Received: 05 August 2023 / Accepted: 17 October 2023 / Published online: 31 October 2023

DOI 10.34689/SH.2023.25.5.005

UDC 611.146.2.

THE ASSOCIATION OF RS11781551 AND RS6988985 WITH HYPERTENSION IN THE GROUP OF KAZAKH INDIVIDUALS

Valeriy Benberin[1,2], http://orcid.org//0000-0003-2422-4853

Raushan Karabayeva[1,2], http://orcid.org//0000-0003-2945-8122

Zhanatgul Turgumbayeva[1], http://orcid.org//0009-0002-6814-4775

Alisher Aitkaliyev[1], http://orcid.org//0009-0002-9624-2663

Ainur Sibagatova*[1,2], http://orcid.org//0000-0001-6399-3810

[1] Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan, Astana, Republic of Kazakhstan;
[2] The Asfendiyarov Kazakh National Medical University, Almaty, Republic of Kazakhstan.

Summary

Background. Arterial hypertension (HT) is a leading risk factor for mortality and morbidity especially in the developing countries. Kazakhstan is not an exception, the first reason of death is cardiovascular diseases which are directly associated with high blood pressure. Among risk factors, the genetic ones are the least understood, so the aim of current study is to find association of some SNPs of eighth chromosome and HT in the group of Kazakh individuals.

Materials and Methods. A total of 606 Kazakh patients were recruited, 394 of them were diagnosed with HT, the remaining 212 were in the control group, i.e. did not have HT. The genotyping was performed using the Open Array technology. The SNPs and phenotype association assessment was taken in pairs of the HT- and HT+ groups, following the case-control design based on a GLM. The genotype and phenotype signs association was esteemed using 4 inheritance models: dominant, co-dominant, recessive, and log-additive inheritance models.

Results. It was found that the rs11781551 in codominant study model (OR 0.370 [0.157-0.871]) and in the dominant study model (OR 0.370 [0.157-0.871]) was associated with the presence of HT.

There is the significant association of rs6988985 and HT in studied population in codominant (for C/T genotype OR = 0.567 [0.336-0.956], for T/T genotype OR = 0.422 [0.224-0.795]), recessive (OR = 0.522 [0.316-0.861]) and log-additive models (OR = 0.648 [0.473-0.887]). These associations were found after the adjustments for gender and age, BMI, gender, glucose, total cholesterol, LDL, HDL and triglycerides.

Discussion. In the current analysis, it was found that two polymorphisms rs11781551 and rs6988985 significantly affected the presence of hypertension, regardless of age, gender, BMI, glucose level and lipid profile in the group of Kazakh individuals. These findings may have implications for the development of personalized approaches to the prevention and treatment of HT.

Key words: *arterial hypertension, Kazakh, single nucleotide polymorphisms, eighth chromosome, phenotype-genotype association.*

Резюме

АССОЦИАЦИЯ ОДНОНУКЛЕОТИДНЫХ ПОЛИМОРФИЗМОВ RS11781551 И RS6988985 С ГИПЕРТЕНЗИЕЙ В ГРУППЕ ПРЕДСТАВИТЕЛЕЙ КАЗАХСКОЙ НАЦИОНАЛЬНОСТИ

Валерий Бенберин[1,2], http://orcid.org//0000-0003-2422-4853

Раушан Карабаева[1,2], http://orcid.org//0000-0003-2945-8122

Жанатгуль Тургумбаеваа[1], http://orcid.org//0009-0002-6814-4775

Алишер Айткалиев[1], http://orcid.org//0009-0002-9624-2663

Айнур Сибагатова*[1,2], http://orcid.org//0000-0001-6399-3810

[1] Больница медицинского центра Управления делами Президента Республики Казахстан, г. Астана, Республика Казахстан;
[2] Казахский Национальный медицинский университет имени С. Асфендиярова, г. Алматы, Республика Казахстан.

Введение. Артериальная гипертензия (АГ) является ведущим фактором риска смертности и заболеваемости, особенно в развивающихся странах. Казахстан не является исключением, первая причина смертности – сердечно-сосудистые заболевания, которые напрямую связаны с повышенным артериальным давлением. Среди факторов

риска генетические наименее изучены, поэтому целью настоящего исследования является обнаружение ассоциации некоторых SNP восьмой хромосомы и АГ в группе представителей казахской популяции.

Материалы и методы. Всего было привлечено 606 казахстанских пациентов, из них у 394 была диагностирована АГ, остальные 212 стали контрольной группой, т.е. не имели ГБ. Генотипирование проводилось с использованием технологии Open Array. Оценка ассоциации SNP и фенотипа проводилась в парах групп АГ- и АГ+, следуя схеме «случай-контроль», основанной на обобщенной линейной модели. Для оценки связи признаков генотипа и фенотипа использовали 4 модели наследования: доминантная, кодоминантная, рецессивная и лог-аддитивная.

Результаты. Было обнаружено, что rs11781551 в кодоминантной модели (OR 0,370 [0,157-0,871]) и в доминантной модели (OR 0,370 [0,157-0,871]) связан с наличием АГ.

Установлена достоверная ассоциация rs6988985 и АГ в изученной популяции в кодоминантной (для генотипа C/T OR = 0,567 [0,336-0,956], для генотипа T/T OR = 0,422 [0,224-0,795]), рецессивной (OR = 0,522 0,316-0,861]) и лог-аддитивной моделях наследования (OR = 0,648 [0,473-0,887]). Эти ассоциации были обнаружены после поправки на пол и возраст, ИМТ, пол, уровень глюкозы, общий холестерин, ЛПНП, ЛПВП и триглицериды.

Обсуждение. В текущем анализе установлено, что два полиморфизма rs11781551 и rs6988985 достоверно влияют на наличие АГ независимо от возраста, пола, ИМТ, уровня глюкозы и липидного профиля в группе казахов. Эти результаты могут иметь значение для разработки персонализированных подходов к профилактике и лечению АГ.

***Ключевые слова**: артериальная гипертензия, казахи, однонуклеотидные полиморфизмы, восьмая хромосома, ассоциация фенотип-генотип.*

Түйіндеме

RS11781551 ЖӘНЕ RS6988985 ПОЛИМОРФИЗМДЕРІНІҢ ҚАЗАҚ ҰЛТЫНДА ГИПЕРТЕНЗИЯМЕН БАЙЛАНЫСЫ

Валерий Бенберин[1,2], http://orcid.org//0000-0003-2422-4853
Раушан Карабаева[1,2], http://orcid.org//0000-0003-2945-8122
Жанатгуль Тургумбаеваа[1], http://orcid.org//0009-0002-6814-4775
Алишер Айткалиев[1], http://orcid.org//0009-0002-9624-2663
Айнур Сибагатова*[1,2], http://orcid.org//0000-0001-6399-3810

[1] Қазақстан Республикасы Президентінің Іс басқармасы Медициналық орталығының ауруханасы, Астана қ., Қазақстан Республикасы;
[2] С. Ж. Асфендияров атындағы Қазақ ұлттық медицина университеті, Алматы қ., Қазақстан Республикасы.

Кіріспе. Артериялды гипертензия (АГ, НТ) дамушы елдерде өлім мен сырқаудың жетекші қауіп факторы болып табылады, Мысалға, жүрек пен қан тамырлары ауруларымен байланысты өлімнің бірінші себебі – қан қысымының жоғарылауымен тікелей байланысты. Дегенмен, тәуекел факторларының ішінде генетикалық факторлары аса анық емес, сондықтан қазіргі зерттеудің мақсаты қазақ этникалық тобында сегізінші хромосоманың кейбір SNP-лардын АГ-мен байланысын табу болып табылады.

Материалдар мен тәсілдер. Барлығы 606 пациент зерттеуде қатысты. Оның ішінде 394 пациент АГ диагнозымен және 212 адам бақылау тобында. Генотиптеу Open Array технологиясы арқылы орындалды. SNP мен фенотиптің байланысы GLM-ге негізделген жағдай-бақылау дизайны бойынша НТ- және НТ+ топтарында анықталды. Генотип пен фенотип белгілерінің байланысы тұқым қуалаудың 4 моделі арқылы бағаланды: доминантты, ко-доминантты, рецессивті және лог-аддитивті тұқым қуалаушылық үлгілері.

Нәтижелер. Кодоминантты зерттеу үлгісіндегі rs11781551 (OR 0,370 [0,157-0,871]) және доминантты зерттеу үлгісінде (OR 0,370 [0,157-0,871]) АГ-ның пайда болуымен байланысты екені анықталды.

Кодоминантты популяцияда rs6988985 мен АГ арасында маңызды байланысы бар (C/T генотипі үшін OR = 0,567 [0,336-0,956], T/T генотипі үшін OR = 0,422 [0,224-0,795 (OR), және лог-аддитивті модельдер (OR = 0,648 [0,473-0,887]). Бұл байланыстар жыныс пен жас, BMI, глюкоза, жалпы холестерин, LDL, HDL және триглицеридтерге арналған түзетулерден кейін табылды.

Талқылау. Бұл талдауда rs11781551 және rs6988985 екі полиморфизмі қазақ пациенттер тобындағы жасына, жынысына, BMI, глюкоза деңгейіне және липидті профильге қарамастан, гипертонияның болуына айтарлықтай әсер еткені анықталды. Бұл тұжырымдар НТ әр пациенттің профилактикасы мен емдеу тәсілдердерінің қолданысына әсер етуі мүмкін.

***Негізгі сөздер:** артериалды гипертензия, қазақ, бір нуклеотидті полиморфизмдер, сегізінші хромосома, фенотип-генотиптік ассоциация.*

Bibliographic citation:

Benberin V., Karabayeva R., Turgumbayeva Zh., Aitkaliyev A., Sibagatova A. The association of RS11781551 and RS6988985 with hypertension in the group of Kazakh individuals // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2023, (Vol.25) 5, pp. 45-51. *doi 10.34689/SH.2023.25.5.005*

Бенберин В., Карабаева Р., Тургумбаева Ж., Айткалиев А., Сибагатова А. Ассоциация однонуклеотидных полиморфизмов rs11781551 и rs6988985 с гипертензией в группе представителей казахской национальности // Наука и Здравоохранение. 2023. 5(Т.25). С. 45-51. *doi 10.34689/SH.2023.25.5.005*

Бенберин В., Карабаева Р., Тургумбаева Ж., Айткалиев А., Сибагатова А. Rs11781551 және rs6988985 полиморфизмдерінің қазақ ұлтында гипертензиямен байланысы // Ғылым және Денсаулық сақтау. 2023. 5 (Т.25). Б.45-51. *doi 10.34689/SH.2023.25.5.005*

Introduction

Arterial hypertension (HT) is a very common condition. Thus, according to the May measurement Month campaign initiated by the International Society of Hypertension, which included 1.5 million people from 92 countries, 34% of participants had HT, while 32% of participants had never measured blood pressure [1]. The importance of HT lies in the fact that it endows the largest contribution of risk factors to overall mortality and morbidity worldwide. According to a systematic review by the Global Burden of Disease Study 2017, elevated systolic blood pressure (SBP) was the most significant risk factor for mortality for 10.4 million deaths and 218 million disability-adjusted life-years [2]. Moreover, the 50% of the total number of economic burden of cardiovascular disease (CVD) in low- and middle- income countries were attributed to hypertension [3].

Similarly, the problem of HT is quite acute in Kazakhstan. The prevalence of HT, according to various data, is in the range of 15-28% [4, 5]. A retrospective cohort study by S. Yerdessov et al. shows a proven increase in prevalence, incidence, and mortality of HT from 2014 to 2019, noting that patients of Russian and other descends are more likely to survive deaths associated with HT than Kazakhs [6], which indirectly indicates a genetic risk factor [7]. Similarly, in Xinjiang Region of China, where the largest population of ethnically Kazakhs lives outside of Kazakhstan, Kazakh people have the highest prevalence of hypertension (36.9%), compared to Han (33.7%) and Uygur people (26.1%) [8]. In general, the relationship between genetic factors and HT has been confirmed by many studies. It is not always clear exactly how it is carried out, although there are some common notions of how genetics influence the susceptibility and treatment of HT. Genetic factors influence a genetic predisposition in interaction with environmental factors, such as the intake of salt and the degree of physical exercise, ultimately determining how severe the rise of blood pressure may be [7].

Albeit that the genetic background of HT are being studied extensively [9, 10], as far as it is known from open sources, similar studies have not been conducted in Kazakhstan. Several studies conducted by Chinese scientists based on data from participants of Kazakh nationality have described some of the genetic factors associated with HT. In particular, *Han Dongfeng Gu et. al* conducted a study of 8p22 chromosome which was previously been reported to affect AH and SBP, where they concluded that alpha1A adrenergic receptor gene, located on chromosome 8p21–p11.2, affects AH [11]. Similarly, genome scan meta-analysis harbored 8th chromosome to be linked to predisposition to hypertension and blood pressure regulation including lipoprotein lipase gene and aldosterone synthase gene in 8th chromosome [12, 13]. Previously, we have genotyped 9 single nucleotide polymorphisms (SNPs) of the 8th chromosome and identified 3SNPs associated with myocardial remodeling and carotid artery remodeling in AH in the ethnically Kazakh population [14]. In this study, the goal was to check whether there is a significant association between some polymorphisms of the eighth chromosome and AH in Kazakhs living in the city of Astana.

Materials and methods

Study participants

This study was carried out following ethical principles and was approved by the Hospital Local Commission on Bioethics, permission note No.5, "27" September 2017. All medical tests and examinations were performed under the Hospital approved standard operating procedures. The recruitment procedure were as follows: the prospective participants were the registered patients of the hospital, and patients with resistant HT and HT were surveyed if they want to participate in the study, and then if they had agreed to be part of the study voluntarily, then they signed the informed consent.

A total of 606 patients of Kazakh ethnicity were recruited at the Medical Centre Hospital of President`s Affairs Administration of the Republic of Kazakhstan, 394 of them were diagnosed with HT, the remaining 212 were in the control group, i.e. did not have HT. HT was diagnosed when the mean SBP was ≥140 mm Hg., and / or DBP ≥90 mm Hg. based on the results of daily monitoring of blood pressure and / or on the basis of the constant intake of antihypertensive drugs.

Blood samples for the study were taken from the cubital vein in the treatment room after a 12-hour fast. The plasma was removed by centrifugation at 1000×g (4C) for 10 minutes. For subsequent biochemical analysis, the plasma was maintained at -30C. After centrifugation, the serum was used for analysis on the day of blood collection. The levels of glucose, total cholesterol, TG, HDL and LDL were determined by the enzymatic method on an Architect s 8000 automatic biochemical analyzer (Abbott Laboratories, USA).

Isolation of DNA

DNA extraction was carried out by the AutoMate Express ™ Instrument in an automatic way. iPrep ™ Purelink ™ gDNA Blood Kit was used as a kit for DNA extraction. Firstly, the previously numbered according to the DNA samples tubes were prepared. Next, the Qubit® working solution was made: the Qubit® dsDNA BR Reagent was diluted in the Qubit® dsDNA BR Buffer, at the rate of 1:

200 per patient. Then 2 µl were taken from the buffer and reagent mix and 2 µl of DNA was added. The concentration was measured on a Qubit ™ 4 Fluorometer by the Qubit® dsDNA BR Assay Kits.

Genotyping

The genotyping was performed using the OpenArray technology, which is a unique platform for reactions in nanoliter volumes. In this technology, special OpenArray slides were used. Each slide brings out 3,072 data points. To genotype, the previously extracted DNA samples were integrated with the reaction mixture in a 384 well sample plate. For one sample OppenArray Real-time master mix - 3.0 µl; DNA sample - 2.0 µl is needed with the concentration 50 ng / µl. The total volume of the reaction mixture per well was 5 µl. Each sample was duplicated. The reaction mixture was blended scrupulously on a plate using a shaker and centrifuge. Then, the probes were designed by the QuantStudio OpenArray AccuFill Plate Configurator. Genotyping plates were provided with dried assays in the indicated throughholes. The unique plate was used for the assay, there were two allele-specific probes, a minor groove binder, and two PCR primers, to ensure high constancy and precision of genotyping calls. OpenArray technology utilizes nanoliter fluidics and can be customized to 3,072 through holes in 6 different formats.

Then, a protocol for the applied samples with analysis information was made in the plate setup file. The protocol was uploaded into QuantStudio ™ 12K Flex software to generate and conduct an experiment. The prepared chips were inserted into the QuantStudio 12K Flex using disposable genotyping blocks. Next, the amplification reaction occurred through real-time PCR microfluidic technology. Analysis of the obtained data as a result of the amplification reaction was accomplished using the online tools of the Termo Fisher Cloud cloud service. The results of bioinformatic analysis of the studied genes allowed to classify them as homozygotes for the major allele, homozygotes for the minor allele, and heterozygotes.

Statistical analysis

The material for the analysis was a database of personal and laboratory data, as well as genotyping data (n = 606). The analysis was carried out using the SPSS (IBM) version 26.0. Non-parametric Wilcoxon test for independent groups was used for quantitative data with abnormal distribution, the results were reported as median [Q1; Q3]. Chi-square test was used for categorical data comparison; the results were reported in percent. Evaluation of the distribution of data (normality test) was carried out based on the Shapiro-Wilks criterion. For the level of statistical significance of differences in indicators, i.e., alpha risk, the value p <0.05 was taken.

The SNPs and phenotype association assessment was taken in pairs of the HT- and HT+ groups, following the case-control design based on a generalized linear model. The genotype and phenotype signs association was esteemed using 4 inheritance models: dominant, co-dominant, recessive, and log-additive inheritance models.

Results

The study participants

A total of 606 participants were recruited They were divided into two groups based on the presence of HT. 394 (65%) participants have HT, 212 (35.0%) participants did not have HT. Comparing two groups, it was found that gender did not differ significantly. In the HT+ the proportion of men in the HT+ group was 51.0%, and in the HT- group was 50.0%. The age was significantly different (p<0.001), the median for the HT- group was 39.5 y.o. and the age median for HT+ group was 46.0 y.o. BMI was significantly different (p<0.001), in the HT+ group it was 28.72 kg/m2, and in the HT- group it was 24.78 kg/m2 (p<0.001). Waist circumference median in the HT- group was 85.31 cm, and in the HT+ group was 96.81 cm (p<0.001). The median of glucose was also significantly higher in the HT+ group and amounted to 5.54 [5.22;6.08] mol/L versus 5.12 [4.82;5.44] mol/L in the HT- group (p<0.001). The lipid profile indicators were also significantly higher in the HT+ group, namely, total cholesterol in the HT- group was 5.13 [4.53;5.62] mol/L versus 5.54 [5.22;6.08]mol/L in the HT+ group; LDL in the HT- group was 3.12 [2.56;3.77] versus 3.47 [2.85;4.11] mol/L in the HT+ group; triglycerides in the HT- group was 1.10 [0.82;1.60] versus 1.51 [1.01;2.05] mol/L in the HT+ group. HDL was 1.37 [1.19;1.50] mol/L in the HT- group and significantly higher than in the HT+ group (1.21 [1.02;1.40], p<0.001). (Table 1).

Table 1.

General characteristics of the MS+ and MS- groups.

Variables	All n=606	Group HT- n=212	Group HT+ n=394	p-value
Gender:				0.865
Male	307 (50.7%)	106(50.0%)	201 (51.0%)	
Female	299 (49.3%)	106(50.0%)	193 (49.0%)	
Age	46.00 [38.00;54.00]	39.50 [33.00;46.00]	49.0 [42.00;56.00]	<0.001
BMI	27.34 [24.16;29.74]	24.78 [22.60;27.01]	28.72 [26.12;31.62]	<0.001
Waist circumference (sm)	93.0 [83.00; 100.00]	85.31 [78.00;92.00]	96.81 [90.00;96.00]	<0.001
Glucose (mol/L)	5.4 [5.02;5.82]	5.12 [4.82;5.44]	5.54 [5.22;6.08]	<0.001
Total cholesterol (mol/L)	5.32 [4.72;6.00]	5.13 [4.53;5.62]	5.49 [4.80;6.22]	<0.001
LDL, low density lipoproteins (mol/L)	3.35 [2.70;3.97]	3.12 [2.56;3.77]	3.47 [2.85;4.11]	<0.001
HDL, high density lipoproteins (mol/L)	1.27 [1,09;1.45]	1.37 [1.19;1.50]	1.21 [1.02;1.40]	<0.001
Triglycerides (mol/L)	1,35 [0.93;1.89]	1.10 [0.82;1.60]	1.51 [1.01;2.05]	<0.001

Genotyping results

Six SNPs of the 8th chromosome were genotyped (rs28834970, rs896854, rs3802177, rs11781551, rs1562430, rs6988985). Based on the results of genotyping, for each SNP in each group, such indicators as the proportion of major and minor alleles, the minor allele frequency (MAF), as well as the p-value for the Hardy-Weinberg law (HWE), the allelic and genotypic frequency distribution were calculated and demonstrated in table 2. rs3802177, rs11781551 and rs6988985 were following the Hardy-Weinberg equation (p> 0.05). The genotype frequency of rs11781551 was significantly different in HT+ and HT- groups.

Table 2.

SNP basic information, allele frequencies in MS- and MS+ and odds ratio estimates for MS+ in allelic model analysis.

RS	Location	Gene	Allele	MAF		p-HWE	p-value	Genotype		p-value
				HT -	HT±			HT -	HT±	
rs28834970	27195121	PTK2B	T/C	0.2576	0.2671	0.00	0,462	22/61/129	36/139/220	0.274
rs896854	95960511	TP53INP1, NDUFAF6	C/T	0.4103	0.4493	0.00	0.192	82/86/44	137/161/97	0.479
rs3802177	118185025	SLC30A8	A/G	0.3867	0.3861	0.63	0.980	78/104/30	145/195/55	0.996
rs11781551	123408091	SMILR,MRPS36P3	A/G	0.2311	0.1911	0.06	0.100	133/60/19	260/119/16	0.047
rs1562430	128387852	CASC8, PCAT1, POU5F1B	T/C	0.2688	0.2455	0.00	0.374	24/66/122	35/124/236	0.614
rs6988985	144007104	LOC105375794	T/C	0.4882	0.4632	0.94	0.407	47/113/52	115/194/86	0.18

The analysis for inheritance patterns (codominant, dominant, recessive, and log-additive) for three SNPs satisfying the HWE was made. It was found that the rs11781551 in codominant study model (OR 0.370 [0.157-0.871]) and in the dominant study model (OR 0.370 [0.157-0.871]) was associated with the presence of HT. These associations were found after the adjustments for gender and age, BMI, gender, glucose, total cholesterol, LDL, HDL and triglycerides.

There is the significant association of rs6988985 and HT in studied population in codominant (for C/T genotype OR = 0.567 [0.336-0.956], for T/T genotype OR = 0.422 [0.224-0.795]), recessive (OR = 0.522 [0.316-0.861]) and log-additive models (OR = 0.648 [0.473-0.887]). The association was significant after adjustments for age, gender, glucose and triglycerides. The results of this analysis are reflected in Table 3.

Table 3.

Relationship between the 8th chromosome SNPs and HT under multiple models of inheritance.

Rs	Model inheritance		Proportion [HT-; HT+]	OR [95%CI]	OR [95%CI] adj. by age, BMI, gender, glucose, total cholesterol, LDL, HDL and triglycerides
rs3802177	CODOM	A/A	[36.8%; 36.7%]	1	1
		A/G	[49.1%; 49.4%]	1.009 [0.701-1.451]	1.127 [0.702-1.810]
		G/G	[14.2%; 13.9%]	0.986 [0.585-1.664]	0.768 [
	DOM	A/G-A/A	[85.8%; 86.1%]	1	1
		G/G	[14.2%; 13.9%]	0.981 [0.607-1.586]	0.717 [0.395-1.302]
	REC	G/G-A/G	[63.2%; 63.3%]	1	1
		A/A	[36.8%; 36.7%]	1.004 [0.710-1.419]	1.029 [0.658-1.610]
	LOG	0,1,2	-	0.997 [0.779-1.276]	0.925 [0.675-1.268]
rs11781551	CODOM	A/A	[62.7%; 65.8%]	1	1
		A/G	[28.3%; 30.1%]	1.015 [0.698-1.475]	1.088 [0.681-1.736]
		G/G	[9.0%;4.1%]	**0.431 [0.215-0.865]***	**0.370 [0.157-0.871]***
	DOM	G/G	[9.0%; 4.1%]	1	1
		A/G-A/A	[91.0%; 95.9%]	**0.429 [0.216-0.853]***	**0.362 [0.155-0.842]***
	REC	G/G-A/G	[37.3%; 34.2%]	1	1
		A/A	[62.7%; 65.8%]	0.874 [0.618-1.237]	0.890 [0.578-1.369]
	LOG	0,1,2	-	0.803 [0.610-1.056]	0.734 [0.516-1.046]
rs6988985	CODOM	T/T	[22.2%; 29.1%]	1	1
		C/T	[53.3%; 49.1%]	0.702 [0.465-1.058]	**0.567 [0.336-0.956]***
		C/C	[24.5%; 21.8%]	0.676 [0.417-1.096]	**0.422 [0.224-0.795]***
	DOM	T/T - C/T	[75.5%; 78.2%]	1	1
		C/C	[24.5%; 21.8%]	0.856[0.578-1.269]	0.625 [0.375-1.042]
	REC	C/T – C/C	[77.8%; 70.9%]	1	1
		T/T	[22.2%; 29.1%]	0.694 [0.470-1.024]	**0.522 [0.316-0.861]***
	LOG	0,1,2	-	0.821 [0.647-1.042]	**0.648 [0.473-0.887]***

** p < 0.05 indicates statistical significance.*

Discussion

In the current analysis, it was found that two polymorphisms rs11781551 and rs6988985 significantly affected the presence of hypertension, regardless of age, gender, BMI, glucose level and lipid profile in the group of Kazakh individuals.

rs11781551 was previously found in association with atherosclerosis, or rather with carotid intima-media complex thickness in Meta-analysis of genome-wide association studies. The common variants associated with carotid intima media thickness and plaque were observed. These data were obtained from 31,211 participants of nine population-based studies, the CHARGE consortium, that performed genome-wide genotyping and imputed to the approximately 2.5 million autosomal SNPs in the Phase II HapMap CEU reference panel. Additionally, the researchers followed-up the results in a second stage that included 11,273 participants from 7 independent studies.

rs11781551 is an intergenic variant and is adjacent to the genes encoding Mitochondrial Ribosomal Protein S36 Pseudogene 3 (MRPS36P3) and smooth muscle induced lncRNA, enhancer of proliferation (SMILR). The former is not well understood, and the latter, SMILR, has been mentioned in a number of studies on vascular smooth muscle remodeling and has even been proposed as a target for potential therapeutic interventions to prevent cardiovascular events (15, 16, 17). We can speculate that the possible association of rs11781551 with vascular smooth muscle determines the association of this polymorphism and HT in the study population.

rs6988985 is an intergenic variant and is adjacent to the genes encoding LY6E-DT, CYP11B2. The GWAS study performed to identify SNPs associated with variation in plasma concentrations of estrone conjugates, Estrone, and androstenedione in 774 postmenopausal women with resected early-stage ER+ breast cancer, rs6988985 was associated with increased androstenedione (p = 6.65E–07). Androstenedione is a steroid hormone that is produced mainly in the adrenal glands and to a lesser extent in the gonads. It is a precursor to testosterone and estrone, which are both important sex hormones. There is no direct evidence to suggest that androstenedione is directly associated with HT(18). However, both testosterone and estrone may influence to blood pressure in a complex and not yet fully understood way.

Testosterone is known to have both beneficial and detrimental effects on the cardiovascular system, and its effects can vary depending on the dose, duration, and timing of exposure(19). Some studies have suggested that higher levels of testosterone may be associated with an increased risk of HT and cardiovascular disease, while others have reported the opposite (20, 21). Estrogen has been shown to have a protective effect on the cardiovascular system, including increasing the production of nitric oxide (which helps dilate blood vessels), reducing inflammation, and improving lipid metabolism. As a result, premenopausal women are generally at lower risk of developing cardiovascular disease compared to men of the same age, due in part to higher levels of estrogen.(22)

Also, a possible explanation for the association of rs6988985 with HT may be its proximity of this polymorphism to CYP11B2. Cytochrome P450 family 11 subfamily B member 2 (CYP11B2) is an enzyme that is primarily responsible for the production of aldosterone in the adrenal glands. Aldosterone is a hormone that regulates the body's salt and water balance, and plays a crucial role in the maintenance of blood pressure.

Several studies have investigated the association between genetic variants in the CYP11B2 gene and hypertension. A meta-analysis by Cheng et al. reported that another variant in the CYP11B2 gene was associated with an increased risk of HT in Asian populations(23). Moreover, pharmacological inhibition of CYP11B2 has been shown to decrease aldosterone production and lower blood pressure in hypertensive patients (24). Taken together, these findings suggest that genetic variants in the CYP11B2 gene may contribute to the development of HT by altering aldosterone production and/or activity.

Another gene nearby LY6E divergent transcript is a gene that encodes a protein called lymphocyte antigen 6 complex, locus E (LY6E). LY6E is a member of the LY6 superfamily of proteins and is expressed in a variety of tissues, including the immune system, brain, and reproductive system. The role of LY6E divergent transcript in hypertension is not well understood, and there is limited research on its association with hypertension. The exact mechanism by which this polymorphism or the LY6E divergent transcript may contribute to HT is not clear and further research is needed.

These findings are significant as HT is a major public health issue globally and is a leading cause of cardiovascular disease, stroke, and kidney failure. The study provides insight into the genetic factors that contribute to the development of HT in the Kazakh population, which may aid in the development of more effective prevention and treatment strategies.

However, it is important to note that the study has some limitations. The sample size was relatively small, and the study was conducted in a specific population group, which may limit the generalizability of the results to the whole populations. Further studies with larger sample sizes and more represent populations are needed to confirm these findings.

In conclusion, the study provides evidence for an association between the rs11781551 and rs6988985 polymorphisms on chromosome 8 and HT in the Kazakh population. These findings may have implications for the development of personalized approaches to the prevention and treatment of HT.

Funding

This research is funded by the Ministry of Health of the Republic of Kazakhstan in the framework of the National Program for the Implementation of Personalized and Preventive Medicine in the Republic of Kazakhstan (2021-2023), Grant No. OR12165486.

Conflict of interest

No potential competing interest was reported by the authors.

Publication details: *This material has not been published in other publications and is not pending review by other publishers.*

Literature:

1. B*eaney T., Schutte A.E., Stergiou G.S., Borghi C., Burger D., Charchar F. et al.* May Measurement Month 2019: The Global Blood Pressure Screening Campaign of the International Society of Hypertension // Hypertension. 2020. 76(2):333-41.

2. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017 // Lancet. 2018. 392(10159):1923-94.

3. *Gheorghe A., Griffiths U., Murphy A., Legido-Quigley H., Lamptey P., Perel P.* The economic burden of cardiovascular disease and hypertension in low-and middle-income countries: a systematic review // BMC Public Health. 2018.18(1):1-11.

4. Kazakhstan MoHotRo. State Program on Health Systems' Development Salamatty Kazakhstan for the Years 2011–2015. Astana, Kazakhstan 2010. S. 9

5. MedInform Health of Population and Health Care in the Republic of Kazakhstan in 2013, Official Statistic [Internet]. [cited 16.03.2023]. www.medinfo.kz.

6. *Yerdessov S., Kadyrzhanuly K., Sakko Y., Gusmanov A, Zhakhina G, Galiyeva D, et al.* Epidemiology of Arterial Hypertension in Kazakhstan: Data from Unified Nationwide Electronic Healthcare System 2014-2019 // J Cardiovasc Dev Dis. 2022.9(2). S. 52

7. J*ordan J., Kurschat C., Reuter H.* Arterial Hypertension // Dtsch Arztebl Int. 2018;115(33-34):557-68.

8. *Wang Y., Zhang J., Ding Y., Zhang M., Liu J., Ma J., et al.* Prevalence of hypertension among adults in remote rural areas of Xinjiang, China // International journal of environmental research and public health. 2016. 13(6):524.

9. *Kelly T.N., Sun X., He K.Y., Brown M.R., Taliun S.A.G., Hellwege J.N. et al.* Insights From a Large-Scale Whole-Genome Sequencing Study of Systolic Blood Pressure, Diastolic Blood Pressure, and Hypertension // Hypertension. 2022. 79(8):1656-67.

10. *Li Y., Zheng H., Yang J., Zhang B., Xing X., Zhang Z. et al.* Association of genetic variants in Leptin, leptin receptor and adiponectin with hypertension risk and circulating Leptin / Adiponectin changes // Gene. 2023. 853:147080.

11. *Gu D., Ge D., Snieder H., He J., Chen S., Huang J. et al.* Association of alpha1A adrenergic receptor gene variants on chromosome 8p21 with human stage 2 hypertension // J Hypertens. 2006. 24(6):1049-56.

12. *Yang W.J., Huang J.F., Yao C.L., Fan Z.J., Ge D.L., Gan W.Q. et al.* Evidence for linkage and association of the markers near the LPL gene with hypertension in Chinese families // J Med Genet. 2003. 40(5):e57.

13. *Newton-Cheh C., Johnson T., Gateva V., Tobin M.D., Bochud M., Coin L. et al.* Genome-wide association study identifies eight loci associated with blood pressure // Nat Genet. 2009. 41(6):666-76.

14. *Raushan K., Benberin V., Vochshenkova T., Babenko D., Sibagatova A.* Association of 3 single nucleotide polymorphisms of the eighth chromosome with remodeling of the myocardium and carotid arteries in the Kazakh population // Medicine. 2021. 100(6). e24608

15. *Lei S., Peng F., Li M.L., Duan W.B., Peng C.Q., Wu S.J.* LncRNA-SMILR modulates RhoA/ROCK signaling by targeting miR-141 to regulate vascular remodeling in pulmonary arterial hypertension // Am J Physiol Heart Circ Physiol. 2020. 319(2):H377-h91.

16. *Mahmoud A.D., Ballantyne M.D., Miscianinov V., Pinel K., Hung J., Scanlon J.P. et al. T*he Human-Specific and Smooth Muscle Cell-Enriched LncRNA SMILR Promotes Proliferation by Regulating Mitotic CENPF mRNA and Drives Cell-Cycle Progression Which Can Be Targeted to Limit Vascular Remodeling // Circ Res. 2019. 125(5):535-51.

17. *Ballantyne M.D., Pinel K., Dakin R., Vesey A.T., Diver L., Mackenzie R. et al.* Smooth Muscle Enriched Long Noncoding RNA (SMILR) Regulates Cell Proliferation // Circulation. 2016. 133(21):2050-65.

18. *Sadeghi M., Izadi A., Hadavi M.M., Fard M.R., Roohafza H.* Comparison of the effect of 12- and 24-session cardiac rehabilitation on physical, psychosocial and biomedical factors in ischemic heart disease patients. Hormone Molecular Biology and Clinical Investigation. 2020. 41(1).20190023.

19. *Malkin C.J., Pugh P.J., Morris P.D., Asif S., Jones T.H., Channer K.S.* Low serum testosterone and increased mortality in men with coronary heart disease // Heart. 2010. 96(22):1821-5.

20. *Marin P., Holmäng S., Gustafsson C., Jönsson L., Kvist H., Elander A. et al.* Androgen treatment of abdominally obese men // Obes Res. 1993.1(4):245-51.

21. *Corona G., Rastrelli G., Monami M., Guay A., Buvat J., Sforza A. et al.* Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study // Eur J Endocrinol. 2011. 165(5):687-701.

22. *Mendelsohn M.E., Karas R.H.* The protective effects of estrogen on the cardiovascular system // N Engl J Med. 1999. 340(23):1801-11.

23. *Cheng X., Xu G.* Association between aldosterone synthase CYP11B2 polymorphism and essential hypertension in Chinese: a meta-analysis // Kidney Blood Press Res. 2009. 32(2):128-40.

24. MedlinePlus: the National Library of Medicine (NIH): Accessed: 01.08.2023 https://medlineplus.gov/genetics/.

Corresponding author:
Ainur Sibagatova, Master of Health Administration, Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan;
Address: Kazakhstan Astana, Mangilik El str. 80.
E-mail: Sibagatova.ainur@gmail.com, Sibagatova@bmc.mcudp.kz,
Phone: +7 707 996 9464, +7(7172) 70-81-02