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Polymorphism of genes involved in the regulation of blood pressure in elderly residents of the Arkhangelsk region

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ABSTRACT

BACKGROUND: Living in the northern climate is associated with increased cardiovascular stress, which highlights the necessity for the study of candidate genes associated with the risk of cardiovascular diseases in both the native population and newcomers. Polymorphic loci of the renin-angiotensin system, NO-synthase, and endothelin-1 system genes have been identified as contributors to cardiovascular dysfunction and age-related blood pressure shifts. It is therefore crucial to assess the genetic polymorphism in the elderly population.

AIM: To compare frequencies of gene alleles and genotypes involved in blood pressure regulation, including angiotensinogen *AGT* (rs699 and rs4762), angiotensin 2 type 1 receptor *AGTR1* (rs5186), angiotensin converting enzyme *ACE* (rs4646994), endothelial NO synthase *NOS3* and endothelin-1 *EDN1* (rs5370) genes, in the native and non-native elderly population of the Arkhangelsk region.

MATERIALS AND METHODS: A cross-sectional study was conducted in a random sample of Arkhangelsk residents between the ages of 60 and 74 years (N=604, with 36.4% of males). The molecular genetic analysis was conducted to determine the alleles and genotypes of six genes that are involved in blood pressure regulation. The Stata 18.0 software was used to assess the deviations of empirical genotype distributions from the predicted Hardy–Weinberg equilibrium and to compare the empirical distributions between the study groups.

RESULTS: Alleles associated with the risk of cardiovascular diseases were minor in the study population. The genotype frequency distributions for the analyzed genetic variants were consistent with the Hardy–Weinberg principle, with the exception of the T704C variant of the *AGT* gene (rs699) in the native participants. The allele and genotype frequency distributions in the study sample were found to be similar to those reported worldwide and in European Russia. One exception was *AGTR1* gene A1166C frequencies, with their 95% confidence intervals falling below the global level for both native and non-native elderly residents of the Arkhangelsk region. This may suggest that this allele is a selection variant associated with adaptation to the climate of the northern regions.

CONCLUSION: The genetic polymorphism in blood pressure regulation was found to be similar between the native and non-native populations of the Arkhangelsk region. However, the *AGTR1* gene A1166C frequency among the native population and newcomers was found to be lower than that observed globally.

Keywords: blood pressure; elderly; native population; genetic polymorphism.

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Полиморфизм генов, вовлечённых в регуляцию артериального давления, у пожилых жителей Архангельской области

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АННОТАЦИЯ

Обоснование. Проживание на Севере предъявляет повышенные требования к функционированию сердечно-сосудистой системы, что обусловливает необходимость изучения генов-кандидатов, связанных с риском развития сердечно-сосудистой патологии у коренных и пришлых жителей региона. Полиморфные локусы генов ренин-ангиотензиновой системы, NO-синтазы, системы эндотелина-1 участвуют в нарушениях нормального функционирования сердечно-сосудистой системы, изменяя с возрастом показатели артериального давления. По этой причине важно проводить оценку полиморфизма данных генов среди пожилых людей.

Цель. Сравнение частот аллелей генов и генотипов, вовлечённых в регуляцию артериального давления, включая гены ангиотензиногена *AGT* (rs699 и rs4762), рецептора 1 типа ангиотензина 2 *AGTR1* (rs5186), ангиотензин-превращающего фермента *ACE* (rs4646994), эндотелиальной NO-синтазы *NOS3* и эндотелина-1 *EDN1* (rs5370), у коренных и некоренных пожилых жителей Архангельской области.

Материал и методы. Проведено поперечное исследование с использованием случайной выборки жителей Архангельска в возрасте 60–74 лет (n=604, мужчины — 36,4%). Молекулярно-генетический анализ включал определение аллелей и генотипов шести генов, вовлечённых в регуляцию артериального давления. Оценка соответствия эмпирических распределений генотипов теоретически ожидаемым по равновесию Харди–Вайнберга и сравнение эмпирических распределений в группах производили в программном обеспечении Stata 18.0.

Результаты. Аллели, ассоциированные с риском развития сердечно-сосудистых заболеваний, в исследуемой популяции были минорными. Частотные распределения генотипов изучаемых вариантов нуклеотидной последовательности генов соответствовали закону Харди–Вайнберга, за исключением варианта T704C гена *AGT* (rs699) у коренных жителей. Не было выявлено значимых отклонений распределения частот аллелей и генотипов в изучаемой выборке от общемировых данных и от данных по жителям европейской части России, кроме частот аллеля 1166C гена *AGTR1*, 95% доверительные интервалы для которых у некоренных и коренных пожилых жителей Архангельской области находились ниже общемирового уровня. Это предположительно свидетельствует, что данный аллель является вариантом отбора, связанным с адаптацией к условиям Севера.

Заключение. Полиморфизм генов, вовлечённых в регуляцию артериального давления, не различался у коренных и некоренных жителей Архангельской области. Однако частоты встречаемости аллеля 1166C гена *AGTR1* среди коренных и некоренных жителей области были ниже в сравнении с общемировыми данными.

Ключевые слова: артериальное давление; пожилые люди; коренное население; полиморфизм генов.

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阿尔汉格尔斯克州老年居民中参与调节血压的基因多态性

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摘要

背景。北方地区的生活对心血管系统提出了更高的要求，因此有必要研究与心血管疾病风险相关的候选基因，这些基因涉及本地和非本地居民。肾素-血管紧张素系统、NO合酶和内皮素-1系统基因的多态性位点与心血管系统功能异常有关，并随着年龄增长影响血压变化。因此，对老年人群中这些基因的多态性进行评估非常重要。

研究目的。比较阿尔汉格尔斯克州本地和非本地老年居民中与血压调节相关基因的等位基因频率和基因型，包括血管紧张素原AGT基因（rs699和rs4762）、血管紧张素II 1型受体AGTR1基因（rs5186）、血管紧张素转化酶ACE基因（rs4646994）、内皮型NO合酶NOS3基因和内皮素-1 EDN1基因（rs5370）。

材料和方法。本研究为横断面研究，采用随机抽样法选取阿尔汉格尔斯克市60-74岁居民（N=604，其中男性占36.4%）。分子遗传学分析包括六个与血压调节相关基因的等位基因和基因型的检测。基因型分布的观察值与哈迪-温伯格平衡的理论预期值的适配性和组间观察分布的比较在Stata 18.0软件中完成。

结果。在研究人群中，与心血管疾病风险相关的等位基因为次要等位基因。除AGT基因的T704C位点（rs699）在本地居民中外，研究基因位点的基因型频率分布符合哈迪-温伯格平衡。阿尔汉格尔斯克州老年本地和非本地居民的等位基因和基因型频率分布与全球数据和俄罗斯欧洲地区居民数据无显著差异，但AGTR1基因1166C等位基因频率的95%置信区间在本地和非本地老年居民中低于全球水平。这可能表明该等位基因是与北方环境适应相关的选择性变体。

结论。阿尔汉格尔斯克州本地和非本地居民中调节血压的基因多态性没有显著差异。然而，AGTR1基因1166C等位基因的频率在该地区本地和非本地居民中均低于全球数据。

关键词：血压；老年人；本地居民；基因多态性。

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BACKGROUND

The global elderly population continues to grow. It is expected that the growth rate will be higher in the coming decades. These demographic changes prompt adaptation in various social sectors, including healthcare [1]. Age is a cardiovascular (primarily arterial hypertension) risk factor. Living in adverse environment is associated with increased cardiovascular stress. In high latitudes, where the Arkhangelsk Region is located, significant annual temperature fluctuations, photoperiodic features, changes in atmospheric pressure, and other factors have an adverse effect. It has been found that during the cold season, residents of the northern regions experience changes in systemic blood pressure (BP) and higher cardiovascular stress [2].

The population gene pool is developed historically based on socio-economic and environmental factors. In this regard, populations living in the northern climate for several generations are of particular interest versus the non-native population. In the Arkhangelsk Region, research was conducted to study the genomic polymorphism of native Caucasian populations [3], i.e. the mitochondrial DNA and the nuclear genome diversity, including variants of *GSTA1, GSTT1, TP53, DRD2*. As the conditions in the North European regions are associated with increased cardiovascular stress, it is important to study the prevalence of genetic cardiovascular risk markers in native and non-native populations of the region [3].

Genetic factors are also considered as cardiovascular risk factors. In particular, polymorphism of the renin-angiotensin system (RAS), NO synthase, and endothelin-1 system genes contributes to the development of hemodynamic disorders [4, 5]. There is evidence that the influence of polymorphic alleles of ASD genes and the *NOS3* gene on blood pressure, pulse pressure, and arterial stiffness manifests with age [6–8].

Most population studies investigating gene polymorphisms involve different age groups. Polymorphic genetic markers influence the quality and duration of life through adverse cardiovascular effects. It is therefore crucial to assess the frequency distribution of alleles and genotypes of polymorphic loci in the elderly population.

AIM: The study aimed to compare the frequencies of gene alleles involved in blood pressure regulation in the native and non-native elderly populations of the Arkhangelsk Region.

MATERIALS AND METHODS

A cross-sectional study was conducted in a random sample of the urban elderly population from May to October 2023. The participants were selected from Arkhangelsk residents included in the random population sample of the Know Your Heart study in 2015–2017. The sampling was made based on an anonymized database of addresses of city residents provided by the regional Mandatory Health Insurance Fund [9]. For this sample, random addresses of insured residents recorded in the mandatory health insurance system were selected; male and female residents were visited and invited to participate in the study.

The Know Your Heart study involved 2,381 residents of Arkhangelsk aged 35 to 69. The response rate of the invited participants was 68%. The informed consents to provide contact information and to be invited in new studies were used to recruit participants of the Know Your Heart study aged 60–74 by telephone and mail to participate in this study. As of April 1, 2023, the sample frame included 982 participants. Participants who agreed to participate were invited to undergo examination at the Consultative and Diagnostic Clinic of the Federal State Budgetary Educational Institution of Higher Education Northern State Medical University (Arkhangelsk) of the Russian Ministry of Health. Exclusion criteria included symptoms of acute infections or exacerbation of chronic diseases the day before or immediately before the examination. In total, 605 participants were examined. The study response rate was 62% of the total sample frame.

The study included an interview to collect information on the participant's place of birth, the place of birth of his/her parents, and the parents of each parent (three generations). Participants who had at least two previous maternal and paternal generations born in the Arkhangelsk Region were defined as native residents. The remaining participants were defined as non-native residents. One participant was excluded as this person had no information required for this classification.

Whole blood samples of the study participants were drawn for DNA analysis from the cubital vein using vacuum systems with EDTA anticoagulant. Biological samples were stored and delivered to the laboratory at the temperature of +4 °C. After delivery, vacutainers containing whole blood were frozen at -20 °C until the molecular genetic testing.

Molecular genetic testing included determination of alleles and genotypes of six genes involved in blood pressure regulation. We studied the genes associated with vasoconstriction determining the synthesis of angiotensinogen (*AGT*), angiotensin II type 1 receptor (*AGTR1*), endothelin-1 (*EDN1*), angiotensin-converting enzyme (*ACE*), and endothelial NO synthase determining the synthesis of the vasodilator (nitric oxide). The analyzed gene variants (see Table 1) were selected based on data from literature, including meta-analyses and original papers [10–23]. When selecting gene variants, we used data from our studies obtained during the examination of young natives of the Arkhangelsk Region. The study showed that the studied gene variants contribute to the imbalance of vasoactive endothelial factors that may be genetic vasoconstriction factors [24–27].

The frequency of alleles of all studied polymorphic variants was analyzed by comparison with global data (https://www.ncbi.nlm.nih.gov/snp/) and data on European Russia residents from RUSeq Project aimed at combining genetic information between clinical laboratories and genomic centers in Russia (http://ruseq.ru/#/).

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Table 1. Candidate arterial hypertension gene variants under consideration

Gene	NCBI, dbSNP	Localization	Polymorphic locus	Changed area in a gene (protein)	Allele increasing the cardiovascular risk	Links
Angiotensinogen (*AGT*)	rs699	1q42.2	T704C	Coding region	C	[11, 20, 23]
Angiotensinogen (*AGT*)	rs4762	1q42.2	C521T	Coding region	T	[20, 23]
Angiotensin II type 1 receptor (*AGTR1*)	rs5186	3q24	A1166C	3, non-coding region	C	[10, 17, 21]
Angiotensin-converting enzyme (*ACE*)	rs4646994	17q23.3	Insertion/ deletion polymorphism in intron 16	Intron region	D	[7, 10, 14]
Endothelial NO synthase (*NOS3*)	rs2070744	7q35-36	T(-786)C	Promoter	C	[12, 13, 22]
Endothelin-1 (*EDN1*)	rs5370	6p24.1	G596T	Coding region	T	[15, 16, 18, 19]

We analyzed human genomic DNA isolated from whole blood leukocytes using reagents manufactured by Lytech (Russia) company. Gene polymorphism was determined by the polymerase chain reaction (PCR) with a real-time fluorescent product detection using two types of reagents and a LightCycler-96 thermocycler (Roche, Switzerland/Germany). To determine the polymorphism of *AGT* Met235Thr, *AGTR1* A1166C, *ACE* Alu ins/del, *AGT* Thr174Met, and *NOS3* C(-786)T, primers required to amplify the polymorphic region and two allele-specific hydrolysis probes containing the polymorphic site were added to the reaction. The probe containing polymorphic allele 1 was labeled with HEX fluorophore and allele 2 was labeled with FAM fluorophore. Alleles were discriminated by Taq polymerase destruction of the fully and partially complementary probe with different degradation efficiency.

Two amplification reactions—with two pairs of allele-specific primers—were performed in parallel with a sample of isolated DNA to determine the *EDN1* Lys198Asn (G596T) gene polymorphism. In this case, SYBR Green, an intercalating dye specific for double-stranded DNA, was used to detect the amplified DNA fragment.

The results of laboratory tests were recorded in an electronic database and hard copies. To avoid errors, the inputs were subsequently compared with the results in hard copy.

Categorical variables were described as absolute numbers (abs.) and percentages (%). Selected categorical variables used to describe the prevalence of the studied parameters in the population are presented with 95% confidence intervals (CI). Frequency distributions of the studied parameters in the analyzed groups were compared using the Pearson chi-square test.

The deviation of empirical genotype distributions in native and non-native groups from the predicted Hardy–Weinberg (HW) equilibrium and the empirical distributions between groups were assessed in Stata software using the genhwcci command proposed by J. Cui et al. [28, 29]. This is a command used for estimating allele frequency, genotype frequencies, disequilibrium coefficients, and the associated standard error for codominant traits or data of completely known genotypes in case-control studies. In this analysis, the native group was defined as the case group and the non-native group was defined as the control group. For the genotypic assessment of each group, we performed asymptotic HW equilibrium tests and HW equilibrium tests for the genotypic distribution of cases, provided that the genotypic distribution of the control group has HW equilibrium, so that the results showed the genotype distribution differences in the native and non-native groups. The analysis is presented as the chi-square likelihood ratio test results.

Results were considered statistically significant if $p < 0.05$. Stata 18.0 (Stata Corp, USA, Texas, College Station) was used for data analysis.

All participants provided written informed consent to participate in the study in the form prepared in accordance with the Helsinki Declaration of the World Medical Association and approved by the local Ethics Committee of the Northern State Medical University (Minutes No. 03/04-23 dated April 26, 2023).

RESULTS

The analyzed sample (N = 604) included 384 (63.6%) female and 220 (36.4%) male participants. All study participants were Caucasian and had lived in the Arkhangelsk Region for more than 10 years. Residents with at least two previous maternal and paternal generations born in the Arkhangelsk Region were defined as the native group (200 [33.1%] participants); the remaining participants were defined as the non-native group (404 [66.9%] participants).

Table 2 shows the comparative analysis of the absolute frequencies of reference and variable alleles of the studied genes and genotypes.

The study of the frequencies of alleles and genotypes of polymorphic markers of the studied genes showed that the

empirical distribution of genotypes in native and non-native elderly populations of the Arkhangelsk Region was similar to the predicted HW equilibrium (p >0.05), save for an *AGT* locus (rs699) deviating from the HW law due to higher heterozygosity; the actual heterozygosity was 14.7% higher (99.4 to 114.0) than the predicted heterozygosity; p=0.037.

Table 3 shows the comparative analysis of frequencies of alleles of polymorphic loci of genes of the Arkhangelsk Region population vs global data [https://www.ncbi.nlm.nih.gov/snp/] and populations of the European Russia [http://ruseq.ru/#/].

It was found that allele frequencies of polymorphic markers of the studied genes are similar to global data and data on European populations, save for the *AGTR1* 1166C frequency. In the native group of the Arkhangelsk Region population, this allele frequency was 0.208 (95% CI: 0.169–0.251), which is lower than the global average (0.275) and the average for the European Russia population (0.256). A lower *AGTR1* 1166C frequency was also observed in the non-native group (0.234; 95% CI: 0.205–0.265) compared with the global average (0.275).

In addition, the comparative analysis of the allele frequencies of the studied polymorphic gene loci in native and non-native elderly populations of the Arkhangelsk Region did not show significant differences in the distribution of alleles associated with high blood pressure (see Table 4).

The comparative analysis of genotype frequencies in native and non-native elderly populations of the Arkhangelsk Region showed similar results (see Table 4).

It was found that alleles increasing the cardiovascular risk were minor for *AGT* (rs4762), *AGTR1* (rs5186), *NOS3* (rs2070744), and *EDN1* (rs5370) variants. Homozygotes of these alleles involved in the development of cardiovascular diseases were significantly less common than other variants. The exceptions included 704C *AGT* (rs699) with a frequency of 47.3% in non-natives and 46.0% in natives and the D allele of the *ACE* gene (48.9% in non-natives and 46.3% in natives).

DISCUSSION

Recently, there has been more and more papers on the frequency of functionally relevant variants in various populations. However, now, there are relatively few studies of gene polymorphism in different age groups. Such studies may be an important source of data on the role and functions of a particular gene for the performance of the human body at a certain stage of life. Old age is of particular interest as the global elderly population is growing and the issue of active longevity is relevant for each person.

In the northern regions, the cardiovascular system experiences the increased stress due to higher energy demand of the human body and distal vessel tone [30]. The cardiovascular system provides adequate blood supply to all organs and tissues; it is a key factor of the quality of life. Cardiovascular diseases develop as a result of a complex interaction of social, environmental, and genetic factors. Variants of genes determining the synthesis of vasoactive factors and contributing to the development of cardiovascular diseases have been identified, including the most studied genes of the renin-angiotensin system, angiotensinogen (*AGT*; rs699 and rs4762), angiotensin II type 1 receptor (*AGTR1*; rs5186), angiotensin-converting enzyme (*ACE*; rs4646994), endothelial NO synthase (*NOS3*; rs2070744), and endothelin-1 (*EDN1*; rs5370).

A population-based study of participants aged 55 and older showed that the participants with the D allele of the *ACE* gene had higher mean systolic and pulse pressure than participants with allele I [7]. Another study [8] showed that the I/D polymorphism of the *ACE* gene modulates systolic and diastolic BP changes with age. In a Japanese population, it was found that the T(-786)C polymorphism of the *NOS3* gene was associated with arterial stiffness and age- and sex-related differences. In particular, the C allele is significantly associated with higher pulse wave velocity in women aged 65 and older [6]. A meta-analysis including 17 articles with more than 8,000 participants showed strong correlations between the *END1* gene polymorphism (rs5370) and the arterial hypertension risk [31]; similar relationships were obtained in the study of ASD polymorphisms [32].

In view of the above, the study of the distribution frequencies of nucleotide sequence variants involved in the blood pressure regulation in the elderly population of the Arkhangelsk Region is relevant.

The empirical genotype distribution of the *AGT* (rs4762), *AGTR1* (rs5186), *NOS3* (rs2070744), and *EDN1* (rs5370) variants in the studied native and non-native elderly populations people of the Arkhangelsk Region was similar to the predicted HW equilibrium. However, the native population showed a deviation from the HW law in the *AGT* locus (rs699) associated with the higher actual heterozygosity.

It was found that alleles increasing the cardiovascular risk were minor for *AGT* (rs4762), *AGTR1* (rs5186), *NOS3* (rs2070744), and *EDN1* (rs5370) variants. Homozygotes of these alleles involved in the development of cardiovascular diseases were significantly less common than other variants, save for 704C *AGT* (rs699) and D allele of the *ACE gene.* A.S. Glotov et al. [33] have obtained similar data showing that the frequency of the heterozygous genotype TC of the *AGT* gene (rs699) in the elderly population of the North-West region of Russia was 2 times more common compared to the group aged 18–45. A higher frequency of the ID genotype of the *ACE* gene was also found in elderly individuals. The authors believe that *AGT* and *ACE* heterozygosity may be considered as a hereditary factor associated with longevity. Deviation of the empirical genotype distribution of the rs699 variant of the *AGT* gene from the predicted HW equilibrium associated with higher heterozygosity in the native population of the Arkhangelsk Region may be considered as a selection variant of adaptation to the climate of the northern regions.

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Table 2. Absolute frequencies of homozygotes for the reference and variant allele and heterozygotes; expected and observed heterozygosity in native and non-native populations aged 60–74 of the Arkhangelsk Region

Group	N	Homozygotes (reference allele), abs.	Heterozygotes, abs.	Homozygotes (variant allele), abs.	Reference allele, abs.	Variant allele, abs.	Predicted heterozygosity, abs.	Observed heterozygosity, abs.	HW equilibrium test, *p*	Genotype differences in native and non-native populations of the Arkhangelsk Region, *p**
					***AGT* (rs699)**					
Native	200	51	114	35	216	184	99.4	114.0	0.037	0.103
Non-native	404	113	200	91	426	382	201.4	200.0	0.889	
					***AGT* (rs4762)**					
Native	200	150	44	6	344	56	48.2	44.0	0.246	0.409
Non-native	404	309	88	7	706	102	89.1	88.0	0.802	
					***AGTR1* (rs5186)**					
Native	200	130	57	13	317	83	65.8	57.0	0.069	0.111
Non-native	404	239	141	24	619	189	144.8	141.0	0.601	
					***ACE* (rs4646994)**					
Native	200	50	85	65	215**	185***	99.0	85.0	0.040	0.083
Non-native	404	106	183	115	413**	395***	201.0	183.0	0.060	
					***EDN1* (rs5370)**					
Native	200	123	68	9	314	86	67.5	68.0	0.918	0.808
Non-native	404	237	147	20	621	187	143.7	147.0	0.645	
					***NOS3* (rs2070744)**					
Native	200	28	88	84	144	256	92.2	88.0	0.520	0.507
Non-native	404	51	166	187	268	540	179.1	166.0	0.140	

* Hardy–Weinberg (HW) equilibrium test for the genotypic distribution of natives, provided that the genotypic distribution of the non-native group is in HW equilibrium; ** I allele of the *ACE* gene; *** D allele of the *ACE* gene.

Table 3. Distribution of alleles of candidate gene polymorphic markers involved in blood pressure regulation in native and non-native populations of the Arkhangelsk region aged 60–74 as compared with global data and data on the European Russia

Gene	Allele	Native population	Non-native population	Global data	European Russia
		Ratio (95% CI)		Ratio	
AGT (rs699)	T	0.540 (0.490–0.590)	0.527 (0.492–0.562)	0.545	0.508
	C	0.460 (0.410–0.510)	0.473 (0.438–0.508)	0.455	0.492
AGTR1 (rs5186)	A	0.793 (0.750–0.831)	0.766 (0.735–0.795)	0.725	0.744
	C	0.208 (0.169–0.251)	0.234 (0.205–0.265)	0.275	0.256
ACE rs4646994	I	0.538 (0.487–0.587)	0.511 (0.476–0.546)	N/A	N/A
	D	0.463 (0.413–0.513)	0.489 (0.454–0.524)		
AGT (rs4762)	C	0.860 (0.822–0.892)	0.874 (0.849–0.896)	0.879	0.842
	T	0.140 (0.108–0.178)	0.126 (0.104–0.151)	0.121	0.158
NOS3 (rs2070744)	C	0.360 (0.313–0.409)	0.332 (0.299–0.365)	0.349	0.382
	T	0.640 (0.591–0.687)	0.668 (0.635–0.701)	0.651	0.619
EDN1 (rs5370)	G	0.785 (0.741–0.824)	0.769 (0.738–0.797)	0.781	0.810
	T	0.215 (0.176–0.259)	0.231 (0.203–0.262)	0.219	0.190

The comparative analysis of the frequency distribution of variants of the studied *AGT* (rs699 and rs4762), *NOS3* (rs2070744), and *EDN1* (rs5370) genes in the elderly population of the Arkhangelsk Region did not show any differences from global data and data on European populations of Russia of different ages.

The study showed that the frequency of the 1166C allele of the *AGTR1* gene in the native group of the Arkhangelsk Region was lower than the global average and the frequency of European Russia population. A lower *AGTR1* 1166C frequency was also observed in the non-native group compared with the global average. This allele is likely a selection variant associated with adaptation to the climate of the northern regions. A lower frequency of the 1166C allele compared to European populations was also found in a study of young natives of the Arkhangelsk Region aged 18–20. Their CC genotype was combined with a vasoactive endothelial factor imbalance towards constrictor factors and the development of some hemodynamic factors of cardiovascular risk [25]. A study of a small group of the small aboriginal Far North population in Yakutia (Evens and Evenki) did not show a single person with the CC genotype of the *AGTR1* gene variant (rs5186) [34].

The advantage of this study is the examination of a random population sample that may be generalized to residents of Arkhangelsk aged 60–74. On the other hand, the sample size is limited to Arkhangelsk residents and it allows to generalize the study to wider areas of the Russian northern regions by only assuming that there are no significant differences between the elderly population of Arkhangelsk and other northern regions.

CONCLUSION

The empirical distribution of genotypes of the studied native and non-native elderly population of the Arkhangelsk Region was similar to the predicted HW equilibrium. However, we found a deviation from the HW law in the *AGT* locus (rs699) associated with the higher actual heterozygosity.

We found no differences in allele and genotype frequencies in residents of the Northern European region of Russia, whose ancestors were born and lived for at least

Table 4. Distribution of *AGT* (rs699), *AGTR1* (rs5186), *ACE* (rs4646994), *AGT* (rs4762), *NOS3* (rs2070744), and *EDN1* (rs5370) alleles and genotypes in non-native and native populations of the Arkhangelsk Region aged 60–74

Polymorphism/ allele/ genotype	Non-native population	Native population	Genotype differences, *p**	Allele frequency differences, *p**
	Ratios, %			
AGT (rs699)			0.186	0.676
T	52.7	54.0		
C	47.3	46.0		
TT	28.0	25.5		
TC	49.5	57.0		
CC	22.5	17.5		
AGTR1 (rs5186)			0.288	0.302
A	76.6	79.3		
C	23.4	20.7		
AA	59.3	65.0		
AC	34.9	28.5		
CC	5.9	6.5		
ACE (rs4646994)			0.593	0.541
D	48.9	46.3		
I	51.1	53.8		
DD	26.2	25.0		
ID	45.3	42.5		
II	28.5	32.5		
AGT (rs4762)			0.595	0.505
C	87.4	86.0		
T	12.6	14.0		
CC	76.5	75.0		
TC	21.8	22.0		
TT	1.7	3.0		
NOS3 (rs2070744)			0.603	0.663
C	33.2	36.0		
T	66.8	64.0		
CC	12.6	14.0		
TC	41.1	44.0		
TT	46.3	42.0		
EDN1 (rs5370)			0.798	0.521
G	76.9	78.50		
T	23.1	215.0		
GG	58.7	61.5		
GT	36.4	34.0		
TT	4.9	4.5		

* Pearson χ-square test.

three generations in the Arkhangelsk Region, and residents who lived in this climate for at least 10 years. It shows that there is no elimination of mutant alleles of the studied variants from the population living in the Northern European region.

The study shows that alleles increasing the cardiovascular risk are mostly minor. The exceptions include the 704C *AGT* (rs699) and the D allele of the *ACE* gene with the frequency comparable to the frequency of the wild-type allele. High frequency of heterozygotes of these markers is typical.

Comparison of data on elderly populations living in the Arkhangelsk Region with global data and data on the population of the European Russia did not show any differences in the allele frequency of the studied genes, except for the 1166C *AGTR1*, which was less common both in native and non-native populations of the Arkhangelsk Region compared to global data and less common in the native population compared to the population of the European Russia. This is probably caused by adverse environmental stress factors in the northern regions, i.e. less mutant alleles of this variant is an adaptation factor..

ADDITIONAL INFO

Authors' contribution. N.A. Bebyakova — general concept of the article, collection and analysis of literary sources, writing the discussion section and the conclusion, editing the article; N.I. Pechinkina — performing molecular genetic analyses, writing the materials and methods section; S.N. Levitsky — literature review, collection and analysis of literary sources, preparation and writing of the text of the article for the results and discussion section; I.A. Shabalina — literature review, collection and analysis of literary sources, preparation and writing the introduction; A.V. Kudryavtsev — general concept of the article, statistical data analysis, description of materials and methods, editing the article, leading the research team. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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