOS3* (*Glu298Asp*), and end-product of glycosylation in the differential response of cells to hyperglycemia has been studied. It is shown that the presence of this genotype contributes to the development of endothelial-dependent vascular complications [42]. Several authors found that the *G894T* polymorphism of the *NOS3* gene is a risk factor for coronary atherosclerosis and HD. At the same time, there may be a connection between the allele *G* of *Glu298Asp* polymorphism and the age of individuals with AH [43]. It has been shown that the polymorphism of *eNOS* — *Glu298Asp* (rs1799983) is associated with the BP levels in adolescents [44]. Besides, numerous studies have found that the endothelium dependent vasodilatation in the presence of the *298Asp* (*894T*) allele is damaged, and this type of polymorphism is connected with CHD and hypertension.

Thus, it has been established that *G894T* polymorphism is associated with an increased carotid intimal medial thickness in the right carotid artery [45]. The association of the *TT* genotype with angina pectoris (odds ratio (OR) = 10.2; 95 % confidence interval

(CI) = 1.51–68.8; $P = 0.025$) was found; in turn, the highest frequency of genotype *GT* occurrence was revealed in the individuals, who had relatives with coronary artery disease [46].

An analysis of literary sources on the databases of Medline, Embase and Wangfang by January 1, 2013 with the participation of 8547 patients and 9117 persons in the control group, showed that the genotype *TT* of *G894T* polymorphism is highly associated with the risk of developing ischemic stroke compared with the genotype of the allele *G* (OR = 1.25, 95 % CI = 1.09 -1.42, $P < 0.001$), which is more relevant for the Asian race than for the Caucasian race [47]. A meta-regression analysis devoted to the establishment of associations between HD and the polymorphic variant of *G894T* in the Han ethnic group (China) showed a positive relationship (OR = 1.32, $P < 0.001$), whereas geographic differences were identified in the relationship between *G894T* and predisposition to this disease. Thus, among the residents of the southern regions of China the indicated polymorphism may be related to HD (OR = 1.59, $P < 0.001$), whereas in the northern regions such association is not observed (OR = 1.16, $P = 0.12$) [48].

In the individuals suffering from excessive body weight, the T allele of the *G894T* polymorphism of the *NOS3* gene increases the risk of hypertension development [49]. There was established an increased risk of developing obesity in the presence of the *TT* *G894T* genotype (OR = 2.62, $P = 0.04$), whereas the gender analysis shows that in men with overweight this genotype is found much more often compared to the control group (9.9 % versus 2.9 %, $P = 0.01$) [50].

Moreover, the authors investigated the relationship between the main effector of the renin-angiotensin system AT II and allelic polymorphism *G894T* of the *eNOS* gene. It has been established that this type of polymorphism determines the systemic and renal hemodynamic response to AT II. This effect is more pronounced in men than in women [51]. In this regard it is of scientific and practical interest to study the combined effect of the common polymorphism on the insertion/deletion of the *ACE* gene and the allele *894T* of the *eNOS* gene on the development of endothelial dysfunction, hypertension, atherosclerosis, and nephropathis.

One of the most studied variants of the *eNOS* polymorphism is tandem repeats in the intron 4 (*4a/b*) (rs869109213. In intron 4 of this gene minisatellite *eNOS 4a/4b* is located, which has two alleles, consisting of 4 or 5 tandem repeats in size of 27 pairs of nucleotides. The normal version contains 5 repeats (denoted as 4b), the mutant variant contains 4 repeats (denoted as 4a).

The variants of polymorphism: 4b/4b — normal variant of polymorphism in a homozygous form; 4b/4a — heterozygous form of polymorphism; 4a/4a — mutant variant of polymorphism associated with the increased risk of disease in a homozygous form.

The effect of variant 4a is associated with a disorder of the expression of the *NOS3* gene, which leads to a decrease in the NO production. For this variant, the associations with atherosclerosis, CHD and myocardial infarction are described. In the patients with type 2 diabetes, the presence of option 4a is a risk factor for hypertension. In 2004 S.Fatini *et al.* showed a connection between the genotype 4a

/ 4a and the onset of acute coronary syndrome, in particular with an acute myocardial infarction [52]. Additionally, in 2012, Chinese scientists in the meta-analysis of American patients have linked the 4a/4a genotype with an increased risk of ischemic stroke [53].

Most authors have shown that the presence of allele C in position 786 of the promoter of the *eNOS* gene results in a decrease in its activity by 52 ± 11 %, and the resulting lack of *eNOS* is responsible for a decrease in the synthesis and release of nitric oxide and endothelial dysfunction [54]. In the people with pathological genotype of the promoter of the *eNOS* gene (*CC* and *TC*) it was observed an increase in the tone of coronary arteries, increased propensity to coronar spasm and perverted coronary artery reaction to the introduction of acetylcholine, which can serve as the basis for the development of coronary heart disease (CHD) and HD [55]. It was shown that the polymorphism of $-786T > C$ promoter is associated with an increased risk of restenosis after the stenting of coronary arteries [56].

When screening the population to determine the prevalence of $-786T > C$ (rs2070744) polymorphism in the 5'- untranslated region of the gene *eNOS* and its association with pathology, it was found that homozygotes $-786C$ are more common among the patients with atherosclerosis of the coronary arteries than in the control group (24.6 % versus 14.5 %). The risk of the pathology development was higher in the homozygote *CC* compared with the homozygotes *TT* [57].

The association of polymorphism $-786T > C$ with the type of vascular reaction to the load was also found among juvenile Caucasian race. In boys (168 persons) with a hypertensive

response to the load the genotype of *CC* was found 3.5 times more often. Such *CC* homozygotes are characterized by a higher peripheral vascular tone and an imbalance of production of major vasoactive endothelial factors, which is manifested in elevated endothelin-1. It is typical that hypertonic vascular responses to load are noted in the individuals with a failure of regulatory mechanisms of supporting the vascular tone, as well as in those with HD and pre-hypertension [58].

Noteworthy, this study focused on the persons with for the moment compensated state of vascular factors, the imbalance of which is revealed only with certain tests. Distinguishing such a group with a hidden pathology of CVD and defining the *NOS3* gene polymorphism in it would help to study the implementation of a particular allele in the phenotype.

Meta-analysis of Casas *et al.* showed that the mutation $-786T > C$ in the promoter region of the *eNOS* gene affects the level of gene expression. A low level of the mRNA of the *eNOS* gene as well as a low serum nitrate/nitrite level are noted in the individuals with the variant $-786C$ [59].

In Canada, 705 middle-aged men without CHD in their history were involved in the study of M.E. Hyndman *et al.* [60]. The ratio of different variants of the genotype (*TT*, *TC*, and *CC*) of the promoter of the *eNOS* gene was close to that of the Caucasians and was distributed respectively 38.9; 46.1 and 15.0 %. The persons with *CC* genotype had markedly higher levels of SBP and were more often diagnosed with AH which allowed the authors to conclude that the *CC* genotype of *eNOS* gene promoter is a risk factor in the development of AH.

In 2013, the data on the association of eNOS gene polymorphisms 4b/4a, T-786C and G894T with metabolic syndrome (MS) have been published. The study included 339 patients with MS and 783 patients without MS who were treated at the Central Taiwanese Hospital. The variant TC+CC on T-786C SNP of the *eNOS* gene was significantly associated with a decrease in the risk of MS (OR = 0.63). Intron 4b/4a genotype of intron 4 27bp repeat polymorphism of the *eNOS* gene is also associated with a decrease in the risk of MS (OR = 0.68). Additionally, the authors have shown that the presence of the *G894T* genotype in obese subjects plays a significant role in comparison with the control group (OR = 1.65) [61]. J. Bressler, J.S. Pankow, J. Coresh, E. Boerwinkle analyzed the polymorphism of the *eNOS* gene (G894T) and obesity as a risk determinant for AH, DM type 2 in 14,374 participants from the United States in the framework of a joint study in 2013. Among the participants there were 728 patients with DM type 2 (African-Americans) and 980 — of Caucasian race. The study shows that the relationship between the indicated parameters is noted only in the individuals of the Caucasian race [62].

Additionally it was noted that for the Italian population two types of the *eNOS* gene polymorphisms are associated with significant angiographical changes. The scientists suggest that the combination of two types of polymorphisms T786C and Glu298Asp in one genome is associated with a high risk of developing CHD and HD compared to one type [63]. Thus, this study demonstrates the importance of identifying not a single polymorphism, but their combination to distinguish the risk groups in CHD and HD.

A four-SNP haplotype, comprising an uncommon variant rs11699009 in the *BPIFB4* gene, has been associated with notable longevity. In the study of Vecchione *et al.* [64], 416 individuals were genotyped to determine their haplotypes. The authors demonstrated that the overexpression of the BPIFB4 uncommon variant in mice impaired eNOS signaling and increased BP, opening the way for the development of new therapeutic strategies. The present study demonstrates that the expression of a rare variant of BPIFB4 — a protein we have previously associated with improved aging when present in its longevity-associated isoform — leads to the maintenance of high blood pressure in the face of treatment of hypertension.

Noteworthy, a number of studies did not reveal the relationship between the polymorphism of the *NOS3* gene and the development of CVD, which may be due to the small sample size in these studies or ethnicity *etc.*

Data from Next-Generation Sequencing technology at hypertension with obesity

The cause of a complex trait, like essential hypertension, remains elusive if examined in the light of the GWAS results. Data from NGS technology offer the possibility to capture a greater range of the single nucleotide variability compared to GWAS.

Genetic variants associated with hypertension, obesity and diabetes based on PolyPhen2 and SIFT algorithmic predictors of mutation pathogenicity were analyzed on the complete exome of 60 people of Kazakh nationality using the technology of Next-Generation Sequencing (NGS) HiSeq2000.

Seven genetic variants were detected in GHRL (rs4684677), MTHFR (rs1801133), OPRM1 (rs1799971), ERBB2 (rs1058808), BDNF (rs6265), PNPLA3 (rs738409), MTRR (rs1801394) genes [65].

The group of Kim *et al.* [66] interrogated 135 Exome Chip SNVs for associations with ten cardiometabolic traits in 14,028 Korean individuals. Three associations were observed with one or more of four cardio-metabolic traits (fasting plasma glucose (FPG), waist-hip ratio (WHR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP),) within the genes *BRAP*, *ACAD10* and *ALDH2* in the 12q24.12 region. The pleiotropic effect of region 12q24.12 was identified for three SNPs (rs3782886 on *BRAP*, rs11066015 on *ACAD10* and rs671 on *ALDH2*) on lipids and other cardio-metabolic traits. The locus was also associated with High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), triglycerides ($p < 1.06 \times 10^{-2}$; effect sizes between -7.60 ± 1.72 and 2.55 ± 0.53) [66].

Conclusions

The study on the polymorphism of the renin-angiotensin system genes and the endothelial synthase nitrogen oxide gene is of great practical importance, since it not only provides an opportunity to predict the complications of hypertension disease but is also the basis for obtaining the expression of positive gene combinations. Thus, the analysis of literature data suggests that identified genotype-phenotype associations and corresponding functional changes in the endothelium can give information about the possibilities of priority and optimal therapeutic effects in each case, will enable optimization of the diagnosis of disor-

ders in patients with combined pathology — hypertension and obesity, at the early stages. The advent of Next-Generation Sequencing provided the opportunity to detect, in a high-throughput way, the entire spectrum of genomic variation ranging from rare to common variants and from Single Nucleotide Polymorphism to insertions, deletions.

However, the analysis of works on this subject showed that in studying the association of the polymorphism of the renin-angiotensin system genes and the endothelial synthase nitrogen oxide gene with the development of cardiovascular diseases, namely, hypertension with obesity, one must take into account both the ethnic belonging of the subjects and a composition of polymorphous variants, and their combinations in the sample of a larger size.

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Поліморфізм генів ренін-ангіотензинової системи та гена ендотеліальної по-синтази у хворих на артеріальну гіпертензію з ожирінням

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У статті представлений клінічно встановлений взаємозв'язок підвищеного артеріального тиску зі збільшенням маси тіла. Показано, що ендотеліальна дисфункція і дисбаланс нейро-гуморальних систем, а саме патологічне підвищення активності ренін-ангіотензинової системи, виступають провідними механізмами патогенезу гіпертонічної хвороби в поєднанні з ожирінням. Даний огляд літератури присвячений інтерпретації наукових досліджень в області поліморфізму генів ренін ангіотензинової системи і гена ендотеліальної синтази оксиду азоту. Складність полягає в правильній оцінці асоціацій алелей, які мають клінічне значення. Особливо важливо завжди точно визначати асоціації поліморфізму генів при гіпертонічній хворобі з ожирінням. Інформація про подібні асоціації і зв'язки надає можливість для пошуку нових тактик і мішеней впливу, що розвиває персоналізовані підходи до терапії пацієнтів з даною комплексною патологією.

Ключові слова: ендотеліальна синтаза оксиду азоту, ренін-ангіотензінова система, поліморфізм генів, гіпертонічна хвороба, ожиріння.

Полиморфизм генов ренин-ангиотензиновой системы и гена эндотелиальной по-синтазы у больных артериальной гипертензией с ожирением

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В статье представлены данные о взаимосвязи повышения уровня артериального давления и увеличения

массы тела. Показано, что эндотелиальная дисфункция и дисбаланс нейрогуморальных систем, а именно патологическое повышение активности ренин-ангиотензиновой системы выступают ведущими механизмами патогенеза гипертонической болезни в сочетании с ожирением. Данный обзор литературы посвящён интерпретации научных изысканий в области полиморфизма генов ренин ангиотензиновой системы и гена эндотелиальной синтазы оксида азота. Трудность заключается в правильной оценке ассоциаций аллелей, которые имеют клиническое значение. Особенно важно точное определение ассоциаций полиморфизма

генов при гипертонической болезни с ожирением. Информация о подобных ассоциациях и связях предоставляет возможности для поиска новых тактик и мишеней для воздействия, что развивает персонализированные подходы к терапии пациентов с данной комплексной патологией.

Ключевые слова: эндотелиальная синтаза оксида азота, ренин-ангитензиновая система, полиморфизм гена, гипертоническая болезнь, ожирение.

Received 26.06.2018