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ASSOCIATION OF *ACE* GENE POLYMORPHISM WITH HYPERTENSION AND RISK FACTORS AMONG INDIGENOUS PEOPLE OF THE NORTHERN TERRITORY OF YAKUTIA

DOI 10.25789/YMJ.2018.64.29

ABSTRACT

A study of the association of insertion-deletion (ID) polymorphism of the ACE gene with arterial hypertension and risk factors of cardiovascular diseases in the indigenous people of the northern territory of Yakutia was conducted. The obtained data show that the representatives of the indigenous population with the ID genotype of the ACE gene are associated with a level of systolic blood pressure, abdominal obesity. Carriers of this genotype of the ACE gene have the greatest chance of developing hypertension, metabolic syndrome. The heterozygous DD genotype is associated with lipid metabolic disorders both in hypertensive patients and persons without hypertension. Therefore, the research confirms influence of the D allele ACE gene polymorphism onto genetic mechanisms of cardiovascular diseases development.

Keywords: polymorphism, ACE gene, arterial hypertension, indigenous people, risk factors.

Introduction. Hypertension (HTN) is one of the main cardiovascular disease risk factors and the main reason for a high mortality among adult population in the world [3, 6]. The prevalence of HTN is rather high in the world: it is on the average by 22% among adult population, according to WHO data [16]. Rising of arterial blood pressure is a multifactorial disease which development is defined by the difficult mechanism of interaction of genetic and not genetic risk factors and

influences of the environment [9, 14]. For today it is proved that the genetic contribution can be considered main in development of HTN. In this process the important role belongs to the genes coding the components of the renin–angiotensin system (RAS), especially to the angiotensin-converting enzyme (*ACE*) [11- 13]. Previously, many researches confirmed the influence of D allele of the *ACE* gene on the development of an idiopathic hypertensia, abdominal obesity and the chronic coronary artery disease [5, 10]. There was a research where the association of *ACE* gene ID polymorphism with a myocardial infarction in men (Yakuts up to 50 years) was revealed [1]. The research of association of *ACE* gene polymorphism with hypertension among indigenous people of arctic territories of Russia is insufficiently studied and remains relevant.

Research objective – studying of association of *ACE* gene polymorphism with hypertension and risk factors among indigenous people of the northern territory of Yakutia.

Materials and methods of the research. The clinico-epidemiological study of indigenous people in remote districts in the North of Yakutia is conducted: in Kolymskoye and Andryushkino rural localities of the Nizhnekolymsky District, Topolinoe rural locality of the Tomponsky District, Nelemnoye rural locality of the Verkhnekolymsky District. 348 people were examined using the continuous method. Patient sample consisted of adult population aged from 20 up to 70 years, 225 women, and 123 men. The response made 75%. Average age of the respondents was 45,71±0,67 years, of women 47,4±0,836 of men 42,6±1,09 years.

Inclusion criteria: representatives of indigenous people of Yakutia (Evens, Chukchi, Yukaghirs, Yakuts).

Exclusion criteria: representatives of non-indigenous nationality.

The program of the research includes the following sections: the questionnaire poll for assessment of an objective state; the informed consent of a respondent to carrying out researches, blood donation (according to the Ethical Committee Protocol); anthropometric examination with measurement of waist circumference, thigh size; blood sampling from basilic vein in the morning on an empty stomach with 12-hour continence from nutrition. Blood drawing for the molecular genetic testing was carried out from a median cubital vein to a test tube with EDTA. Genomic DNA allocated from leucocytes of a peripheral blood with phenol–chloroform extraction technique [Maniatise-tal. 1982]. Genotyping of ID polymorphic marker of *ACE* gene was carried out by means of sets (LLC NPF Litekh, Moscow) according to the manufacturing company instruction on Real-time CFX96 amplifier ("BioRad", the USA).

Laboratory methods of the research included blood lipids test (TC, TG, HDL Cholesterol, LDL Cholesterol), glucose test.

When judging the incidence of disorders of the blood lipid profile in a population, we used the Russian recommendations of the V revision of Society of cardiology of Russian Federation (VNOK), 2012, into account the European recommendations, 2011. Hypercholesterolemia (HCS) is the level of total cholesterol (TC) ≥ 5,0 mmol/l, the high LDL Cholesterol level >3,0 mmol/l, the low HDL Cholesterol level <1,0 mmol/l in men; <1,2 mmol/l in women, the hypertriglyceridemia (HTG) is the TG level is ≥1,7 mmol/l; a hyperglycemia on an empty stomach (a glucose in a blood plasma on an empty stomach ≥ 6,1 mmol/l) or glucose intolerance (a glucose in a blood plasma in 2 hours after glucose loading within ≥7,8 and ≤11,1 mmol/l).

The measurement of blood pressure was carried out according to the standard procedure World Health Organization/ International Organization of Hypertension (1999). Hypertension is present at the 140/90 mmHg (The Russian references developed by Committee of experts of VNOK, 2004, 2009).

The abdominal obesity (AO) is exposed to the value of the waist measurement (WM) ≥ 80 cm on women, ≥94 cm on men.

The study was conducted according to Ethics Committee protocol YSC CMP on the respondent's informed consent to the processing of personal data and the study.

Statistical data processing was carried out by means of standard methods of mathematical statistics, using the software package of SPSS (version 17.0). Data are submitted as M±m where M – average value of the sign size, and m – an average error of the sign size. Intergroup differences were estimated by means of the variance analysis or nonparametric criteria. When comparing frequencies of genotypes the standard criterion χ2 with Yeats's amendment was used. The relative risk (RR) of a disease with a certain genotype was calculated by a standard formula OP=a/bxd/c where an and b – the number of the patients having and not having a mutant genotype respectively, and d, c – a number of people in the control group, having and not having a mutant genotype. RR had a 95% confidence interval. The differences were considered as statistically significant at p<0,05.

The research was conducted within research projects of YSC CMP "A contribution of a metabolic syndrome to development of atherosclerosis of coronary arteries in residents of Yakutia", R & D "Development of new technologies of treatment and risk prediction of hypertension and insult in the Republic of Sakha (Yakutia)" (Government contract No. 1133).

Results of researches and discussion. In the general population distribution of genotype frequencies is shown in table 1. As you see, *ACE* gene ID genotype (65,2%) is the most frequent. The groups were created for the research: the persons having arterial hypertension (175 people), and the group of control – the persons without HTN (173 people). Average age of hypertensive patients was 53,11±0,51 years, the persons without HTN - 38,88±0,60 years.

Results of the comparative analysis of distribution of allele frequencies and genotypes in groups of hypertensive patients

Table 1

PDistribution of genotype frequencies of a polymorphic site ID *ACE* gene

Genotype	Frequency	%
II	68	19,5
ID	227	65,2
DD	53	15,2

Table 2

Distribution of allele frequencies and genotypes of a polymorphic site ID *ACE* gene in groups of hypertensive patients and control

Allele frequencies and genotypes		Patients	Control
I	N	186	177
	%	53.1	51.2
	χ^2(P); OP (95% ДИ)	0.20 (0.6536) 1.08 (0.80-1.47)	
D	N	164	169
	%	46.9	46.8
	χ^2(P); OP (95% ДИ)	0.20 (0.6536) 0.92 (0.68-1.26)	
I/I	N	35	33
	%	20	19.1
	χ^2(P); OP (95% ДИ)	0.01 (0.9343) 1.06 (0.60-1.86)	
I/D	N	116	111
	%	66.3	64.2
	χ^2(P); OP (95% ДИ)	0.09 (0.6774) 1.10 (0.69-1.75)	
D/D	N	24	29
	%	13.7	16.8
	χ^2(P); OP (95% ДИ)	0.44 (0.5058) 0.78 (0.42-1.47)	

and control didn't show statistically significant differences (Tab. 2). We carried out the comparison of average concentration of fats and glucose in the carriers of this or that genotype of *ACE* gene. By comparison of TC average values, significant differences between the carriers of ID genotype and DD genotype (4,97±0,06, 4,91±0,12, respectively, p=0,000) and ID and II (4,97±0,06, 4,87±0,11, p=0,000) are identified.

Comparing the median concentration of LDL Cholesterol, it is taped that carriers of the genotype II had reliable differences in comparison with the genotypes ID and DD (II-3,07±0,09, ID - 3,19±0,05, DD - 3,18±0,09, p=0,000). Also, there were the differences in comparative analysis of median values of HDL Cholesterol (II - 1,31±0,04; ID - 1,29±0,02; DD - 1,20±0,04, p=0,000). Statistically significant differences in Tg median values between the compared groups were among the DD genotype carriers in comparison with two others (DD - 1,11±0,06; II - 1,07±0,06; ID - 1,07±0,03, respectively, p=0,000). By comparison of median values of glucose, the significant differences isn't identified (II - 4,45±0,11; ID - 4,62±0,10; DD - 4,36±0,11, p>0,05).

In the general population, frequency of hypercholesterolemia is 51,5% in carriers of II homozygous genotype, 42,7% in carriers of ID heterozygous genotype, and 49,1% in carriers of DD heterozygous genotype; the differences were doubtful. Frequency of atherogenous LDL hypercholesterolemia was significantly higher in carriers of DD genotype (64,2%), in comparison with carriers of genotypes II and ID (54,4 and 54,6% respectively). The frequency of Hypo-alpha-cholesterolemia among the compared groups of the significant differences are not identified (II – 33,8%, ID – 34,8%, DD - 35,8%, p>0,05). Also, there were not the significant differences of TSH in carriers of different genotypes (II – 11,8%, ID – 11,9%, DD - 11,3%, p>0,05). The greatest frequency of hyperglycemia is identified in ID genotype carriers - 6,6%, and, in comparison with other genotypes, has significant difference (II - 2,9%, p=0,035 and DD - 3,8%, p=0,13).

Furthermore, we carried out the comparison of fats and glucose median values among carriers of genotypes II, ID, DD separately in the groups of hypertensive patient and control.

By comparison of median concentration of fats and carbohydrate spectrum in persons with HTN and in the group of control, the significant differences were identified only in carriers of genotypes ID: TC (5,15±0,09 and 4,79±0,07 respectively, p=0,004), LDL Cholesterol (3,32±0,08, 3,05±0,06, p=0,008), Tg (1,21±0,05, 0,91±0,03; p=0,000), blood glucose (5,02±0,17; 4,19±0,08, p=0,000), except the HDL Cholesterol (1,26±0,03; 1,33±0,03, p>0,05). The significant differences of TC median values were not identified in homozygous carriers of genotypes II (5,05±0,14; 4,68±0,16, respectively, p>0,05), and in comparing LDL Cholesterol (3,24±0,13; 2,88±0,13, respectively, p>0,05), HDL Cholesterol (1,26±0,05; 1,37±0,06, p>0,05), Tg (1,21±0,09, 0,92±0,07; p>0,05), glucose (4,48±0,18; 4,41±0,14, p p>0,05). The comparisons between groups of DD carriers also did not reveal the significant differences: TC (5,13±0,16, 4,71±0,16, p>0,05), LDL Cholesterol (3,32±0,14; 3,07±0,12, p>0,05), HDL Cholesterol (1,28±0,06; 1,14±0,05, p>0,05), Tg (1,16±0,10, 1,07±0,08; p>0,05), glucose (4,48±0,27; 4,25±0,14, p>0,05).

We carried out the assessment of frequency of lipid and metabolism disorders separately among hypertensive patients and persons without HTN. Hypertensive patients have the largest frequency of hypercholesterolemia (66,7%) (Fig. 1), atherogenic hypercholesterolemia (70,8%) - in persons with DD genotype. The most frequent hypo-alpha-cholesterolemia and hyperglycemia are identified in heterozygous carriers, and HTG - in II homozygous carriers. Differences between them did not reach statistically significant values.

In the control group, the largest frequency of hypercholesterolemia is identified in the group of II genotype carriers (42,4%) (fig. 2). Atherogenic hypercholesterolemia was high in all persons without HTN, DD homozygous carriers had the highest frequency of atherogenic hypercholesterolemia (58,6%). There is the same situation with the frequency of hypo-alpha-cholesterolemia (44,8%). Thus, the influence of DD genotype on lipid storage disease is revealed.

Also, we surveyed the association of

Table 3

Mean concentrations of lipid spectrum and glucose among hypertensive patients and control group depending on ID genotypes of *ACE* gene

Blood parameters	Genotype II		Genotype ID		Genotype DD		p
	with HTN	without HTN	with HTN	without HTN	with HTN	without HTN	
TC	5.05±0.14	4.68 ±0.16	5.15±0.09*	4.79±0.07*	5.13±0.16	4.71±0.16	*0.004
LDL CS	3.24±0.13	2.88±0.13	3.32±0.08*	3.05±0.06*	3.32±0.14	3.07±0.12	*0.008
HDL CS	1.26±0.05	1.37±0.06	1.26±0.03	1.33±0.03	1.28±0.06	1.14±0.05	
TG	1.21±0.09#	0.92±0.07#	1.21±0.05*	0.91±0.03*	1.16±0.10	1.07±0.08	*0.000 #0.023
Glucose	4.48±0.18	4.41±0.14	5.02±0.17*	4.19±0.08*	4.48±0.27	4.25±0.14	*0.000

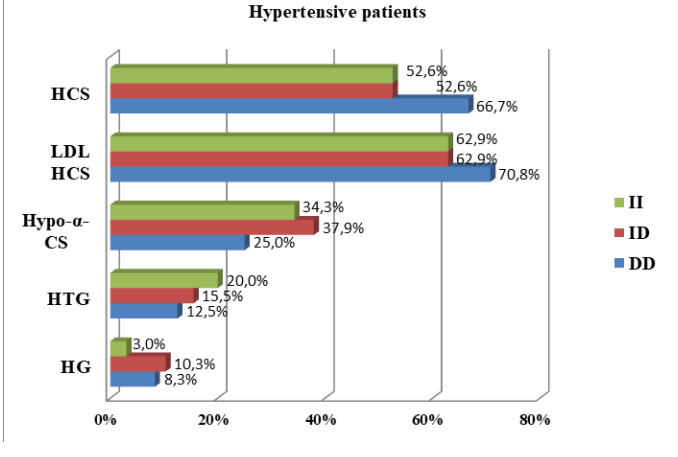

Fig.1. Frequency of lipid and metabolism disorders separately depending on the genotype *ACE* gene among hypertensive patients

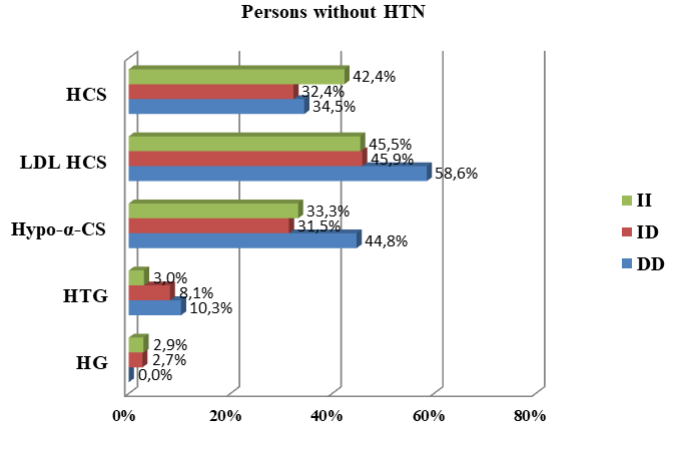

Fig.2. Frequency of lipid and metabolism disorders separately depending on the genotype *ACE* gene among persons without HTN

ACE genotypes with the level of the systolic blood pressure. The average level of systolic blood pressure in carriers of ID heterozygous genotype (144,2±1,2 mmHg) was significantly higher in comparison with the carriers of homozygous genotypes II and DD (136,6±2,8 and 138,8±2,1 mm Hg., respectively, p=0,02).

Abdominal Obesity is independent risk factor of metabolic syndrome and cardiovascular diseases. We defined associativity of genotypes to the average waist measurement (WM) and AO. By comparison the average WM, we received significant differences between ID genotype carriers and carriers of other genotypes (OT_{ID}=89,61±0,65, OT_{II}=86,46±1,49, OT_{DD} = 86,75; p<0,05). There are statistically significant differences in the frequency of AO between ID carriers (59,9%) and II and DD carriers (55,9%, 50,9%).

We compared WM separately in groups with HTN and without HTN. It is shown that, among persons with HTN, significant differences are in carriers of genotype ID (WM=96,23±0,89) comparing with II homozygous carriers (OT =91,43±1,99, p=0,033), DD (OT =92,63±1,27, p=0,022). Among persons without HTN there are no significant differences: ID -82,68±0,68, II - 81,18±1,85, DD - 81,90±1,21. In general, hypertensive patients had a high frequency of AO. Among genotypes the highest frequency of AO is in ID genotype - 84,5%. It statistically differed from DD - 66,7% (p=0,001), and didn't differ from II - 71,4%. Frequency of AO in persons without HTN among carriers of this or that genotype had no significant differences; it varied within II – 39,4%, ID - 34,2%, DD - 37,9%.

Conclusion. The obtained data show that representatives of indigenous people of the North of Yakutia with ID genotype of *ACE g*ene, abdominal obesity is associated with the level of systolic arterial blood pressure. Thus, carriers of this genotype have the highest probability of idiopathic hypertension, metabolic syndrome. It is also confirmed by the researchers conducted by some foreign authors [4, 7, 8, 15]. The DD heterozygous genotype is connected with lipid storage disease, both in hypertensive patients, and persons without hypertension.

Therefore, the research confirms influence the D allele *ACE* gene polymorphism onto genetic mechanisms of cardiovascular diseases development. Data are compounded with references of foreign researchers [2, 5, 10].

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