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SEARCH FOR THE ASSOCIATION OF THE A1166C POLYMORPHIC MARKER OF THE *AGTR1* (RS5186) GENE WITH ESSENTIAL HYPERTENSION IN INDIGENOUS ETHNIC GROUPS OF YAKUTIA

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The aim of case-control study was to assess the possible association between angiotensin II type 1 receptor *(A1166C)* gene polymorphism and essential hypertension in the indigenous population of Yakutia (Yakuts-56, Chukchi-34, Yukagirs-77, Evens-184). 168 subjects with the essential hypertension (cases) were compared to 179 normotensive subjects (controls). The frequency of the C allele was 17.9 and 19.4% among cases and controls, respectively (p = 0.600). No association was found between the angiotensin II type 1 receptor *(A1166C)* gene polymorphism and essential hypertension in the study population.

Keywords: essential hypertension, genotype, *AGTR1* gene, A1166C, rs5186, Yakutia, risk factors.

Arterial hypertension (AH) is a common risk factor for chronic noncommunicable diseases, contributing significantly to the risk of mortality and disability from its complications. Essential hypertension makes up to 95% of all cases of hypertension. Epidemiological indicators of the prevalence and effectiveness of hypertension treatment depend not only on concomitant conditions and diseases, but also on the genetic characteristics of populations. The renin-angiotensin system plays an important role in the regulation of blood pressure and electrolyte homeostasis. In studies of genes of candidates for predisposition to essential hypertension, genes whose products provide individual biochemical links of the renin-angiotensin system were actively studied. Angiotensin II implements its biological effects through two types of receptors: type 1 (AT1R) and type 2. The AGTR1 gene encodes a type 1 angiotensin II receptor protein. The most studied SNP is rs5186, known as A1166C, which is located in the 3'-untranslated region of the type 1 angiotensin II receptor gene AGTR1. At position 1166, adenine (A) is replaced by cytosine (C), which alters the regulation of gene expression. In some populations, the link between being a carrier of the C allele rs5186 and an increased risk of developing essential hypertension has been demonstrated [7, 13].

The Republic of Sakha (Yakutia) is a region where extreme climatic factors have a depleting effect on the functional reserves of the human body. Stresses of adaptive mechanisms often manifest itself in the form of an increase in blood pressure. Changes in diet and physical activity have led to widespread overweight and obesity among indigenous populations of the North, which also contribute to higher blood pressure levels [1]. Under these conditions, the search for genetic markers of predisposition to the development of hypertension is of both scientific and practical interest.

The aim of the study was to research the distribution of alleles and genotypes of the A1166C polymorphic markers of the *AGTR1* gene (rs5186) and their link with essential hypertension in the group of representatives of the indigenous ethnic groups of Yakutia.

Materials and methods. A single-stage epidemiological study of the population of Nizhnekolymsky and Tomponsky districts of the Republic of Sakha (Yakutia) was carried out. The "case" and "control" groups were formed. A total of 351 participants (228 women and 123 men) were examined, including 56 Yakuts, 34 Chukchi, 77 Yukagirs and 184 Evens. The average age was 45.9 ± 12.5 years. The study was approved by the local ethical committee of the Yakut Science Centre of Complex Medical Problems. All participants were informed and have signed a voluntary informed consent for participation in the study and for blood sampling. Determination of nationality was carried out on the basis of self-identification of the participants.

The criteria for inclusion in the group of "cases" (AH +) include: belonging to an indigenous ethnic group of Yakutia (Yakuts, Evens, Chukchi, Yukagirs), being 18 years and older, and presence of hypertension at any stage. The group of "controls" (AH -) included persons without AH, representatives of the indigenous ethnic groups of Yakutia at the age of 18 and older. Exclusion criteria: belonging to a non-indigenous nationality, symptomatic arterial hypertension according to medical history and outpatient records.

The research program included the following sections: a questionnaire for objective assessment of state; blood pressure measurement, survey by a cardiologist, blood sampling from the cubital vein in the morning on an empty stomach with 12-hour abstinence from food, measurement of the waist circumference (WC) in cm was carried out below the chest above the navel, in the middle of the distance between the lower lateral edge of the ribs and the apex of the ridge the ilium (NIH, 1998); the circumference of the thighs at the level of the buttocks.

The abdominal obesity (AO) is exposed to the value of the waist measurement (WM) ≥ 80 cm on women, ≥94 cm on (VNOK, 2009).

Blood pressure (BP) was measured twice with an OMRON M2 Basic automatic tonometer (Japan) in a sitting position with calculation of average blood pressure with a margin of permissible measurement error of ± 3 mm Hg (ESH/ESC, 2013). Hypertension is present at the 140/90 mmHg or taking antihyperten-

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sive drugs during the study (2017 ACC/AHA Guideline). Out of 172 people who met these criteria, 4 people were excluded, whose condition was assessed as "secondary arterial hypertension". Thus, the “cases” group was represented by 168 participants, the “control” group by 179 normotensive individuals.

Laboratory methods of the research included analysis of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL Cholesterol), low-density lipoprotein cholesterol (LDL Cholesterol), very low-density lipoprotein cholesterol (VHDL Cholesterol), levels glucose. The genetic study included the identification of the polymorphic marker A1166C of the *AGTR1* gene (rs5186).

When judging the incidence of disorders of the blood lipid profile in a population, we used the Russian recommendations of the VII revision of Society of cardiology of Russian Federation, 2020, into account the European recommendations, 2019. Hypercholesterolemia (HCS) is the level of TC ≥ 5,0 mmol/l (190 mg/dl) taking into account the risk of cardiovascular death on the SCORE scale, the high LDL Cholesterol level >3,0 mmol/l (115 mg/dl) with low, > 2.6 mmol/l with moderate, >1,8 mmol/l with high, > 1,4 mmol/l with very high and extreme risk, the low HDL Cholesterol level <1,0 mmol/l on men; <1,2 mmol/l on women, the hypertriglyceridemia (HTG) is the TG level is >1,7 mmol/l. The atherogenic index (IA) was determined by the formula: IA (cu) = (TC - HDL Cholesterol) / HDL Cholesterol (Klimov A.N., Nikulcheva N.G., 1999). A hyperglycemia (HG) on an empty stomach (a glucose in a blood plasma on an empty stomach > 5,6 mmol/l). Respondents with these disorders also included participants receiving specific medication for these conditions.

Genomic DNA was isolated from peripheral blood leukocytes by the method of phenol-chloroform extraction. Genotyping 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). For quality control, 10% of randomly selected samples were subjected to repeated genotyping.

The verification of the correspondence of the distribution of genotypes to the Hardy-Weinberg equilibrium law was carried out using an online calculator at https://wpcalc.com/en/ equilibrium-hardy-weinberg. Statistical analysis of the data was carried out using the SPSS STATISTICS 22 package. The frequencies of alleles and genotypes are presented with 95% confidence intervals (95% CI). When comparing groups depending on the number of groups and data type, the Mann-Whitney, Kruskal-Wallis, Pearson $\chi 2$ tests were used. The odds ratio (OR) was calculated with a 95% CI. The statistical significance of the differences (p) was taken equal to 5%.

Results and discussion. The distribution of genotype frequencies of the polymorphic marker A1166C of the *AGTR1* gene (rs5186) in the groups of Yakuts, Evens, and Yukagirs corresponded to the Hardy-Weinberg equilibrium. In the Chukchi group, which was represented by 34 participants, the distribution differed from the equilibrium (Table 1). The frequency of detection of the C allele varied from 0.13 in the Evens to 0.35 in the Chukchi. According to the ALFA (Allele Frequency Aggregator) project, the frequency of C allele carriage averages 0.28 (n = 238604), varying depending on population: from 0.009 among Africans (n = 354) to 0.30 among Hispanics with predominantly European and Native American origin (n = 6874). Among the populations of Southeast Asia, the prevalence of the C allele is 0.08–0.09 [8]. Thus, according to the presented study, the frequency of the C allele in the indigenous ethnic groups of Yakutia is, on average, higher than in the population of Southeast Asia and Africa.

Comparative analysis of the distribution of alleles and genotypes of the A1166C polymorphic marker of the *AGTR1* gene (rs5186) in the groups of cases and controls did not show statistically significant differences between the groups (Table 2). Thus, the study did not reveal a link between the studied polymorphic marker and the frequency of essential hypertension in groups of representatives of the population of the North. In academic literature, information on the link between the polymorphic marker A1166C of the *AGTR1* gene (rs5186) and essential hypertension is contradictory [2, 6, 7, 10, 12, 13]. In China, when comparing three genetically different populations with significant differences in the prevalence of essential hypertension, it was suggested that allele A may be a predisposing factor for essential hypertension in Tibetan men, while no association

Table 1

Distribution of alleles and genotypes of the polymorphic marker A1166C of the *AGTR1* gene (rs5186) in the indigenous ethnic groups of Yakutia

Allele/Genotype	Indicator	Yakuts n=56	Evens n=184	Chukchi n=34	Yukagirs n=77	All groups n=351
A	Total	90	321	44	116	571
	Frequency (95% CI)	80.4 (71.5-87.2)	87.2 (83.3-90.4)	64.7 (51.9-75.9)	80.6 (72.9-86.6)	81.3 (78.3-84.1)
C	Total	22	47	24	38	131
	Frequency (95% CI)	19.6 (12.8-28.5)	12.8 (9.6-16.7)	35.3 (24.1-48.1)	26.4 (19.5-34.5)	18.7 (15.9-21.7)
AA	Total	36	140	10	43	229
	Frequency (95% CI)	64.3 (50.0-76.7)	76.1 (69.2-81.9)	29.4 (14.5-48.5)	55.8 (44.0-67.1)	65.2 (60.0-70.1)
AC	Total	18	41	24	30	113
	Frequency (95% CI)	32.1 (20.2-46.4)	22.3 (16.6-29.1)	70.6 (51.5-85.5)	38.9 (28.1-50.9)	32.2 (27.4-37.3)
CC	Total	2	3	0	4	9
	Frequency (95% CI)	3.6 (0-14.3)	1.6 (0-5.3)	0	5.2 (0.7-14.0)	2.6 (1.1-5.0)
$\chi 2$ to the Hardy-Weinberg		0.019	8.08	10.1	0.179	1.284
p		0.892	0.99	0.001	0.673	0.257

Note. Table 1-3 p - the achieved level of significance; 95% CI - 95% confidence interval.

was found in the other two populations [2]. In a case-control study conducted in Poland (250 people with stable essential hypertension and 150 people with normal blood pressure), allele C and CC genotype were statistically significantly more frequent in patients with hypertension [12]. In a similar study conducted in India, individuals with CC genotypes were 2.4 times more likely to develop essential hypertension (p = 0.0001) than individuals with AC and AA genotypes [6]. At the same time, in the study by Suita, conducted in Japan, involving 1492 patients with hypertension and 2426 normotensive individuals, no association was found between the A1166C variants of the *AGTR1* gene and hypertension [10]. Researchers who studied similar groups in Tunisia came to the same results [3].

References contain information on the link between the polymorphic marker A1166C of the *AGTR1* gene and non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, liver fibrosis, dyslipidemia, insulin resistance and metabolic syndrome [4, 5, 9, 11]. In light of this data, in further analysis, the groups of carriers of alleles A and C, with different rs5186 genotypes, were compared in terms of the level of metabolic parameters and the frequency of its disorders (Table 3). Taking into account the fact that these parameters depend on the age and sex of the surveyed, a comparison of the groups by these indicators was carried out. The analysis showed that there were no differences in the age of the subjects, both between carriers of different alleles (p = 0.987) and different genotypes (p = 0.576). There were also no differences in the distribution of individual alleles (p = 0.786) and genotypes (p = 0.960) in men and women. Thus, the groups were comparable in terms of age and gender structure. The analysis did not reveal differences in blood pressure levels between carriers of different genotypes. It should be noted that systolic (SBP) and diastolic (DBP) levels were compared for all study participants, including those taking antihypertensive drugs, which could change the results of the assessment. Carriers of allele A were characterized by a statistically significantly larger waist circumference, lower serum HDL cholesterol levels, and high values of the atherogenic index (Table 3). These differences persisted when the group was divided depending on the genotype, including when the carriers of the AC and CC genotypes were combined.

When studying the link between the alleles and genotypes of polymorphic marker A1166C of the *AGTR1* gene (rs5186) with the frequency of metabolic disorders, statistically significant differences were obtained only in relation to hypo-alpha-cholesterolemia. Thus, the frequency of decreased levels of HDL cholesterol was 38.1% in carriers of the A allele versus 27.7% in carriers of the C allele (p = 0.026). When comparing carriers of different genotypes in terms of the frequency of hypo-alpha-cholesterolemia, the indicators were: AA genotype - 40.5%, AC - 28.6%, CC - 22.2%, respectively (p = 0.005).

Taking into account the data obtained, an analysis of the strength and direction of the link between the content of HDL cholesterol and certain metabolic parameters was carried out. The variable that can distort the reflection of these links may be the age of the surveyed. The concentration of HDL cholesterol did not correlate with the age of the subjects (r = -0.07, p = 0.076). No correlation was found between the content of HDL cholesterol and the levels of SBP (r = -0.06, p = 0.113), DBP (r = -0.09, p = 0.013), glucose (r = -0.07, p = 0.069), LDL cholesterol (r = -0.03, p = 0.412). A negative correlation was found with WC (r = -0.26, p <0.001) and TG content (r = -0.58, p <0.001). It is possible that the link discovered between carrying the *AGTR1* allele A and the level of HDL cholesterol is due to the association between waist circumference and HDL cholesterol. To test this assumption, we compared the levels of HDL cholesterol for different genotypes in groups divided by the presence of abdominal obesity. Nonparametric analysis of variance revealed no statistically significant differences in the group of persons with normal waist circumference (p = 0.180). Thus, it should be assumed that the revealed differences in the levels of HDL cholesterol in carriers of different genotypes and alleles of the A1166C polymorphic marker of the *AGTR1* gene are due to differences in WC.

Conclusion. Thus, the results of the study in the group of representatives of the indigenous ethnic groups of Yakutia did not reveal an association of

Table 2

Distribution of alleles and genotypes of the polymorphic marker A1166C of the *AGTR1* gene (rs5186) in hypertensive and normotensive individuals

Ethnos	Group	Allele/Genotype, n (%)			OR (95% CI), p
		A	**C**		
Yakuts	AH-	31 (77.5)	9 (22.5)		0.76 (0.29-1.97) p=0.750
	AH+	59 (81.9)	13 (18.1)		
Evens	AH-	176 (87.1)	26 (12.9)		0.98 (0.53-1.8) p=1.0
	AH+	145 (87.3)	21 (12.7)		
Chukchi	AH-	29 (65.9)	15 (34.1)		1.16 (0.41-3.27) p=0.988
	AH+	15 (62.5)	9 (37.5)		
Yukagirs	AH-	59 (73.8)	21 (2.2)		0.84 (0.40-1.75) p=0.776
	AH+	57 (77.0)	17 (23.0)		
All groups	AH-	295 (80.6)	71 (19.4)		0.90 (0.62-1.32) p=0.600
	AH+	276 (82.1)	60 (17.9)		
		AA	**AC**	**CC**	
Yakuts	AH-	12 (60)	7 (35.0)	1 (5.0)	AA and AC 0.79 (0.24-2.54). p=0.920 AA and CC 0.50 (0.03-8.71) p=1.0 AA and AC+CC 0.75 (0.24-2.33) p=0.835
	AH+	24 (66.7)	11 (30.6)	1 (2.8)	
Evens	AH-	77 (76.2)	22 (21.8)	2 (2.0)	AA and AC 1.06 (0.53-2.12) p=1.0 AA and CC 0.61 (0.05-6.89) p=1.0 AA and AC+CC 1.02 (0.52-2.0) p=1.0
	AH+	63 (75.9)	19 (22.9)	1 (1.2)	
Chukchi	AH-	7 (31.8)	15 (68.2)		AA and AC 1.40 (0.29-6.83) p=0.982
	AH+	3 (25.0)	9 (72.0)		
Yukagirs	AH-	22 (55.0)	15 (37.5)	3 (7.5)	AA and AC 1.05 (0.41-2.66) p=0.922 AA and CC 0.35 (0.03-3.63) p=0.696 AA and AC+CC 0.93 (0.38-2.29) p=1.0
	AH+	21 (56.8)	15 (40.5)	1 (2.7)	
All groups	AH-	118 (64.5)	59 (32.2)	6 (3.3)	AA and AC 0.97 (0.62-1.55) p=0.997 AA and CC 0.53 (0.13-2.18) p=0.581 AA and AC+CC 0.93 (0.60-1.45) p=0.841
	AH+	111 (66.1)	54 (32.1)	3 (1.8)	

Note. OR - odds ratio; AH + – the presence of essential hypertension, AH- – persons with normal blood pressure.

Table 3

Comparison of age and metabolic parameters in carriers of different alleles and genotypes of the polymorphic marker A1166C of the *AGTR1* gene (rs5186)

Indicator	Me (Q_1-Q_3)			p
Allele				
	A		**C**	
Age, years	48.0 (36.0-55.0)		47.0 (35.0-55.0)	0.987
WC, cm	88.0 (78.0-98.0)		83.0 (35.0-98.0)	**0.044**
SBP mm Hg	130.0 (120.0-150.0)		130.0 (35.0-150.0)	0.337
DBP, mm Hg	80.0 (80.0-90.0)		80.0 (35.0-90.0)	0.347
Glucose (mmol/l)	4.4 (3.9-5.0)		4.2 (35.9-5.0)	0.099
TG (mmol/l)	1.0 (0.7-1.4)		0.9 (35.7-1.4)	0.129
TC (mmol/l)	4.9 (4.4-5.5)		4.9 (35.4-5.5)	0.385
HDL Cholesterol (mmol/l)	1.2 (1.0-1.5)		1.4 (35.0-1.5)	**0.011**
LDL Cholesterol (mmol/l)	3.2 (2.7-3.7)		3.0 (35.7-3.7)	0.122
VHDL Cholesterol (mmol/l)	0.4 (0.3-0.6)		0.4 (35.3-0.6)	0.069
IA (cu)	2.9 (2.2-3.8)		2.7 (35.2-3.8)	**0.014**
Genotype				
	AA	**AC**	**CC**	
Age, years	47.0 (35.0-55.0)	48.0 (37.8-55.0)	33.0 (29.5-58.5)	0.576
WC, cm	88.5 (78.3-98.0)	86.0 (37.0-98.0)	81.0 (75.3-82.0)	**0.032**
SBP mm Hg	130.0 (120.0-150.0)	130.0 (37.0-150.0)	120.0 (117.5-145.0)	0.565
DBP, mm Hg	80.0 (80.0-90.0)	80.0 (37.0-90.0)	80.0 (77.5-90.0)	0.569
Glucose (mmol/l)	4.5 (4.0-5.0)	4.3 (37.8-5.0)	3.8 (3.3-4.4)	0.121
TG (mmol/l)	1.0 (0.7-1.4)	0.9 (37.7-1.4)	0.9 (0.7-1.1)	0.295
TC (mmol/l)	4.9 (4.4-5.5)	4.9 (37.3-5.5)	4.9 (4.1-5.5)	0.669
HDL Cholesterol (mmol/l)	1.2 (1.0-1.5)	1.3 (37.1-1.5)	1.4 (1.2-1.6)	**0.027**
LDL Cholesterol (mmol/l)	3.2 (2.7-3.7)	3.0 (37.6-3.7)	3.1 (2.6-3.6)	0.261
VHDL Cholesterol (mmol/l)	0.4 (0.3-0.7)	0.4 (37.3-0.7)	0.4 (0.3-0.5)	0.170
IA (cu)	3.0 (2.2-4.0)	2.7 (37.0-4.0)	2.6 (2.0-3.5)	**0.034**
	AA		**AC+CC**	
Age, years	47.0 (35.0-55.0)		47.5 (36.8-55.0)	0.750
WC, cm	88.5 (78.3-98.0)		84.5 (77.0-98.0)	0.127
SBP mm Hg	130.0 (120.0-150.0)		130.0 (120.0-150.0)	0.405
DBP, mm Hg	80.0 (80.0-90.0)		80.0 (80.0-90.0)	0.292
Glucose (mmol/l)	4.5 (4.0-5.0)		4.2 (3.8-5.0)	0.194
TG (mmol/l)	1.0 (0.7-1.4)		0.9 (0.7-1.4)	0.134
TC (mmol/l)	4.9 (4.4-5.5)		4.9 (4.2-5.5)	0.394
HDL Cholesterol (mmol/l)	1.2 (1.0-1.5)		1.3 (1.1-1.5)	**0.007**
LDL Cholesterol (mmol/l)	3.2 (2.7-3.7)		3.0 (2.6-3.7)	0.102
VHDL Cholesterol (mmol/l)	0.4 (0.3-0.7)		0.4 (0.3-0.7)	0.065
IA (cu)	3.0 (2.2-4.0)		2.7 (2.0-4.0)	**0.010**

Note. Me (Q1-Q3) - median and interquartile range.

the A1166C polymorphic marker of the *AGTR1* gene (rs5186) with essential hypertension. The limitations of the study were: the small number of groups, the inability of conducting a full, comprehensive examination of the participants to exclude the secondary nature of hypertension. A positive aspect of the research was the usage of controls from the same population, in the same time period. In further studies, an additional verification of the studied link is possible by using the hospital population as" cases", excluding the secondary nature of hypertension.

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