

RESEARCH ARTICLE

Open Access



Genetic forms and pathophysiology of essential arterial hypertension in minor indigenous peoples of Russia

Tatyana Mulerova, Evgenya Uchasova*, Michael Ogarkov and Olga Barbarash

Abstract

Background: To study the genetic forms and pathophysiology of arterial hypertension by evaluating plasma renin activity in the Shors, minor indigenous peoples inhabiting the south of Western Siberia.

Methods: A single-stage study of indigenous (the Shors) and non-indigenous peoples living in the villages of Gornaya Shoria of the Kemerovo region in the south of Western Siberia was conducted in the period from 2013 to 2017. One thousand four hundred nine adults (901 Shors and 508 non-indigenous inhabitants) were recruited in the study using a continuous sampling plan. Arterial blood pressure was measured according to 2018 ESC/ESH guidelines for the management of arterial hypertension. All the respondents underwent clinical and instrumental examination. Plasma renin activity was determined by enzyme-linked immunoassay with the BRG kits (Germany). Polymorphisms of *ACE* (I/D, rs 4340), *AGT* (c.803 T > C, rs699), *AGTR1* (A1166C, rs5186), *ADRB1* (c.145A > G, Ser49Gly, rs1801252) and *ADRA2B* (I/D, rs 28,365,031) genes were tested using polymerase chain reaction.

Results: Renin-dependent hypertensive patients prevailed in both ethnic groups (65.6% in the indigenous group vs. 89.8% in the non-indigenous group, $p = 0.001$). Prevalence of a volume-dependent AH was low in both groups (34.4% in the indigenous group vs. 10.2% in the non-indigenous group, $p = 0.001$). The D/D and T/T genotypes of the *ACE* [OR = 6.97; 95% CI (1.07–55.58)] and *AGT* [OR = 3.53; 95% CI (1.02–12.91)] genes were associated with the renin-dependent AH in the Shors. The C/C genotype of *AGTR1* gene was found to predispose to the volume-dependent AH [OR = 5.25; 95% CI (1.03–27.89)]. The C/C genotype of *AGTR1* gene was associated with moderate or high renin levels suggesting essential AH in the non-indigenous group [OR = 5.00; 95% CI (1.21–22.30), $p = 0.029$].

Conclusion: An in-depth understanding of AH pathophysiology and its genetic forms ensures the optimal choice of blood pressure-lowering treatment and optimizes AH control.

Keywords: Arterial hypertension, Pathophysiology, Genetic forms, Plasma renin activity, Ethnic groups

* Correspondence: evg.uchasova@yandex.ru

Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Diseases", 6, Sosnoviy Blvd, 650002 Kemerovo, Russia



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Essential arterial hypertension (AH) is one of the most prevalent modifiable cardiovascular risk factor worldwide. Its monitoring and effective control is a global goal focused on reducing morbidity and mortality of cardiovascular diseases [1].

The interaction of the sympathoadrenal system (SAS) and the renin-angiotensin-aldosterone system (RAAS) plays a major role in blood pressure (BP) control in the human body. Both, RAAS and SAS, are multifunctional players in AH that are closely related with each other. Increased SAS activity enhances the renin synthesis in the juxtaglomerular cells through renal sympathetic nerves activated by intrarenal β 1-adrenoreceptors and circulating catecholamine stimulation [2]. Renin is a proteolytic enzyme that catalyzes the first step in the activation of the RAAS cascade and the subsequent production of angiotensin II, the main effector molecule of the RAAS [3].

Systemic RAAS activation occurs with elevated plasma renin activity (PRA) which is generally considered to reflect the level of renin activity [4]. It has a direct vasoconstrictive effect that may promote the development of AH associated with medium to high renin levels (a renin-dependent AH). However, low levels of renin may be also associated with AH. An increased salt intake induces a rise in plasma sodium leading an increase in extracellular fluid volume and resulting in a volume-dependent AH [5].

The genetic contribution to the onset of arterial hypertension have been recently discussed. Extensive research has been performed on the analysis of pathophysiological mechanisms, gene polymorphisms and gene expression levels associated with increased BP. Current evidence suggests that gene polymorphisms encoding components of the RAAS play an important role in the onset of essential AH. Angiotensin converting enzyme is a central component of the RAAS. The ACE gene is located on long arm of chromosome 17 (17q23). More than two dozen ACE gene polymorphisms have been reported so far. However, the I/D polymorphism which is distinguished by the insertion or deletion of an Alu element within intron 16 is considered as the most significant. The angiotensinogen gene (*AGT*) is located on chromosome 1 q42–43. Several *AGT* polymorphisms have been described, particularly that with the thymine nucleotide (T) replaced with cytosine (C) in the coding region of the gene (c.803 T > C, rs699). It leads to the substitution of threonine to methionine at position 235 (Met235Thr). This substitution changes the properties of angiotensinogen. Angiotensinogen II receptor type 1 (*AGTR1*) plays an important role in the pathogenesis of AH. It is located on long arm of chromosome 3 (3q21–25). About 20 polymorphisms of this gene have been

described. The most well studied *AGTR1* SNP is rs5186 (also referred as A1166C). It has been previously shown that a single-nucleotide polymorphism in the 3' untranslated region leads to the transversion of adenine to cytosine at position 1166. The effects of SAS on the cardiovascular system is mediated through adrenoceptors. The chronotropic and inotropic effects of the SAS on the cardiac function are manifested through β 1-adrenoceptors. The role of two major genes (*ADRB1* and *ADRA2B*) in the development of hypertension has been also discussed.

Hence, candidate genes play a special role in the pathogenesis of AH. They determine the synthesis of angiotensin-converting enzyme (*ACE*), angiotensinogen (*AGT*), angiotensinogen II receptor type 1 (*AGTR1*), β 1-adrenoreceptor (*ADRB1*), α 2 β -adrenoreceptor (*ADRA2B*) [6, 7]. These gene products are involved in the regulation of BP, electrolyte and fluid balance and the activation of sympathetic nervous system and functional capacities of the body. Nevertheless, the effects of polymorphisms in candidate genes on the levels of circulating factors of the RAAS and predominantly PRA remain unclear [8]. They are of particular concern for minor indigenous peoples that might have slightly different physiological mechanisms of adaptation, morphological and functional features.

Thus, measurements of PRA coupled with a comprehensive assessment of the genetic contribution to the onset of essential AH may provide new insights into the understanding of the interaction of these mechanisms and their role in the disease onset.

Purpose

Our study was aimed at evaluating the genetic contribution to the onset of pathophysiological arterial hypertension by measuring plasma renin activity in the Shors, minor indigenous peoples living in the south of Western Siberia.

Methods

A single-stage study of indigenous (the Shors) and non-indigenous population living in the villages of Gornaya Shoria of the Kemerovo region in the south of Western Siberia was performed in the period from 2013 to 2017. The Shors are minor indigenous peoples of the South-Siberian Mongoloid race. Using a continuous sampling method, 1409 adults (901 Shors and 508 non-indigenous inhabitants) were recruited into the study. The ethnic groups were comparable of gender and age. The recruitment of study participants was supported and facilitated by the local government. All participants gave written informed consent in accordance with the declaration of Helsinki. Respondents participating in the study were fully informed about the research objectives. Each participant received a unique identification number. The

study design was approved by the Local Ethics Committee of the Federal State Budgetary Institution “Research Institute for Complex Issues of Cardiovascular Diseases” (Kemerovo, Russian Federation). The clinical examination included medical history review and collection, physical exam and a visit to a cardiologist.

Arterial blood pressure was measured in accordance with 2018 ESC/ESH guidelines for the management of arterial hypertension by an Omron automatic tonometer (Japan). Arterial hypertension was defined as a systolic blood pressure of 140 mmHg or more, a diastolic blood pressure of 90 mmHg or more, and / or taking antihypertensive medication. Patients with AH were allocated from each ethnic cohort (367 participants (40.7%) among the Shors and 230 subjects (45.3%) among non-indigenous population). Two hundred fifty-five participants (69.5%) out of 367 Shors did not take any antihypertensive medication just as 115 non-indigenous participants (50.0%). Main clinical and demographic data of hypertensive and non-hypertensive participants depending on the ethnic group are presented in Tables 1 and 2.

PRA was measured in all participants who did not receive any antihypertensive medication (255 Shors participants and 115 non-indigenous participants). Of them, 1.6% of the Shors and 5.8% of non-indigenous participants

had the estimated glomerular filtration rate below 60 ml/min/1.73 m², 21.0 and 30.1% - below 90 ml/min/1.73 m², and 77.4 and 64.1% - \geq 90 ml/min/1.73 m², respectively.

The morning after an overnight fast, venous blood samples were withdrawn from the cubital vein in all patients. Blood samples were centrifuged; serum was frozen and banked for analysis at deep freeze temperature. Samples were delivered to the laboratory in the liquid nitrogen containers avoiding thawing. PRA was measured by enzyme-linked immunoassay using the BRG kits (Germany). The upper limit of the reference range of renin level in healthy people in an upright position is 47.85 pg/ml. Therefore, all hypertensive participants were subdivided into 2 groups. Patients with plasma renin levels over 47.85 pg/ml were assigned to Group 1 and patients with plasma renin levels below or equal to 47.85 pg/ml were assigned to Group 2. The onset of AH in Group 1 patients was associated with the excessive renin release and the subsequent RAAS activation, whereas in Group 2 patients it was associated with the suppression of renin release and sodium retention in the body.

Polymorphisms of *ACE* (I/D, rs4340), *AGT* (c.803 T > C, rs699), *AGTRI* (A1166C, rs5186), *ADRB1* (c.145A > G, Ser49Gly, rs1801252) and *ADRA2B* (I/D, rs28365031) genes were tested using polymerase chain reaction. The

Table 1 Characteristic of patients with AH among the population of Mountain Shoria taking into account the ethnic peculiarities

Indicator	Indigenous population			Non-indigenous population			P (1 VS 3)
	AH	Without AH	p	AH	Without AH	p	
	1	2		3	4		
Age, years, M \pm SD	59.0 \pm 12.3	42.3 \pm 13.4	0.000	59.4 \pm 11.6	41.5 \pm 14.5	0.000	0.700
Height, cm, M \pm SD	155.3 \pm 7.7	157.7 \pm 8.2	0.000	161.3 \pm 9.5	163.9 \pm 8.4	0.001	0.0001
Weight, kg, M \pm SD	64.8 \pm 13.5	60.2 \pm 12.7	0.000	80.5 \pm 18.0	72.0 \pm 20.6	0.000	0.0001
Smoking, n(%)	95(25.9)	201(37.6)	0.001	53(23.0)	113(40.7)	0.000	0.434
BMI, kg/m ² , M \pm SD	26.9 \pm 5.5	24.2 \pm 4.7	0.000	30.9 \pm 6.4	27.1 \pm 6.3	0.000	0.0001
BMI \geq 30 kg/m ² , n(%)	101(27.5)	61(11.4)	0.000	123(53.5)	72(25.9)	0.000	0.0001
WC, cm, M \pm SD	88.0 \pm 12.2	80.3 \pm 11.4	0.000	97.6 \pm 15.2	85.0 \pm 14.7	0.000	0.0001
WC \geq 80 cm in women and \geq 94 cm in men, n(%)	136(37.1)	102(19.1)	0.000	135(58.7)	82(29.5)	0.000	0.0001
SBP, mmHg, M \pm SD	158.1 \pm 20.4	117.7 \pm 11.6	0.000	150.3 \pm 19.0	119.7 \pm 10.7	0.000	0.0001
DBP, mmHg, M \pm SD	93.0 \pm 11.0	75.4 \pm 7.3	0.000	90.2 \pm 12.99	76.2 \pm 7.2	0.000	0.004
TC, mmol/l, M \pm SD	5.83 \pm 1.26	5.16 \pm 1.21	0.000	5.89 \pm 1.35	5.20 \pm 1.29	0.000	0.583
TC, mmol/l, n(%)	243(75.5)	230(51.7)	0.000	163(79.5)	127(58.3)	0.000	0.282
LDL-C, mmol/l, M \pm SD	3.50 \pm 1.08	2.93 \pm 1.05	0.000	3.53 \pm 1.02	3.18 \pm 1.22	0.004	0.766
LDL-C > 3.0 mmol/l, n(%)	175(63.2)	141(40.1)	0.000	124(70.5)	83(49.7)	0.001	0.111
HDL-C, mmol/l, M \pm SD	1.42 \pm 0.52	1.45 \pm 0.54	0.404	1.22 \pm 0.35	1.30 \pm 0.41	0.054	0.0001
HDL-C < 1.2 mmol/l in women, < 1.0 mmol/l in men, n(%)	76(27.5)	78(22.4)	0.135	79(45.1)	56(33.9)	0.035	0.0001
TG, mmol/l, M \pm SD	1.70 \pm 1.44	1.36 \pm 0.95	0.000	2.23 \pm 1.49	1.70 \pm 1.23	0.000	0.0001
TG > 1.7 mmol/l, n(%)	103(31.9)	99(22.3)	0.003	113(54.9)	75(34.4)	0.001	0.0001
Glucose, mmol/l, M \pm SD	5.86 \pm 1.77	5.35 \pm 0.94	0.000	6.14 \pm 1.89	5.31 \pm 0.82	0.000	0.108

BMI Body mass index, *WC* Waist circumference, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *TC* Total cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *HDL-C* High-density lipoprotein cholesterol, *TG* Triglycerides

Table 2 Characteristic of patients with R-D AH and V-D AH among the population of Mountain Shoria taking into account the ethnic peculiarities

Indicator	R-D AH			V-D AH		
	Indigenous population	Non-indigenous population	p	Indigenous population	Non-indigenous population	p
Age, years, M ± SD	55.8 ± 14.0	60.3 ± 11.4	0.003	61.9 ± 11.7	58.4 ± 12.1	0.089
Height, cm, M ± SD	156.0 ± 7.4	160.6 ± 9.2	0.000	154.8 ± 7.8	162.2 ± 9.8	0.000
Weight, kg, M ± SD	64.9 ± 13.2	81.2 ± 17.2	0.000	64.8 ± 13.6	79.7 ± 20.0	0.000
Smoking, %	30.5	22.3	0.088	23.9	25.3	0.791
BMI, kg/m ² , M ± SD	26.7 ± 5.4	31.5 ± 6.2	0.000	27.2 ± 5.6	30.3 ± 7.1	0.000
BMI ≥ 30 kg/m ² , %	24.6	56.6	0.000	28.9	48.0	0.002
WC, cm, M ± SD	89.2 ± 12.1	99.4 ± 14.9	0.000	87.3 ± 12.2	94.5 ± 15.3	0.000
WC ≥ 80 cm in women and ≥ 94 cm in men, %	43.0	63.3	0.000	34.2	50.7	0.010
SBP, mmHg, M ± SD	154.6 ± 20.1	147.8 ± 20.8	0.038	162.7 ± 20.5	152.4 ± 16.5	0.000
DBP, mmHg, M ± SD	90.3 ± 11.4	88.6 ± 13.8	0.292	95.9 ± 10.8	91.4 ± 11.7	0.044
TC, ммоль/л, M ± SD	5.70 ± 1.16	5.93 ± 1.46	0.182	5.88 ± 1.30	5.79 ± 1.13	0.101
TC, mmol/l, %	73.4	78.9	0.191	77.7	79.5	0.627
LDL-C, mmol/l, M ± SD	3.45 ± 1.10	3.59 ± 1.08	0.284	3.55 ± 1.07	3.47 ± 0.83	0.344
LDL-C > 3.0 mmol/l, %	58.3	70.8	0.056	66.1	69.9	0.920
HDL-C, mmol/l, M ± SD	1.39 ± 0.53	1.24 ± 0.37	0.008	1.44 ± 0.51	1.18 ± 0.26	0.002
HDL-C < 1.2 mmol/l in women, < 1.0 mmol/l in men, %	32.3	44.4	0.059	24.9	46.8	0.004
TG, mmol/l, M ± SD	1.69 ± 1.22	2.23 ± 1.47	0.010	1.71 ± 1.52	2.23 ± 1.48	0.014
TG > 1.7 mmol/l, %	32.9	53.4	0.000	31.0	55.5	0.000
Glucose, mmol/l, M ± SD	5.66 ± 1.63	6.32 ± 2.16	0.028	5.92 ± 1.81	5.79 ± 0.92	0.425

V-D AH Volume-dependent arterial hypertension, R-D AH Renin-dependent arterial hypertension, BMI Body mass index, WC Waist circumference, SBP Systolic blood pressure, DBP Diastolic blood pressure, TC Total cholesterol, LDL-C Low-density lipoprotein cholesterol, HDL-C High-density lipoprotein cholesterol, TG Triglycerides

detailed description of the laboratory protocol was previously described in [9].

The statistical analysis was performed using the commercially available Statistica 6.0 (StatSoft Inc., USA) software. The normality of the distribution was tested using the Kolmogorov-Smirnov test. Continuous variables are presented as the mean and the standard deviation (M ± SD). Categorical variables are presented as the frequencies or the percentages. For categorical variables, the weights were calculated to eliminate any possible biases. To estimate the statistical significance of the differences between categorical variables, contingency tables were generated with the subsequent calculation of Pearson's chi-squared test. Logistic regression adjusted to the age and gender was used to determine the presence of any relationships between the genetic factors and pathophysiological forms of AH. Odds ratios (OR) and 95% confidence intervals (CI) were estimated.

Results

The overall prevalence of AH in Gornaya Shoria was 42.4%. Out of 42.4, 40.7% cases were found among the Shors and 45.3% among the non-indigenous participants ($p = 0.098$). The renin-dependent AH was more commonly found in

both ethnic groups as compared to the volume-dependent AH (65.6% vs 34.4% ($p = 0.001$) among the indigenous group and 89.8% vs 10.2% ($p = 0.001$) among the non-indigenous group).

The mean renin level was lower (86.1 ± 65.4 pg/ml) in the hypertensive Shors than that in non-indigenous participants (115.9 ± 73.9 pg/ml, $p = 0.0001$). In addition, the defined differences between the ethnic groups in the mean renin values were consistent with the differences of the polymorphisms in candidate genes encoding the components of the RAAS and SAS. Thus, the Shors who were the carriers of the I/D, A/A and D/D genotypes of the *ACE*, *ADRB1* and *ADRA2B* genes had lower renin levels (73.9 ± 53.0 pg/ml, 80.7 ± 52.3 pg/ml and 99.2 ± 64.6 pg/ml), compared with non-indigenous participants who had the same genotypes – 111.6 ± 71.0 pg/ml ($p = 0.010$), 116.1 ± 65.3 pg/ml ($p = 0.004$) and 161.5 ± 89.4 pg/ml ($p = 0.0001$), respectively. Moreover, the D/D genotype of *ACE* gene among the Shors was associated with the highest renin levels (125.0 ± 71.3 pg/ml) as compared to those who were the carriers of the I/D genotype (73.9 ± 53.0 pg/ml, $p = 0.004$) and the I/I genotype (87.1 ± 57.0 pg/ml, $p = 0.030$). A similar pattern was determined for *ADRA2B* gene polymorphism: the indigenous participants who were the

carriers of the minor D allele in the homozygous state had a higher renin level as compared to participants with the I/D genotype (99.2 ± 64.6 pg/ml vs. 62.3 ± 30.4 pg/ml, $p = 0.011$). Non-indigenous participants carrying the homozygous D/D genotype of *ADRA2B* gene demonstrated a higher renin level as compared to the carriers of the I/I genotype (161.5 ± 89.4 pg/ml vs. 106.7 ± 58.0 pg/ml, respectively, $p = 0.047$).

Table 3 summarizes the frequency distribution of the genotypes of candidate genes encoding the components of the RAAS and SAS among participant from different ethnic groups. Renin-dependent and volume-dependent AH were encoded by different genes based on participants' ethnicity.

The frequency of the D/D genotype of *ACE* gene prevailed among the Shors with renin-dependent AH than among the Shors with volume-dependent AH (21.1% vs. 3.8%, $p = 0.035$). The T/T genotype (rs699) of *AGT* gene was commonly found among hypertensive participants with increased renin levels than among participants with low-renin AH (46.9% vs. 20.0%, $p = 0.046$). Thus, the D/D and T/T genotypes of *ACE* and *AGT* genes were

Table 3 Genotype frequency of candidate genes (*ACE*, *AGT*, *AGTR1*, *ADRB1*, *ADRA2B*) in the indigenous population and non-indigenous population of Mountain Shoria with various pathophysiological forms of AH

Genotype	Indigenous population			Non-indigenous population		
	V-D AH	R-D AH	p	V-D AH	R-D AH	p
Gene <i>ACE</i> , rs4340						
I/I	44.4	42.3	0.719	22.2	29.6	0.534
I/D	51.8	36.6	0.130	44.4	53.7	0.829
D/D	3.8	21.1	0.035	33.3	16.7	0.321
Gene <i>AGT</i> , rs699						
T/T	46.9	20.0	0.046	45.4	47.0	0.812
T/C	31.2	40.0	0.480	27.3	17.7	0.283
C/C	21.9	40.0	0.177	27.3	35.3	0.529
Gene <i>AGTR1</i> , rs5186						
A/A	65.6	55.6	0.426	35.7	19.2	0.229
A/C	28.1	18.5	0.261	42.9	23.1	0.112
C/C	6.3	25.9	0.041	21.4	57.7	0.029
Gene <i>ADRB1</i> , rs1801252						
A/A	59.2	63.0	0.621	50.0	72.9	0.108
A/G	33.8	25.9	0.371	50.0	22.9	0.059
G/G	7.0	11.1	0.520	0.0	4.2	0.582
Gene <i>ADRA2B</i> , rs28365031						
I/I	23.9	50.0	0.115	29.6	50.0	0.104
I/D	53.5	31.3	0.163	37.0	31.3	0.886
D/D	22.6	18.7	0.287	33.4	18.7	0.098

V-D AH Volume-dependent arterial hypertension, R-D AH Renin-dependent arterial hypertension

associated with the renin-dependent AH in the indigenous group [OR = 6.97; 95% CI (1.07–55.58)] and [OR = 3.53; 95% CI (1.02–12.91)]. The minor C/C genotype of *AGTR1* gene was associated with the volume-dependent AH. The odds ratios increased 5-fold to determine the volume-dependent AH in the C/C genotype carriers as compared to the A/A and A/C genotype carriers [OR = 5.25; 95% CI (1.03–27.89)]. The prevalence of the mutant allele C in the homozygous state among volume-dependent AH participants was 25.9 and 6.3% among renin-dependent AH participants ($p = 0.041$).

The presence of *AGTR1* gene polymorphism was associated with the onset of AH in the non-indigenous group. The frequency of C/C genotype of this gene was higher among patients with renin-dependent AH (57.7%) as compared to patients with volume-dependent AH (21.4%) [OR = 5.00; 95% CI (1.21–22.30), $p = 0.029$].

Discussion

Measuring PRA gives an opportunity to determine one of two underlying mechanisms responsible for the onset of AH [3]. Egan et al. (2009) have previously demonstrated the significance of PRA estimation in patients with AH [10]. Unfortunately, this method has not got a wide application in the Russian Federation.

Our data from the epidemiological study in Gronaya Shoria are consistent with recent evidences that have proved that two-thirds of patients have renin-dependent AH, while the others are present with volume-dependent AH [11, 12]. Renin-dependent AH prevailed in both ethnic groups. Given similar prevalences of AH in the study groups, the mean renin level was lower among the Shors than among non-indigenous participants. This pattern may be explained by the presence of other mechanisms increasing blood pressure among minor indigenous peoples in addition to the RAAS and SAS. The Shors consume more alcohol, which is considered as a risk factor for hypertension. The indigenous group consumed more alcohol than the non-indigenous group (43.5% vs. 18.8%, $p = 0.005$). The Shors people are hunter-gatherers who spend a lot of time in the Taiga (so-called Russian forest in Siberia) eating food with excessive salt content. This nutrition pattern contributes to the elevation of blood pressure. Our data were consistent with the data reported by Akintunde et al. (2018), who found that the Caucasians had a higher renin activity as compared to people from other ethnic groups [13].

The genetic contribution to the onset of AH is beyond doubt [14]. However, the studies describing the effects of the alleles of the candidate genes of the RAAS and SAS on the development of various pathophysiological types of AH are still limited. In 1999, Francke et al. [15] focused at assessing the presence of the associations between the polymorphisms of 5 genes involved in AH

pathogenesis (angiotensin converting enzyme, kallikrein, angiotensinogen, angiotensin II type I receptor and renin) and salt sensitivity. The obtained data suggested that the volume-dependent AH was associated with the I/D polymorphism of *ACE* gene (D-allele). Kato et al. and Giner et al. determined the association of the *ACE* gene with BP increase in response to salt intake in patients with AH [16, 17]. The study on the Japanese cohort reported the presence of the association between the onset of the volume-dependent AH and the I/I genotype of the *ACE* gene [18]. In our study, we found the association of the D/D genotype of *ACE* gene with renin-dependent AH in the Shors. Therefore, the treatment effectiveness for hypertensive patients carrying the mutant allele D may be optimized through the medications inhibiting the RAAS (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors).

We have previously shown that the minor allele C of *AGTR1* gene was associated with AH in both ethnic groups [19]. Many studies have demonstrated a positive association of the C allele of *AGTR1* gene with AH [20–22]. A recent meta-analysis of published studies with 28,952 patients allowed identifying the association between the polymorphism of *AGTR1* gene with the increased risk of AH in the Asians and the Caucasians [22]. The carriers of C/C genotype among the Egyptians showed more severe complications of this disease [23]. However, there are no data suggesting the relationship of the polymorphism of this gene with PRA. In our study, we identified that the C/C genotype was associated with the development of various pathophysiological forms of AH in the individuals from different ethnic groups. The C/C genotype of *AGTR1* in the Shors was associated with the development of the volume-dependent AH, whereas in the non-indigenous group with the renin-dependent AH.

Conclusion

The measurement of PRA plays the key role in the evaluation of AH underlying pathology based on the understanding of the interaction between the RAAS and the mechanism of maintaining the fluid balance in the body through kidney sodium reabsorption and fluid retention. Our results allow identifying the genetic markers indicative for pathophysiological variant of AH. The D/D and T/T genotypes of the *ACE* and *AGT* candidate genes were associated with renin-dependent AH and the C/C genotype of *AGTR1* gene with the volume-dependent AH in the Shors. Alternatively, the C/C genotype of *AGTR1* gene was associated with the renin-dependent AH in non-indigenous participants. An in-depth understanding of the pathophysiological mechanism underlying AH and genetic contribution may facilitate the choice of antihypertensive medication and optimize the treatment of this disease.

Abbreviations

ACE: Angiotensin-converting enzyme candidate gene; *ADRA2B*: $\alpha 2\beta$ -adrenoreceptor candidate gene; *ADRB1*: $\beta 1$ -adrenoreceptor candidate gene; *AGT*: Hypertensinogen candidate gene; *AGTR1*: Angiotensinogen II receptor type 1 candidate gene; AH: Arterial hypertension; BMI: Body mass index; BP: Blood pressure; CI: Confidence interval; DBP: Diastolic blood pressure; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; OR: Odds ratio; PRA: Plasma renin activity; RAAS: Renin-angiotensin-aldosterone system; R-D AH: Renin-dependent arterial hypertension; SAS: Sympathoadrenal system; TC: Total cholesterol; SBP: Systolic blood pressure; TG: Triglycerides; V-D AH: Volume-dependent arterial hypertension; WC: Waist circumference

Acknowledgements

The authors wish to thank Elena Semibratova for assistance in writing this article.

Authors' contributions

TM: principal investigator, study coordinator, and investigator, participated in all stages of recruitment of the patients and in analysis of the data, and drafted and critically reviewed the manuscript. EU: drafted and critically reviewed the manuscript. MO and OB: were principal investigators. All authors have read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The Ethics Committee restricts access to the original patient database that requests can be directed to them. Although the database is not available, we can provide anonymous patient data at a reasonable to the appropriate author.

Ethics approval and consent to participate

All study was carried out in compliance with the Helsinki Declaration, and its protocol was approved by the Ethical Committee of Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Diseases" (extract from the protocol №10 of July 10, 2015) and all patients participated in the study gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 8 July 2019 Accepted: 2 April 2020

Published online: 15 April 2020

References

- Kaveshnikov VS, Serebryakova VN, Trubacheva IA. Factors associated with the prevalence of arterial hypertension in the general working age population. *Complex Issues Cardiovasc Dis*. 2018;7(4):6–14. <https://doi.org/10.17802/2306-1278-2018-7-4-6-14>.
- Castrop H, Hocherl K, Kurtz A, et al. Physiology of kidney renin. *Physiol Rev*. 2010;90:607–73. <https://doi.org/10.1152/physrev.00011.2009>.
- Laragh JH, Sealey JE. The plasma renin test reveals the contribution of body sodium volume content (V) and renin-angiotensin (R) vasoconstriction to long-term blood pressure. *Am J Hypertens*. 2011;24:1164–80. <https://doi.org/10.1038/ajh.2011.171>.
- Kravtsova OA, Kotovskaya YV, Kobalava ZD. Characteristics of the renin profile of patients with untreated arterial hypertension and its association with the parameters of arterial stiffness. *Vestnik RUDN*. 2014;2:42–5.
- Kotovskaya YV, Kravtsova OA, Pavlova EA. Determination of plasma renin activity as a strategy for selecting and modifying antihypertensive therapy. *Arterial Hypertens*. 2013;5:380–8 (Russian).
- Orlova NV, Sitnikov VF, Chukayeva II, et al. The study of the genetic causation of arterial hypertension as a risk factor for cardiovascular diseases. *Med Almanac*. 2011;16(3):81–4 (Russian).
- Martinez-Aguayo A, Fardella C. Genetics of hypertensive syndrome. *Horm Res*. 2009;71(5):253–9. <https://doi.org/10.1159/000208798>.

8. Lieb W, Chen MH, Teumer A, de Boer RA, et al. Genome-wide meta-analyses of plasma renin activity and concentration reveal association with the kininogen 1 and prekallikrein genes. *Circ Cardiovasc Genet*. 2015;8(1):131–40. <https://doi.org/10.1161/CIRCGENETICS.114.000613>.
9. Barbarash OL, Voevoda MI, Artamonova GV, Mulerova TA, et al. Genetic determinants of arterial hypertension in two national cohorts of mountain Shoria. *Therapeutic Archive*. 2017;89(9):68–77. (Russian). <https://doi.org/10.17116/terarkh201789968-77>.
10. Egan BM, Basile JN, Rehman SU, et al. Plasma renin test- guided drug treatment algorithm for correcting patients with treated but uncontrolled hypertension: a randomized controlled trial. *Am J Hypertens*. 2009;22:792–801.
11. Laragh JH. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. *Am J Hypertens*. 2001;14(12):733–42.
12. Obarzaneck E, Proschan MA, Vollmer WM, et al. Individual blood pressure responses to changes in salt intake. Results from the DASH-sodium trial. *Hypertension*. 2003;42(4):459–67.
13. Akintunde AA, Salawu AA, Oloyede T, Adeniyi DB. Renin activity and aldosterone assay among Nigerians with hypertension and Normotension: an insight into normative values and clinical correlates. *Curr Hypertens Rev*. 2018;14(1):29–34. <https://doi.org/10.2174/1573402114666171213145049>.
14. Sanada H, Yatabe J, Midorikawa S, Hashimoto S, et al. Single-nucleotide polymorphisms for diagnosis of salt-sensitive hypertension. *Clin Chem*. 2006;52(3):352–60.
15. Francke S, Hager S, Frognel P, et al. Quantitative association study with five candidate genes for essential hypertension and salt-sensitivity in normotensive subjects. *Hypertension*. 1999;17(3):87.
16. Kato N, Kanda T, Sagara M, et al. Genetic analysis of candidate gene polymorphism in salt sensitive blood pressure increase. *Ibid*. 2002;20(4):16.
17. Giner V, Poch E, Oriola J, et al. Angiotensin converting enzyme (ACE) gene polymorphism and salt-sensitivity in essential hypertension. *Ibid*. 1999;17(3):171.
18. Hiraga H, Oshima T, Yoshimura M, et al. Polymorphic factors and salt five candidate genes for essential hypertension and salt-sensitivity in normotensive subjects. *Ibid*. 1999;17(3):87.
19. Mulerova TA, Ponasenko AV, Cepokina AV, Ogarkov MY. Polymorphism of the A1166C gene of the receptor type 1 to angiotensinogen (AGTR1) among the indigenous and non-indigenous people of mountain Shoriya. *Mod Probl Sci Educ*. 2017;3. <http://www.science-education.ru/article/view?id=26436>. (Russian).
20. Bayramoglu A, Kurt H, Gunes HV, et al. Angiotensin II type 1 receptor (AT1) gene A1166C is associated with the risk of hypertension. *Genet Test Mol Biomarkers*. 2015;19(1):71–4. <https://doi.org/10.1089/gtmb.2014.0233>.
21. Valencia DM, Naranjo CA, Parra MV, et al. Association and interaction of AGT, AGTR1, ACE, ADRB2, DRD1, ADD1, ADD2, ATP2B1, TBXA2R and PTGS2 genes on the risk of hypertension in Antioquian population. *Biomedica*. 2013;33(4):598–614.
22. Liu DX, Zhang YQ, Hu B, et al. Association of AT1R polymorphism with hypertension risk: an update meta-analysis based on 28,952 subjects. *J Renin-Angiotensin-Aldosterone Syst*. 2015;16(4):898–909. <https://doi.org/10.1177/1470320315584096>.
23. Niu W, Qi Y. Association of the angiotensin II type I receptor gene +1166 a>C polymorphism with hypertension risk: evidence from a meta-analysis of 16474 subjects. *Hypertens Res*. 2010;33(11):1137–43. <https://doi.org/10.1038/hr.2010.156>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

