International Journal of Biomedicine 11(3) (2021) 361-366
http://dx.doi.org/10.21103/Article11(3)_OA14

ORIGINAL ARTICLE

Population Genetics

INTERNATIONAL JOURNAL OF BIOMEDICINE

Association of the *AGTR1* Gene A1166C (rs5186) Polymorphism with Essential Hypertension in the Indigenous Population of the Arctic

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Abstract

The research objective was to study the association of the AGTR1 rs5186 SNP (the A1166C variant) with essential hypertension among indigenous people of the Arctic territory of Yakutia.

Methods and Results: A total of 351 participants (224 women and 127 men) were examined, including 56 Yakuts, 34 Chukchi, 77 Yukaghirs, and 184 Evens. The Case (n=168) and Control (n=183) groups were formed. Allelic variants of the AGTR1 rs5186 SNP were tested by real-time PCR. We did not find statistically significant differences in the frequency distribution of the alleles and genotypes of the AGTR1 rs5186 SNP between the Case group and the Control group.

Conclusion: The obtained data show no association of the AGTR1 A1166C polymorphism with EHT in the representatives of indigenous people of the Arctic territory of Yakutia.(**International Journal of Biomedicine. 2021;11(3):361-366.**)

Key Words: essential hypertension • genotype • *AGTR1* gene • A1166C • rs5186 • Yakutia

For citation: Sofronova SI, Klimova TM, Kirillina MP, Nikolaev VM, Kononova IV, Kuzmina AA, Romanova AN. Association of the AGTR1 Gene A1166C (rs5186) Polymorphism with Essential Hypertension in the Indigenous Population of the Arctic. International Journal of Biomedicine. 2021;11(3):361-366. doi:10.21103/Article11(3)_OA14

Abbreviations

AGTR1, angiotensin II type I receptor; **AO**, abdominal obesity; **AH**, arterial hypertension; **BP**, blood pressure; **DBP**, diastolic BP; **EHT**, essential hypertension; **FPG,** fasting plasma glucose; **GWAS**, genome-wide association studies; **HDL-C**, high-density lipoprotein cholesterol; **HWE**, Hardy-Weinberg equilibrium; **LDL-C**, low-density lipoprotein cholesterol; **RAAS**, renin–angiotensin–aldosterone system; **SBP**, systolic BP; **TC**, total cholesterol; **TG**, triglycerides; **WC**, waist circumference.

Introduction

Arterial hypertension (AH) is still one of the most common problems in cardiology and is responsible for high cardiovascular morbidity and mortality. Essential hypertension (EHT) is a multifactorial disease with a complex genetic basis. Large-scale GWAS have successfully established ~800 genetic loci for SBP, DBP, and hypertension in multiple ethnic groups.[1] Several reviews and meta-analyses summarize the vast number of studies of the RAAS genes in cardiovascular physiology, disease, and treatment.[2-4] The RAAS plays a fundamental role in blood pressure maintenance and is implicated in the pathogenesis of hypertension. However, the results of the gene studies of individual RAAS candidates vary depending on population or ethnicity. Among the great number of gene candidates encoding the RAAS components, the *AT1R* gene is of great interest. Polymorphisms within this gene have

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been extensively studied in association with hypertension; however, findings are conflicting.[5]

The most well-studied of the *AGTR1* SNP is rs5186 (also termed the A1166C variant) located in the 3′ UTR. Frequencies of this variant range from 0.19–0.31 in populations of European descent,[6-9] 0.03–0.11 in populations of Asian descent,[10-13] and 0.05–0.08 in studies of populations of African descent. Numerous studies have been published associating polymorphisms of the *AGTR1* gene with AH; however, results have been inconsistent.[5,17,18]

It has been hypothesized that the *AGTR1* rs5186 SNP, an AC nucleotide substitution at position 1166 in the 3′ untranslated region of chromosome 3, may affect mRNA-155 stability and transcription. In some populations, a link between being a carrier of the C allele rs5186 and an increased risk of developing essential hypertension has been demonstrated.[17,18]

The Republic of Sakha (Yakutia) (RS(Y)) is a region where extreme climatic factors have a depleting effect on the functional reserves of the human body. The tension of the adaptive mechanisms often manifests itself in the form of an increase in BP. Changes in diet and physical activity have led to widespread overweight and obesity among indigenous populations of the North, which also contributes to an increase in BP.[19] Under these conditions, the search for genetic markers of predisposition to the development of hypertension is of both scientific and practical interest

Our research objective was to study the association of the *AGTR1* rs5186 SNP (the A1166C variant) with EHT among indigenous people of the Arctic territory of Yakutia.

Materials and Methods

A one-stage epidemiological study was carried out in the Arctic territory of the RS(Y). The Case (EHT+) and Control (EHT-) groups were formed. A total of 351 participants (224 women and 127 men) were examined, including 56 Yakuts, 34 Chukchi, 77 Yukaghirs, and 184 Evens. The average age was 45.9±12.5 years. Nationality was determined through participants' self-identification.

The study was approved by the Ethics Committee of the Yakut Science Center of Complex Medical Problems. Written informed consent was obtained from each patient.

Inclusion criteria for the Case group (n=168) were representatives with EHA of indigenous peoples of Yakutia (the Yakuts, the Evens, the Chukchi, the Yukaghir), and being 18 years and older. Inclusion criteria for the Control group (n=183) were representatives without EHT of indigenous peoples of Yakutia (the Yakuts, the Evens, the Chukchi, the Yukaghir), and being 18 years and older. Exclusion criteria were representatives of non-indigenous nationality and those with secondary hypertension.

The research program included the following sections: a questionnaire for objective assessment of state; informed consent of the respondent to conduct research and donate blood; anthropometric examination; and blood sampling from the cubital vein in the morning on an empty stomach, with 12-hour abstinence from food.

Abdominal obesity (AO) was confirmed at WC ≥ 94 cm in males and ≥ 80 cm in females (VNOK, 2009).

Blood pressure (BP) was measured twice with an OMRON M2 Basic automatic tonometer, with subjects in a sitting position. Average BP was calculated with a margin of permissible measurement error of ±3 mmHg, according to the instructions for the correct measurement of BP outlined in the European clinical guidelines for the diagnosis and treatment of hypertension. The diagnosis of AH was based on 2017 ACC/AHA Guideline for or the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[20]

Laboratory methods of the research included the assessment of FPG and blood levels of TG, HDL-C, and LDL-C. Lipid metabolism disorders were diagnosed according to the Russian national recommendations of the VII revision(the Russian Society of Cardiologists [RSC, 2020]), considering the European recommendations (2019): TC >5,0 mmol/l; TG>1.7 mmol/l; HDL-C <1.0 mmol/l in males and <1.2 mmol/l in females; LDL-C >3.0 mmol/l. The atherogenic index (IA) was determined by the formula: IA=(TC-HDL-C)/HDL-C (Klimov AN, Nikulcheva NG, 1999). Impaired fasting glucose was defined as FPG level >5.6 mmol/l. Respondents with these disorders also included participants receiving specific medication for these conditions.

Genotyping of *the AGTR1* rs5186 SNP (the A1166C variant)

Genomic DNA was isolated from the peripheral blood leukocytes using a standard phenol–chloroform extraction technique. Allelic variants of the AGTR1 rs5186 SNP_were tested by real-time PCR on the «Real-time CFX96» amplifier (BioRad, USA) using Lytech kits (Lytech R&D LLC, Moscow) in accordance with the manufacturer's instructions. For quality control, 10% of samples were randomly repeated, with complete congruence.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as median (interquartile range (IQR; 25th to 75th percentiles) for continuous variables. Mann-Whitney U test and Kruskal-Wallis test were used, respectively, to compare differences between 2 and 3 or more independent groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Deviation from Hardy-Weinberg equilibrium and differences in allele distributions between the two groups were assessed by χ^2- test with 1 degree of freedom (df). A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

The frequencies of the AA, AC and CC genotypes of the *AGTR1* rs5186 SNP (the A1166C variant) in the groups of Yakuts, Evens, and Yukaghirs corresponded to the HWE. In the Chukchi group, which was represented by 34 participants, the distribution of the genotype frequency was not in the HWE (Table 1).

The frequency 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 the C allele carriage averages 0.28 (n=238604), varying, depending on population, from 0.009 among Africans (n=354) to 0.30 among Hispanics (n=6874). Among the populations of Southeast Asia, the prevalence of the C allele is 0.08–0.09.[21] 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 populations of Southeast Asia and Africa.

We did not find statistically significant differences in the frequency distribution of the alleles and genotypes of the *AGTR1* rs5186 SNP between the Case group and the Control group (Table 2).

In research literature, the data on the link between the AGTR1 rs5186 SNP and essential hypertension is contradictory.[17,18,22-25] Regarding China, a comparison of three genetically different populations with significant differences in the prevalence of EHT suggested that the A allele may

Table 1.

The frequency distribution of the alleles and genotypes of the AGTR1 rs5186 SNP (the A1166C variant) in the groups of Yakuts. Evens. and Yukaghirs

Allele /Genotype	Indicator	Yakuts (n=56)	Evens (n=184)	Chukchi (n=34)	Yukaghirs (n=77)	Total (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)
χ^2 (HWE)		0.019	8.08	10.1	0.179	1.284
P-value		0.892	0.99	0.001	0.673	0.257

Table 2.

The frequency distribution of the alleles and genotypes of the AGTR1 rs5186 SNP (the A1166C variant) between the Case group and the Control group

Ethnos	Group	Allele/Genotype, n (%)			OR (95% CI); *P*-value
		A	C		
Yakuts	EHT-	31 (77.5)	9 (22.5)		0.76 (0.29-1.97); *P*=0.750
	EHT+	59 (81.9)	13 (18.1)		
Evens	EHT-	176 (87.1)	26 (12.9)		0.98 (0.53-1.8); *P*=1.0
	EHT+	145 (87.3)	21 (12.7)		
Chukchi	EHT-	29 (65.9)	15 (34.1)		1.16 (0.41-3.27); *P*=0.988
	EHT+	15 (62.5)	9 (37.5)		
Yukaghirs	EHT-	59 (73.8)	21 (2.2)		0.84 (0.40-1.75); *P*=0.776
	EHT+	57 (77.0)	17 (23.0)		
All groups	EHT -	295 (80.6)	71 (19.4)		0.90 (0.62-1.32); *P*=0.600
	EHT+	276 (82.1)	60 (17.9)		
		AA	AC	CC	
Yakuts	EHT-	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
	EHT+	24 (66.7)	11 (30.6)	1 (2.8)	
Evens	EHT-	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
	EHT+	63 (75.9)	19 (22.9)	1 (1.2)	
Chukchi	EHT-	7 (31.8)	15 (68.2)		AA and AC: 1.40 (0.29-6.83); *P*=0.982
	EHT+	3 (25.0)	9 (72.0)		
Yukaghirs	EHT-	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
	EHT+	21 (56.8)	15 (40.5)	1 (2.7)	
Total	EHT-	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
	EHT+	111 (66.1)	54 (32.1)	3 (1.8)	

be a predisposing factor for EHT in Tibetan men, while no association was found in the other two populations.[22] In a case-control study conducted in Poland (250 patients with stable EHT and 150 individuals with normal BP), the C allele and CC genotype were statistically significantly more frequent in patients with hypertension.[25] In a similar study conducted in India, individuals with the CC genotype were 2.4 times more likely to develop EHT (P=0.0001) than individuals with the AC and AA genotypes.[23] At the same time, in the study by Suita, conducted in Japan, involving 1492 hypertensive subjects and 2426 normotensive subjects, no association was found between the A1166C variants of the *AGTR1* gene and hypertension.[24] Similar results were obtained by researchers in Tunisia.[26]

The *AGTR1* A1166C polymorphism was found to be linked to the presence and severity of nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver fibrosis, dyslipidemia, insulin resistance, and metabolic syndrome.[27-30] Considering the above data, in our analysis, the carriers of the A allele and C allele were compared in terms of the level of metabolic parameters (Table 3). The carriers of different alleles and genotypes were comparable in age and gender structure. We did not find any differences in BP levels between carriers of different genotypes. It should be noted that the levels of SBP and DBP were compared for all study participants, including those taking antihypertensive drugs, which could change the results obtained.

Table 3.

Comparison of age and metabolic parameters in carriers of different alleles and genotypes of the A1166C polymorphism of the AT1R gene

Indicator	Me (Q_1-Q_3)			*P*-value
	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, mmHg	130.0 (120.0-150.0)		130.0 (35.0-150.0)	0.337
DBP, mmHg	80.0 (80.0-90.0)		80.0 (35.0-90.0)	0.347
FPG, mmol/	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-C, mmol/l	1.2 (1.0-1.5)		1.4 (35.0-1.5)	0.011
LDL-C, mmol/l	3.2 (2.7-3.7)		3.0 (35.7-3.7)	0.122
VHDL-C, mmol/l	0.4 (0.3-0.6)		0.4 (35.3-0.6)	0.069
IA	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, mmHg	130.0 (120.0-150.0)	130.0 (37.0-150.0)	120.0 (117.5-145.0)	0.565
DBP, mmHg	80.0 (80.0-90.0)	80.0 (37.0-90.0)	80.0 (77.5-90.0)	0.569
FPG, 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-C, mmol/l	1.2 (1.0-1.5)	1.3 (37.1-1.5)	1.4 (1.2-1.6)	0.027
LDL-C, mmol/l	3.2 (2.7-3.7)	3.0 (37.6-3.7)	3.1 (2.6-3.6)	0.261
VHDL-C, mmol/l	0.4 (0.3-0.7)	0.4 (37.3-0.7)	0.4 (0.3-0.5)	0.170
IA	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, mmHg	130.0 (120.0-150.0)		130.0 (120.0-150.0)	0.405
DBP, mmHg	80.0 (80.0-90.0)		80.0 (80.0-90.0)	0.292
FPG, 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-C, mmol/l	1.2 (1.0-1.5)		1.3 (1.1-1.5)	0.007
LDL-C, mmol/l	3.2 (2.7-3.7)		3.0 (2.6-3.7)	0.102
VHDL-C, mmol/l	0.4 (0.3-0.7)		0.4 (0.3-0.7)	0.065
IA	3.0 (2.2-4.0)		2.7 (2.0-4.0)	0.010

Carriers of the A allele and AA genotype were characterized by a statistically significantly larger WC, lower HDL-C level, and high values of the atherogenic index (Table 3). In carriers of the AC+CC genotypes, the identified features persisted.

We found a significantly higher incidence of decreased HDL-C level in carriers of the A allele than in carriers of the C allele (38.1% vs. 27.7%, P=0.026), and a higher incidence in AA carriers than in carriers of the AC and CC genotypes (40.5%, 28.6%, 22.2%, respectively; P=0.005).

The HDL-C level did not correlate with the age of the subjects (r=-0.07, P=0.076). No correlation was found between the HDL-C level and SBP (r=-0.06, P=0.113), DBP (r=-0.09, P=0.013), FPG (r=-0.07, P=0.069), LDL-C (r=-0.03, P=0.412). Negative correlations were found between the HDL-C level and WC (r=-0.26, P<0.001) and TG levels (r=-0.58, P<0.001). The revealed differences in the HDL-C levels in carriers of different genotypes and alleles of the *AGTR1 A1166C* polymorphism were associated with differences in WC.

Conclusion

The obtained data show no association of the *AGTR1* A1166C polymorphism with EHT in the representatives of indigenous people of the Arctic territory of Yakutia. The limitations of the study were: the small number of groups and the inability to conduct 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 would be possible by using the hospital population as "cases," excluding the secondary nature of hypertension

Competing Interests

The authors declare that they have no competing interests.

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