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Research article

ACE I/D GENETIC POLYMORPHISM AS A RISK FACTOR OF ESSENTIAL HYPERTENSION

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Examining genetic mechanisms of essential hypertension as a cardiovascular risk factor will make it possible to provide monitoring of public health using a personified approach to early diagnostics of cardiovascular pathologies. This will raise effectiveness of preventive activities aimed at reducing population mortality.

Our research goal was to examine features of ACE (the angiotensin-converting enzyme) I/D gene polymorphism (rs4646994) as a risk factor of essential hypertension.

Our test group included 35 people with diagnosed essential hypertension; the reference group was made of 34 relatively healthy people. Lipid spectrum indicators were estimated with an automated or semi-automated analyzer or by calculation. Insulin and cytokines were determined by using the enzyme immunoassay. Genotyping was performed by using the polymerase chain reaction in real time mode.

The research results revealed that the examined patients with essential hypertension had authentic differences from the reference group regarding BMI, lipid spectrum indicators with very low density lipoproteins and triglycerides contents being by 1.3 times higher; insulin contents, by 1.9 times higher; IL-6 contents, by 2.2 times higher; and VEGF, by 1.4 times higher. Genetic analysis revealed 1.3-time higher prevalence of the D-allele of the ACE I/D gene in the patients with essential hypertension (we showed that the dominant inheritance was adequate, P = 0.041). The carriage of this allele was associated with the analyzed disease (OR = 3.16; 95 % CI = 1.08–9.20).

We showed an association between insertion-deletion polymorphisms of the ACE (the angiotensin-converting enzyme) I/D gene and developing essential hypertension in the examined test group (the relative risk was RR = 1.87; 95 % CI =1.07–3.61). This polymorphism can be considered a potential marker of sensitivity to developing essential hypertension.

Keywords: *essential hypertension, angiotensin-converting enzyme, ACE I/D polymorphism, dyslipidemia, proinflammatory cytokines.*

At present, cardiovascular diseases are the major reason for incidence and mortality. Their etiology includes both genetic peculiarities and environmental factors. The renin-angiotensin-aldosterone system (RAAS) is a key regulator of electrolysis balance in the body; SNP-variants of its components are assumed to have substantial influence on cardiovascular homeostasis [1, 2]. Gene examinations and transgenic studies on mice established a crucial role that belongs to *ACE* (the angiotensin-converting enzyme) gene in blood pressure regulation. This resulted in formulating a hypothesis about *ACE* being a probable candidate gene that had an association with essential hypertension [3].

Over the last decades, polymorphisms of *ACE* gene located in the 17q23 chromosome have been examined actively due to developing cardiovascular complications. Insertion/

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deletion (*I/D*) polymorphism of Alu-element with its size being 287 base pairs in the intron 16 of *ACE* gene attracted a lot of attention within the range of cardiovascular phenotypes. It happened due to its correlation with *ACE* activity in blood serum; however, any associations between *ACE I/D* and essential hypertension still remain disputable. Since any associations, as a rule, tend to differ depending on a sex or an ethnic group or under different socio-ecological conditions, it is important to consider potential genetic and genetic-environmental interactions [4, 5].

Our research goal was to examine features of ACE (the angiotensin-converting enzyme) I/D gene polymorphism (rs4646994) as a risk factor of essential hypertension.

Materials and methods. We examined adults who lived in Perm region and were diagnosed with "Essential [primary] hypertension" as per the ICD-10. They were included into the test group, 35 people overall, with their average age being 50.31 ± 1.39 years. Our reference group was made of 34 relatively healthy people with their average age being 48.5 ± 1.36 years. Both groups were comparable in terms of sex, age and lifestyle ($p > 0.05$).

All the examined people gave their voluntary informed written consent to take part in the study. It was accomplished in accordance with the Declaration of Helsinki issued by the World Medical Association (2013 edition) and approved by the Ethical Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies.

Body mass index (BMI) was calculated as per the following formula: BMI = weight (kg) / height $(m)^2$. We took systolic and diastolic blood pressure (SBP and DBP accordingly) by using a sphygmomanometer.

Biochemical indicators of the lipid spectrum (high density lipoproteins or HDLP, low density lipoproteins or LDLP, and triglycerides) were examined with Keylab (BPC+Biosed, Italy) automated clinical chemistry analyzer and Humalyzer 2000 (Human GmbH, Germany) semi-automated one. We calculated levels of very low density lipoproteins as per the following formula: VLDLP = triglycerides $(mmol/dm^3)$ / 2.2. Insulin was examined by ELISA that was performed with Infinite F50 microplate reader (Tecan, Austria) in accordance with the procedure provided by the manufacturer. We calculated insulin resistance index as per the following formula: HOMA-IR = insulin $(\mu IU/cm^3)\cdot$ glucose $(mmol/dm^3)$ / 22.5. We identified markers of immune regulation, namely, interleukins (IL-1beta, IL-6, TNFalfa) and vascular endothelial growth factor (VEGF), by ELISA performed with ELx808 microplate reader (BioTek, USA).

The results were analyzed with "Statistica 6.0" software package (StatSoft, USA). The data are given as the simple mean and standard error of the mean ($M \pm m$). In case distribution was not normal, we applied normalizing log-transformation. Authenticity of differences between mean values determined for different groups was estimated using Student's t-test and differences were considered significant at $p < 0.05$. We applied logistic regression analysis and maximum likelihood estimation to estimate risk factors of essential hypertension, calculated odds ratio *OR* and its 95 % confidence interval (95 % CI) as well as relative risk *RR* and its 95 % confidence interval (95 % CI).

We used biomaterials taken from the oral pharynx mucosa in our genetic analysis. DNA was extracted by using a sorbent. *ACE I/D* (rs4646994) polymorphism was identified with "SNP-screen" kits (Sintol, Russia). We applied the polymerase chain reaction in real time mode using CFX96 thermal cycler (Bio-Rad, USA). The data were analyzed with "Gene Expert" software package. We performed logistic regression analysis that involved building a co-dominant, dominant and recessive inheritance model. Frequencies of alleles and genotypes were calculated according to the Hardy – Weinberg equilibrium based on diagnostics of single nuclear polymorphisms (SNP). We determined whether intergroup dif-

ferences were authentic by using Fischer's exact test and analyzed data on frequency of genotypes and alleles by calculating odds ratio *OR* and 95 % confidence interval (95 % CI). Intergroup differences were considered authentic at $p < 0.05$.

All the tests were accomplished by certified laboratories according to conventional procedures and with certified equipment.

Results. Our examination of patients with essential hypertension established authentic differences ($p = 0.000$) between the test and reference groups as per BMI, SBP and DBP (Table 1). Lipid spectrum indicators were also authentically different between the groups since VLDLP levels were by 1.3 times higher in the test group with a simultaneous decrease in HDLP levels by 13 % ($p = 0.032–0.037$). Triglycerides levels were by 1.3 times higher ($p = 0.036$). We also detected that insulin levels were by 1.9 times higher in the test group than in the reference one and, accordingly, the HOMA-IR index was also higher ($p = 0.022–0.035$).

We examined immune regulation to identify any possible peculiarities and established certain changes in indicators of "the cytokine storm" as IL-6 levels were by 2.2 times higher and VEGF levels by 1.4 times higher in the test group against the reference one ($p = 0.005–0.018$).

Genetic examination identified by 1.3 times more frequent *D* allele of *ACE I/D* gene among the patients with essential hypertension (Table 2); carriage of the allele was associated with the disease ($OR = 3.16$; 95 % CI = 1.08–9.20). We showed that the dominant inheritance model was adequate ($P = 0.041$) and a share of heterozygotes *ID* and variant homozygotes *DD* amounted to 80 % in the test group against 55.9 % in the reference one. Peculiar ratios of frequent genotypes and alleles in the examined groups corresponded to the Hardy – Weinberg equilibrium ($\chi^2 = 0.01–2.32$; $p = 0.13–0.91$).

Logistic regression analysis established risk factors that were independently associated with essential hypertension developing in the examined people (Table 3). Significant intergroup differences were identified for such indicators as VLDLP (by 6.4 times

Table 1

Basic, biochemical and immune indicators in examined patients with essential hypertension and reference group

Indicator	Reference level	Test group	Reference group	*p*
Age, years	-	50.31 ± 1.39	46.5 ± 1.36	0.060
Sex, males/females	-	7/28	4/30	0.513
BMI, kg/m^2	18.5–24.9	33.34 ± 1.59	24.84 ± 1.04	0.000
SBP, mm Hg	120–130	139.41 ± 4.77	119.57 ± 4.06	0.000
DBP, mm Hg	80–85	87.79 ± 3.10	75.86 ± 2.48	0.000
Insulin, μIU/cm^3	2–25	9.61 ± 3.90	5.27 ± 0.80	0.028
HOMA-IR index	0–2.7	2.23 ± 0.99	1.20 ± 0.19	0.041
HDLP, mmol/dm^3	1.42–10	1.63 ± 0.12	1.86 ± 0.15	0.024
LDLP, mmol/dm^3	0–3.9	3.17 ± 0.23	3.12 ± 0.31	0.783
VLDLP, mmol/dm^3	0.26–1.04	0.79 ± 0.14	0.57 ± 0.11	0.014
Triglycerides, mmol/dm^3	0.3–1.7	1.73 ± 0.30	1.24 ± 0.24	0.014
VEGF, pg/cm^3	10–700	327.74 ± 62.39	245.61 ± 45.66	0.039
IL-1beta, pg/cm^3	0–11	1.39 ± 0.31	1.41 ± 0.33	0.917
IL-6, pg/cm^3	0–10	2.56 ± 0.76	1.21 ± 0.56	0.006
TNFalfa, pg/cm^3	0–6	3.14 ± 1.29	3.70 ± 1.09	0.509

N o t e : *p* is the level of significance determined for difference between the test and reference groups.

Table 2

Peculiarities of *ACE I/D* genetic polymorphism in the examined patients with essential hypertension

Genotype, allele	Test group, %	Reference group, %	*P*	*OR* (95 % CI)
Co-dominant model				
II	20	44.1	0.076	0.32 (0.11–0.92)
ID	51.4	29.4		2.54 (0.94–6.85)
DD	28.6	26.5		1.11 (0.39–3.20)
Frequency of alleles				
I	45.7	58.8	0.416	0.59 (0.30–1.16)
D	54.3	41.2		1.70 (0.86–3.33)
Dominant model				
II	20	44.1	0.041	0.32 (0.11–0.92)
ID+DD	80	55.9		3.16 (1.08–9.20)
Recessive model				
II+ID	71.4	73.5	1.0	0.90 (0.31–2.59)
DD	28.6	26.5		1.11 (0.39–3.20)

N o t e : P is Fischer's exact test.

Table 3

Logistic analysis of risk factors that could cause essential hypertension in the examined patients

Indicator	*OR* (95 % CI)	χ^2	*p*
Allele *D ACE I/D*	3.16 (1.06–9.39)	4.70	0.030
BMI	1.29 (1.13–1.47)	28.93	0.000
HDLP	0.24 (0.07–0.85)	5.51	0.019
VLDLP	6.40 (1.27–32.33)	6.62	0.010
Triglycerides	2.35 (1.12–4.95)	6.60	0.010
IL-6	2.51(1.17–5.39)	8.50	0.004

N o t e : *p* is the level of significance determined for intergroup differences; χ^2 is chi-square test adjusted as per likelihood.

higher in the test group), carriage of allele *D ACE I/D* (by 3.16 times), IL-6 levels (by 2.37 times), and triglycerides (by 2.35 times) (p = 0.007–0.030). At the same time, when we assessed risks of essential hypertension in the group associated with allele *D ACE I/D*, this assessment established an authentic probability that the disease would develop as per the relative risk criterion: *RR* = 1.87; 95 % CI =1.07–3.61.

Discussion. The research showed that carriage of allele *D ACE I/D* in the examined group was associated with essential hypertension against developing dyslipidemia and 'the cytokine storm" as risk factors that caused hypertension. *ACE I/D* polymorphism is associated with elevated *ACE* levels in plasma that increase a concentration of angiotensin II, a key factor in regulation of peripheral vascular resistance, and decrease bradykinin levels. All this may act as a risk factor of developing cardiovascular pathology [2, 6].

ACE is the key enzyme in the RAAS. It, together with the kallikrein-kinin system, facilitates physiological functioning of the heart, vessels and kidneys through regulation of blood pressure, blood flow, homeostasis and the vasomotor system. Angiotensin II is a powerful vasoconstrictor agent. It is generated from angiotensin I with help from *ACE*. Angiotensin II influences structures of arterial walls and potentiates atherosclerosis by

stimulating proliferation of smooth muscle cells and synthesis of extracellular matrix. Average *ACE* contents in plasma of people carrying *DD* genotype is approximately by 2 times higher than in *I* genotype carriers. Therefore, allele D indicates that *ACE* is highly active and vice versa. Though *ACE* activity is very different in different people, in general, it remains constant in various tissues or organs in the same person since it is hardly ever influenced by any external factors [7, 8].

There is accumulated evidence that *ACE I/D* gene polymorphism is associated with various cardiovascular diseases including myocardial infarction, heart failure, essential hypertension, atherosclerosis, and endothelial dysfunction [1, 9]. Allele *D* carriage was shown to be associated with elevated blood pressure in patients, susceptibility to hypertensive crises, and authentically more apparent myocardial hypertrophy of the left ventricle. *DD* genotype was more frequent in patients with essential hypertension, ischemic heart disease, diabetes mellitus and their complications and such risk factors as hyperlipidemia, smoking or diseases in family anamnesis [10, 11].

Hypertension-associated genes are grouped together with genes that determine obesity, dyslipidemia and resistance to insulin; however, it is still rather unclear how the RAAS influences lipid metabolism. Some studies show that adipocytes are able to release *ACE* and elevated levels of the enzyme stimulate production of angiotensin II, adhesion molecules and chemokines, LDLP oxidation and formation of foam cells out of macrophages. There is an association between *ACE DD* genotype, developing abdominal obesity and elevated risks of atherosclerosis [6, 12, 13]. Elevated activity of system and fat components in the RAAS is considered a potential way for obesity to result in hypertension and resistance to insulin. It is by this way that *ACE I/D* polymorphism might be associated with these health disorders [14, 15].

A contribution made by cytokines to essential hypertension pathogenesis is primarily associated with their function as inflammation mediators. Research works have shown that patients with essential hypertension tend to have higher levels of IL-6, IL-1 and TNFalfa in their plasma than normotensive people. There is an association between pro-inflammatory markers and systems that regulate blood pressure, the RAAS included. Angiotensin II is able to enhance synthesis of TNFalfa and IL-6 by activating NF-κB nuclear factor. IL-6 was shown to have an important role in developing essential hypertension that was caused by chronic elevated angiotensin II levels. This happened, among other things, due to induced expression of its receptors [16, 17]. IL-6 is able to stimulate production of proteins typical for acute inflammation, to increase cell adhesion in vascular endothelium and ROS concentrations, and to facilitate atherogenesis by disrupting lipoprotein metabolism [18].

Endothelial dysfunction and elevated vascular reactivity are also considered a way for inflammation to contribute to development of essential hypertension. Inflammation can lead to disrupted endothelium-dependent vasodilatation through weakened expression of NO-synthases and lower NO production by such mediators as TNFalfa and C-reactive protein. Besides, activated sections in the immune system can damage endothelial cells and induce remodeling in vascular walls thereby accelerating development of atherosclerosis and ischemic damage in case of essential hypertension [17, 19]. Pathologic angiogenesis develops, among other things, due to VEGF participation which is considered a potential marker of hypertension-induced disorders. VEGF production is initiated by angiotensin II and correlated with blood pressure, cardiovascular risks and early microvascular lesions. However, elevated VEGF levels in patients with essential hypertension are rather a protective mechanism aimed at reducing blood pressure and

are associated with endothelial dysfunction and stimulation of angiogenesis in case vascular walls are damaged [20].

We should note that accumulated data on associations between *ACE I/D* gene polymorphism and essential hypertension are rather controversial. Many studies have established significant differences in distribution of *ACE D/I* gene polymorphism between various ethnic groups and even within the same ethnic group. At the same time, it is necessary to consider possible genetic interactions and a role played by epigenetic changeability, including that occurring under influence of environmental factors, in formation of hereditary predisposition [3, 7, 21–25].

Conclusion. We examined patients with essential hypertension. As a result, insertion-deletion polymorphism of *ACE I/D* gene was established to be associated with a risk of essential hypertension in the examined group (*RR* = 1.87; 95 % CI = 1.07–3.61); in addition, we showed factors related to dyslipidemia and immune inflammation to be also significant (in particular, BMI: OR = 1.29, 95 % CI = 1.13–1.47; IL-6: *OR* = 2.51, 95 % CI = 1.17–5.39; allele *D* of *ACE I/D* gene*: OR* = 3.16, 95 % CI = 1.09–9.39). Therefore, carriage of allele *D* of *ACE* gene can be considered a genetic predictor of essential hypertension; however, the examined sampling was rather small and this calls for further research. This would probably involve examining roles of other RAAS polymorphisms and their interactions that can be applied to solve specific tasks related to prevention and monitoring of essential hypertension.

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