Kononov S. I., Azarova Yu. E., Klyosova E. Yu., Bykanova M. A., Solodilova M. A., Polonikov A. V.
Kursk State Medical University, Kursk, Russia

The Protective Effect of Polymorphisms rs2681472 and rs17249754 of the *ATP2B1* Gene Against Coronary Artery Disease and Hypertension is Abolished by Tobacco Smoking

Aim	To study the relationship of single nucleotide polymorphisms rs2681472 and rs17249754 in the *ATP2B1* gene with risk of ischemic heart disease (IHD) and arterial hypertension (AH) among residents of Central Russia and to evaluate the trigger role of smoking as a risk factor for development of IHD and AH in carriers of *ATP2B1* gene polymorphic variants.
Material and methods	The study included DNA samples from 1960 residents of Central Russia of Slavic origin. Among them, there were 1261 patients with cardiovascular diseases and 699 healthy persons. The vast majority of patients had both IHD and AH. Genotyping was performed using the iPLEX technique on a MassARRAY-4 genomic mass-spectrometer. The relationship of *ATP2B1* alleles, genotypes, and haplotypes with the risk of diseases was calculated by logistic regression analysis with adjustments for sex and age.
Results	Carriage of AG and GG (rs2681472) genotypes and GA (rs17249754) genotype was associated with a reduced risk of both IHD (p=0.0057 and p=0.022 for rs2681472 and rs17249754, respectively) and AH (p=0.016 and p=0.036, respectively). Rare rs2681472G-rs17249754G and rs2681472A-rs17249754A haplotypes were associated with a reduced risk of IHD (odds ratio, OR, 0.22; 95% CI: 0.11–0.46, p=0.0001) and AH (OR, 0.22; 95% CI: 0.10–0.47, p=0.0001). Analysis of the groups stratified by the smoking status showed that in smokers, the studied polymorphic variants did not have a protective action with respect of either IHD or AH. However, in non-smokers, the genotypes AG and GG rs2681472 (OR, 0.62; 95% CI: 0.47–0.80, p=0.0004) and GA rs17249754 (OR, 0.61; 95% CI: 0.47–0.81, p=0.0004) were associated with a reduced risk of IHD and AH (OR, 0.63; 95% CI: 0.48–0.83, p=0.0004 for rs2681472; OR, 0.63; 95% CI: 0.48–0.83, p=0.001 for rs17249754), as well as the carriage of the minor alleles rs2681472-G and rs17249754-A.
Conclusion	It was shown for the first time that the polymorphic variants rs17249754 and rs2681472 of the *ATP2B1* gene are associated with a reduced risk for IHD and AH only in non-smokers.

Keywords	Ischemic heart disease, polymorphism; *ATP2B1;* arterial hypertension; risk; smoking; predisposition; genetics; rs2681472; rs17249754
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Corresponding author Kononov S. I. E-mail: ck325@yandex.ru

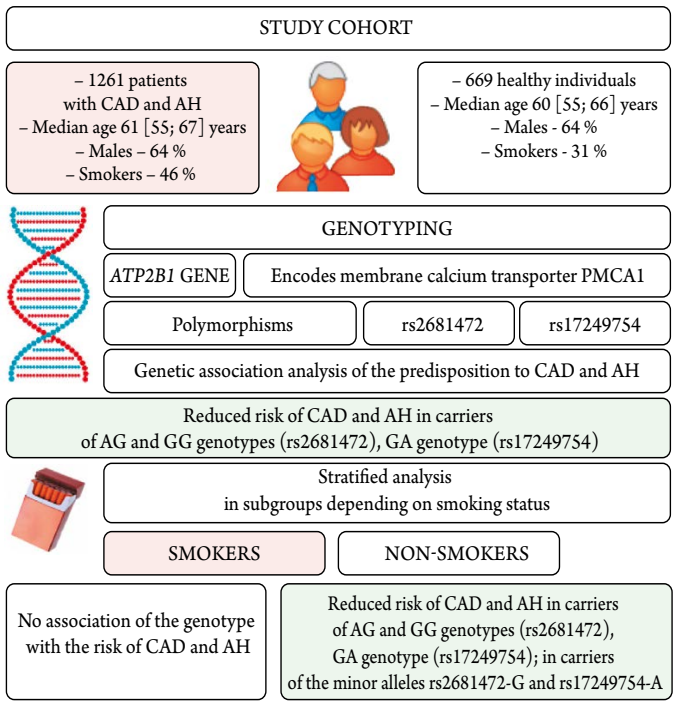
Relevance

Carrying out analysis of the statistics of circulatory diseases mortality in the Russian Federation, attention is drawn to the fact that this category remains the leading one in the structure of causes of death with 640.8 cases per 100 thousand people in 2020 [1]. Personalized medicine technologies, such as patient genotyping, allows establishing a predisposition to development of cardiovascular disease (CVD) [2, 3]. The first genome-wide association studies of coronary artery disease (CAD) were conducted in 2007, and 161 relevant loci had been identified by 2018 [4]. The studies using the candidate gene approach identified about 300 genes involved in metabolic pathways taking part in the development of this disease [5]. Despite the abundance of data, the feasibility of further expanding of knowledge in the field of CVD genetics is explained by the fact that the results of genome-wide association studies should be replicated in various populations worldwide in order to identify ethnicity-specific markers of disease predisposition. Moreover, genetic diagnostics is a way to medicine personalization by the fact that different molecular mechanisms may be involved in the development of a certain pathology [4].

A significant contribution to the pathogenesis of CAD and arterial hypertension (AH) is made by impaired vascular tone as a result of high intracellular concentrations of calcium transported by plasma membrane Ca^{2+} ATPase isoform 1

(PMCA1), which regulates intracellular calcium homeostasis and the production of nitric oxide [6]. Single nucleotide polymorphisms (SNPs) rs2681472 and rs17249754 in the *ATP2B1* gene encoding the above-described PMCA1 protein are associated with the risk of development of AH in various world populations (Europe, East Asia, East Africa) [7–9]. The SNPs of interest are associated with the risk of both CAD and AH development [10–14]. In Russia, the association of rs2681472 with AH was studied but no associations were found [15]. Despite the genetic predisposition, the risk of CVD development can vary due to modifiable risk factors, such as smoking: gene-environment interaction is characteristic of the risk of AH in carriers of one of these variants (rs17249754) [16]. Nevertheless, no data were published in the world literature on the ability of smoking to neutralize or enhance the genotype effect on the risk of CAD development due to this SNP and the risk of CAD and AH development due to another polymorphic variant in the same gene (rs2681472). Thus, the aim of this study was to investigate the association of polymorphisms of the *ATP2B1* gene (rs2681472 and rs17249754 SNPs) with the risk of CAD and AH among the residents of Central Russia and to analyze the trigger role of smoking as a CVD risk factor in carriers of *ATP2B1* polymorphisms.

Central illustration. The Protective Effect of Polymorphisms rs2681472 and rs17249754 of the *ATP2B1* Gene Against Coronary Artery Disease and Hypertension is Abolished by Tobacco Smoking



Material and methods

Sample characteristics

The study was carried out in compliance with all ethical principles: Declaration of Helsinki, signed voluntary informed consent, approval of the local Ethics Committee of Kursk State Medical University. The data from the biobank of the Research Institute for Genetic and Molecular Epidemiology of Kursk State Medical University accumulated in genetic and epidemiological studies of CVD were used in this study [17–19]. The study included DNA samples and phenotypic data from 1960 residents of Central Russia of Slavic origin. Data from 1261 and 1160 patients with CAD and AH respectively and 699 healthy individuals were used to analyze the associations of the *ATP2B1* gene polymorphisms. The vast majority of patients (n=1144) had both CAD and AH, which was 98.5% of persons with AH and 90.7% of patients with CAD. The CAD diagnosis included patients with stable angina pectoris and postinfarction cardiosclerosis. Stable angina pectoris was diagnosed based on the clinical picture of the disease in combination with stress tests (treadmill test, bicycle ergometry) and 24-hour ECG monitoring. Persistently increased blood pressure above 140/90 mm Hg or oral antihypertensive therapy with previously diagnosed AH was used as a criterion for arterial hypertension. The median age of healthy individuals was 60 (55; 66) years and the median age of patients with CAD was 61 (55; 67) years (p=0.33). Distribution of patients by sex was the following: 447 male and 252 female patients (64% versus 36%) in the control group and 809 male and 452 female patients (64% versus 36%) in the main group. The groups did not differ from each other by this parameter (p=0.93). There were fewer smokers among healthy people (219 (31.3%) individuals) than in the main group (585 (46.4%) patients; p=0.0006). Body mass index was 26.2 (24.0; 29.6) kg/m^2 in the group of healthy individuals and 28.5 (25.5; 32.3) g/m^2 in the group of patients with CAD (p<0.0001). 434 patients (34.4%) had a history of myocardial infarction.

Drug therapy of patients with CAD most of whom had AH included an antiplatelet agent (acetylsalicylic acid 75 mg/day), lipid-lowering drugs (rosuvastatin (5–40 mg/day) or atorvastatin (20–40 mg/day) in individual doses sufficient to attain target levels of low-density lipoprotein cholesterol), an angiotensin-converting enzyme inhibitor (mainly perindopril 2.5–10 mg/day). A beta-blocker (mainly bisoprolol 2.5–10 mg/day), a dihydropyridine calcium channel blocker (amlodipine 5–10 mg/day) were used as antianginal therapy. Patients with congestive heart failure received diuretics: loop diuretics (torasemide 2.5–10 mg/day), mineralocorticoid receptor antagonists (spironolactone 25–50 mg/day).

Genetic association analysis

SNPs rs2681472 and rs17249754 of the *ATP2B1* gene were selected based on the known data on their associations with the risk of AH [7–9], CAD [10–14], and in relation with the biological function of *ATP2B1* and its involvement in processes related to the pathogenesis of CVD: regulation of vascular tone and functional activity of endothelium [6, 20].

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SNP genotyping was performed using the iPLEX technology on a genomic mass spectrometer MassARRAY-4 (Agena Bioscience, USA). MassARRAY Assay Design Suite (https://agenacx.com) was used to design the multiplex panel. A total of 1954 of 1960 (99.7%) samples were genotyped for rs2681472, and 1952 (99.6%) samples for rs17249754.

Statistical analysis

The test of the genotype distribution for Hardy-Weinberg equilibrium was performed using the Fisher exact test. The association of alleles, genotypes, and haplotypes of *ATP2B1* with the risk of diseases was assessed by logistic regression with the calculation of odds ratio (OR) and 95% confidence interval (CI) adjusted for sex and age. SNPStats (https://SNPStats.net) was used to analyze the associations [21]. Descriptive statistics and the comparison of the patient group and healthy individuals by quantitative parameters were performed in Statistica version 13.3 (TIBCO, USA). All results of the statistical analysis were considered significant at $p<0.05$.

Results

Genotype frequency distribution of both polymorphisms of interest (rs2681472 (p=0.57) and rs17249754 (p=0.63)) were in Hardy-Weinberg equilibrium. Table 1 presents the frequencies of genotypes of *ATP2B1* polymorphisms in patients with CAD, as well as patients with AH, and healthy individuals. It was found that both *ATP2B1* SNPs were associated with the risk of CAD and AH. Carriers of the rs2681472 G minor allele had a reduced risk of CAD (p=0.0057) and AH (p=0.016). As for rs17249754, carriers of the heterozygous GA genotype had a reduced risk of both diseases (p=0.022 and p=0.036 for CAD and AH, respectively). The rs2681472 G allele was associated with a reduced risk of both diseases (p=0.006 and p=0.019 for CAD and AH, respectively, Table 1).

The results of the analysis of the associations of *ATP2B1* haplotypes with the risk of CAD and AH are given in Table 2, according to which rare haplotypes rs17249754G-rs2681472G and rs17249754A-rs2681472A were associated with a reduced risk of both CAD and AH (p=0.0001 for CAD and AH) independently of sex and age of patients.

Smoking is a known leading risk factor of CVD [22]. In this regard, it was of interest to study the effect of smoking on the genetic predisposition to the development of CAD and AH in individuals with different *ATP2B1* genotypes in the subgroups stratified by smoking status. The results of analysis are provided in Table 3.

The most noteworthy was the complete absence of associations of the genotype with the risk of both CAD and AH development in a group of smokers. Both polymorphisms were associated in non-smokers with reduced risks of both diseases (the same genotypes as in the general samples but with higher levels of significance, Table 3). Moreover, attention can be paid to the association of the rs17249754 A minor allele with a reduced risk of both diseases in non-smokers (p=0.01 and p=0.021 for the risk of CAD and AH, respectively), while this association was not observed in the general patient samples (before stratification by smoking status). The protective effect of the minor allele of another SNP studied rs2681472 G of the *ATP2B1* gene on the risk of CAD and AH development was more significant in non-smokers (p=0.001 and p=0.003 for the risk of CAD and AH respectively, Table 3) compared with the analysis results in the general samples (p=0.006 and p=0.019 for the risk of CAD and AH respectively, Table 1). The identified associations did not depend on the patients' sex and age.

Discussion

Table 1. Allele and genotype frequencies of the ATP2B1 gene single nucleotide polymorphisms in the studied groups

Gene (SNP)	Genotype, allele	Healthy subjects, n (%)[1]	Patients, n (%)[1]	OR (95% CI)[2]	p
Associations with coronary artery disease					
rs2681472	A/A	492 (70.4)	954 (76.0)	1.00	0.0057
	A/G	189 (27.0)	278 (22.1)	0.77 (0.64–0.93)	
	G/G	18 (2.6)	23 (1.8)		
		N=699	N=1255		
	G	225 (16.1)	324 (12.9)	0.77 (0.64–0.93)	0.006
rs17249754	G/G	505 (72.2)	956 (76.3)	1.00	0.022
	A/A	9 (1.3)	22 (1.8)		
	G/A	185 (26.5)	275 (21.9)	0.78 (0.63–0.96)	
		N=699	N=1253		
	A	203 (14.5)	319 (12.7)	0.86 (0.71–1.04)	0.115
Associations with arterial hypertension					
rs2681472	A/A	492 (70.4)	870 (75.4)	1.00	0.016
	A/G	189 (27.0)	261 (22.6)	0.77 (0.62–0.95)	
	G/G	18 (2.6)	23 (2.0)		
		N=699	N=1154		
	G	225 (16.1)	307 (13.3)	0.80 (0.66–0.96)	0.019
rs17249754	G/G	505 (72.2)	873 (75.8)	1.00	0.036
	A/A	9 (1.3)	22 (1.9)		
	G/A	185 (26.5)	257 (22.3)	0.79 (0.64–0.98)	
		N=699	N=1152		
	A	203 (14.5)	301 (13.1)	0.88 (0.73–1.07)	0.210

[1] Absolute number and % of patients with genotypes or alleles shown.
[2] Odds ratio (95% confidence interval) adjusted for sex and age.

In the present study, the role of the rs2681472 and rs17249754 polymorphisms of the *ATP2B1* gene in the development of CVDs. such as CAD and AH was established. Associations of the SNPs studied with the risk of AH development were previously studied in various world populations [7–9], however, these associations were established in the residents of Central Russia for the first time. Known associations with the risk of CAD [10–14] were also confirmed in this study for the residents of Central Russia. The effect of smoking on the predisposition to CAD for rs17249754 and CAD and AH for rs2681472 was established for the first time. The findings indicate that smoking is an important risk modifier for the development of CVD, the contribution of which significantly outweighs the contribution of genotypes of the *ATP2B1* gene polymorphisms. Reduced risk of CAD and AH development in the carriers of rs2681472 G and rs17249754 A minor alleles was characteristic only of non-smokers, while smokers did not have a protective effect against CAD and AH given by the genotype.

It is necessary to consider the function of the *ATP2B1* gene to understand the mechanisms by which the SNPs of interest influence CVD risk. This gene encodes an ATP-dependent calcium channel (PMCA1) that provides the transfer of calcium ions from the cell [19], which regulates vascular tone, and alters the production of nitric oxide in the endothelium [6]. It was shown that reduced expression of this gene causes an increase in calcium levels in vascular smooth muscles, which leads to vasoconstriction and increased blood pressure, and some polymorphisms of this gene are associated with treatment-resistant arterial hypertension [20]. Both *ATP2B1* gene SNPs (rs2681472, rs17249754) of interest are intronic, and the association with the risk of CVD is assumed to be due to their effect on the *ATP2B1* gene expression [7], which results in changes in vascular reactivity and arterial wall stiffness [23, 24], as well as ionic homeostasis. In this context, the results of studies showing the relationship of the studied *ATP2B1* gene polymorphisms with sensitivity to dietary salt, calcium and potassium, and sodium retention in the body, are of interest [7, 25]. It was shown that carriers of the rs17249754 G allele are susceptible to AH only if they have low levels of calcium and potassium and high concentration of sodium in food [25]. The mechanism of rs2681472 influence on the risk of CAD may be associated with the location of SNP in the genome region close to the GALNT4 gene that encodes the N-acetyl-galactosaminyltransferase 4 involved in the modification of glycoproteins and affecting platelets and vascular endothelial cells [12]. This fact is confirmed by the genomic transcriptomic data of eQTLGen Consortium (https://eqtlgen.org) which indicates the association of both SNPs with changes in the GALNT4 expression [26].

The link of the established associations with smoking was studied earlier in one work and only in relation to rs17249754

Table 2. Haplotype frequencies of the ATP2B1 gene single nucleotide polymorphisms rs17249754, rs2681472 in patients with coronary artery disease, arterial hypertension and healthy individuals

Haplotype		Haplotype frequencies		OR (95% CI)[1]	p
rs17249754 G>A	rs2681472 A>G	Healthy subjects	Patients		
Associations with coronary artery disease					
Frequent haplotypes					
G	A	0.84	0.87	1.00	–
A	G	0.15	0.13	0.88 (0.73–1.07)	0.11
Rare haplotypes					
G	G	0.02	0.002	0.22 (0.11–0.46)	0.0001
A	A	0.002	0.002		
		N=699	N=1253		
Associations with arterial hypertension					
Frequent haplotypes					
G	A	0.84	0.86	1.00	–
A	G	0.14	0.13	0.88 (0.73–1.07)	0.22
Rare haplotypes					
G	G	0.008	0.003	0.22 (0.10–0.47)	0.0001
A	A	0.002	0.001		
		N=699	N=1152		

[1] Odds ratio (95% confidence interval) adjusted for sex and age.

and the risk of AH [16], but the molecular mechanism of such interaction remains unknown. It can be assumed that the identified gene-environment interaction can be explained by the influence of both nicotine or other chemical components of tobacco smoke and the product of the gene of interest on the same targets: vascular tone and endothelial dysfunction, taking into account that the studied polymorphisms can change the expression of calcium ion transporter [7]. Supposably, the increased expression of this gene leads to a decrease in the levels of calcium in vascular smooth muscles, which reduces the likelihood of vasoconstriction, normalizes the production of nitric oxide [6, 20], but the components of tobacco smoke (such as nicotine) negatively affect these processes, reducing the bioavailability of nitric oxide [22] and provoking vasoconstriction. However, these assumptions should be confirmed experimentally.

A certain limitation of this study is the investigation of only two described variants, but not the entire spectrum of known polymorphisms of the *ATP2B1* gene. Besides that, the study is based on the principle of including patients predominantly having both pathologies (CAD and AH), thus it is incorrect to interpret the results for patients with CAD without AH based on our findings. This characteristic of the sample can be considered, on the one hand, a certain limitation, but on the other hand, the sample reflects the characteristics of real-world clinical practice, such as the presence of AH in a large number

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Table 3. Allele and haplotype frequencies of the ATP2B1 gene polymorphisms in patients with coronary artery disease, arterial hypertension and healthy individuals, residents of Central Russia, in smoker and non-smoker subgroups

Gene (SNP)	Genotype, allele	Healthy subjects, n (%)[1]	Patients, n (%)[1]	OR (95% CI)[2]	p
Associations with coronary artery disease					
Non-smokers					
rs2681472	A/A	320 (67,7)	512 (76,8)	1,00	0,0004
	A/G	141 (29,8)	143 (21,4)	0,62 (0,47–0,80)	
	G/G	12 (2,5)	12 (1,8)		
		N=473	N=667		
	G	165 (17,4)	167 (12,5)	0,68 (0,54–0,86)	0,001
rs17249754	G/G	324 (68,5)	513 (76,7)	1,00	0,0004
	A/A	5 (1,1)	11 (1,6)		
	G/A	144 (30,4)	145 (21,7)	0,61 (0,47–0,81)	
		N=473	N=669		
	A	154 (16,3)	167 (12,5)	0,73 (0,58–0,93)	0,01
Smokers					
rs2681472	A/A	166 (75,8)	440 (75,2)	1,00	0,96
	A/G	47 (21,5)	134 (22,9)	0,99 (0,69–1,43)	
	G/G	6 (2,7)	11 (1,9)		
		N=219	N=585		
	G	59 (13,5)	156 (13,3)	0,99 (0,72–1,36)	0,94
rs17249754	G/G	175 (79,9)	441 (75,9)	1,00	0,27
	A/A	4 (1,8)	11 (1,9)		
	G/A	40 (18,3)	129 (22,2)	1,25 (0,84–1,85)	
		N=219	N=581		
	A	48 (11,0)	151 (13,0)	1,21 (0,86–1,70)	0,27

Gene (SNP)	Genotype, allele	Healthy subjects, n (%)[1]	Patients, n (%)[1]	OR (95% CI)[2]	p
Associations with arterial hypertension					
Non-smokers					
rs2681472	A/A	320 (67,7)	481 (76,2)	1,00	0,0004
	A/G	141 (29,8)	138 (21,9)	0,63 (0,48–0,83)	
	G/G	12 (2,5)	12 (1,9)		
		N=473	N=631		
	G	165 (17,4)	162 (12,8)	0,70 (0,55–0,88)	0,003
rs17249754	G/G	324 (68,5)	482 (76,2)	1,00	0,001
	A/A	5 (1,1)	11 (1,7)		
	G/A	144 (30,4)	140 (22,1)	0,63 (0,48–0,83)	
		N=473	N=633		
	A	154 (16,3)	162 (12,8)	0,75 (0,59–0,96)	0,021
Smokers					
rs2681472	A/A	166 (75,8)	440 (75,2)	1,00	0,96
	A/G	47 (21,5)	134 (22,9)	0,99 (0,69–1,43)	
	G/G	6 (2,7)	11 (1,9)		
		N=219	N=585		
	G	59 (13,5)	156 (13,3)	0,99 (0,72–1,36)	0,94
rs17249754	G/G	175 (79,9)	441 (75,9)	1,00	0,27
	A/A	4 (1,8)	11 (1,9)		
	G/A	40 (18,3)	129 (22,2)	1,25 (0,84–1,85)	
		N=219	N=581		
	A	48 (11,0)	151 (13,0)	1,21 (0,86–1,71)	0,27

[1] Absolute number and % of patients with genotypes or alleles shown.
[2] Odds ratio (95% confidence interval) adjusted for sex and age.

of patients with CAD. The association of polymorphisms with only AH in patients without CAD was already shown earlier in multiple studies [7–9] in various populations.

Conclusion

In this study, the association of the rs2681472 and rs17249754 polymorphisms of the *ATP2B1* gene and the risk of CAD and AH development was established in the residents of Central Russia for the first time. The carriage of the minor G allele of rs2681472 SNP and the rs17249754 GA genotype was associated with a reduced risk of these diseases. Smoking is an important trigger factor that modifies the association of the *ATP2B1* gene SNPs with the risk of CAD and AH development, by elimination of the protective effect of the genotype in smokers.

No conflict of interest is reported.

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REFERENCES

1. Federal State Statistics Service. Health in Russia. 2021. Statistical book. -M.: Rosstat;2021. - 171 p. [Russian: Федеральная служба государственной статистики. Здравоохранение в России. 2021. Статистический сборник. - М.: Росстат, 2021. - 171с. Доступно на: https://rosstat.gov.ru/storage/mediabank/Zdravoohran-2021.pdf]
2. Medvedeva M.V. Associations of rs2305948 and rs1870377 polymorphic variants of the vascular endothelial growth factor receptor type 2 (KDR) gene with the risk of coronary heart disease. Research Results in Biomedicine. 2021;7(1):32–43. [Russian: Медведева М.В. Ассоциации полиморфных вариантов rs2305948 и rs1870377 гена рецептора фактора роста сосудистого эндотелия 2 типа (KDR) с риском развития ишемической болезни сердца. Научные результаты биомедицинских исследований. 2021;7(1):32-43]. DOI: 10.18413/2658-6533-2020-7-1-0-3
3. Dolzhenkova E.M., Baryshev A.S., Ivanova N.V., Bushueva O.Yu., Ivanov V.P., Polonikov A.V. The relationship between -1612 5A/6A polymorphism of MMP3 gene and 2003g>a of MMP9 gene and coronary heart disease risk in population of Central Russia. Humans and their Health. 2016;3:63–6. [Russian: Долженкова Е.М., Барышев А.С., Иванова Н.В., Бушуева О.Ю., Иванов В.П., Полоников А.В. Иссле-

дование взаимосвязи полиморфизмов -1612 5A/6A гена MMP3 и 2003G>A гена MMP9 с риском развития ишемической болезни сердца у русских жителей Центральной России. Человек и его здоровье. 2016;3:63-6]. DOI: 10.21626/vestnik/2016-3/10

4. van der Harst P, Verweij N. Identification of 64 Novel Genetic Loci Provides an Expanded View on the Genetic Architecture of Coronary Artery Disease. Circulation Research. 2018;122(3):433–43. DOI: 10.1161/CIRCRESAHA.117.312086
5. Gorre M, Rayabarapu P, Battini SR, Irgam K, Battini MR. Analysis of 61 SNPs from the CAD specific genomic loci reveals unique set of SNPs as significant markers in the Southern Indian population of Hyderabad. BMC Cardiovascular Disorders. 2022;22(1):148. DOI: 10.1186/s12872-022-02562-4
6. Long Y, Xia J, Chen S, Gao C, Liang G, He X et al. *ATP2B1* gene Silencing Increases Insulin Sensitivity through Facilitating Akt Activation via the Ca2+/calmodulin Signaling Pathway and Ca^{2+}-associated eNOS Activation in Endothelial Cells. International Journal of Biological Sciences. 2017;13(9):1203–12. DOI: 10.7150/ijbs.19666
7. Xie M, Yuan S, Zeng Y, Zheng C, Yang Y, Dong Y et al. *ATP2B1* gene polymorphisms rs2681472 and rs17249754 are associated with susceptibility to hypertension and blood pressure levels: A systematic review and meta-analysis. Medicine. 2021;100(15):e25530. DOI: 10.1097/MD.0000000000025530
8. Takeuchi F, Akiyama M, Matoba N, Katsuya T, Nakatochi M, Tabara Y et al. Interethnic analyses of blood pressure loci in populations of East Asian and European descent. Nature Communications. 2018;9(1):5052. DOI: 10.1038/s41467-018-07345-0
9. Lu X, Wang L, Lin X, Huang J, Charles Gu C, He M et al. Genome-wide association study in Chinese identifies novel loci for blood pressure and hypertension. Human Molecular Genetics. 2015;24(3):865–74. DOI: 10.1093/hmg/ddu478
10. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S et al. A cross-population atlas of genetic associations for 220 human phenotypes. Nature Genetics. 2021;53(10):1415–24. DOI: 10.1038/s41588-021-00931-x
11. Koyama S, Ito K, Terao C, Akiyama M, Horikoshi M, Momozawa Y et al. Population-specific and trans-ancestry genome-wide analyses identify distinct and shared genetic risk loci for coronary artery disease. Nature Genetics. 2020;52(11):1169–77. DOI: 10.1038/s41588-020-0705-3
12. Takeuchi F, Isono M, Yamamoto K, Yokota M, Akiyama K, Katsuya T et al. Heterogeneous Effects of Association Between Blood Pressure Loci and Coronary Artery Disease in East Asian Individuals. Circulation Journal. 2015;79(4):830–8. DOI: 10.1253/circj.CJ-14-0841
13. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S et al. A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease. Nature Genetics. 2015;47(10):1121–30. DOI: 10.1038/ng.3396
14. Lieb W, Jansen H, Loley C, Pencina MJ, Nelson CP, Newton-Cheh C et al. Genetic Predisposition to Higher Blood Pressure Increases Coronary Artery Disease Risk. Hypertension. 2013;61(5):995–1001. DOI: 10.1161/HYPERTENSIONAHA.111.00275
15. Mazdorova E.V., Maksimov V.N., Orlov P.S., Shakhmatov S.G., Ryabikov A.N., Voevoda M.I. et al. Analysis of associations of hypertension with 16 genetic markers selected according to genome-wide studies. Arterial Hypertension. 2022;28(1):46–57. [Russian: Маздорова Е.В., Максимов В.Н., Орлов П.С., Шахматов С.Г., Рябиков А.Н., Воевода М.И. и др. Анализ ассоциаций артериальной гипертензии с 16 генетическими маркерами, отобранными по данным полногеномных исследований. Артериальная гипертензия. 2022;28(1):46-57]. DOI: 10.18705/1607-419X-2022-28-1-46-57
16. Sung YJ, Winkler TW, De Las Fuentes L, Bentley AR, Brown MR, Kraja AT et al. A Large-Scale Multi-ancestry Genome-wide Study Accounting for Smoking Behavior Identifies Multiple Significant Loci for Blood Pressure. The American Journal of Human Genetics. 2018;102(3):375–400. DOI: 10.1016/j.ajhg.2018.01.015
17. Bushueva O.Yu. Single nucleotide polymorphisms in genes encoding xenobiotic metabolizing enzymes are associated with predisposition to arterial hypertension. Research Results in Biomedicine. 2020;6(4):447–56. DOI: 10.18413/2658-6533-2020-6-4-0-1
18. Polonikov A, Bocharova I, Azarova I, Klyosova E, Bykanova M, Bushueva O et al. The Impact of Genetic Polymorphisms in Glutamate-Cysteine Ligase, a Key Enzyme of Glutathione Biosynthesis, on Ischemic Stroke Risk and Brain Infarct Size. Life. 2022;12(4):602. DOI: 10.3390/life12040602
19. Lazarenko V, Churilin M, Azarova Yu, Klyosova E, Bykanova M, Ob'edkova N et al. Comprehensive Statistical and Bioinformatics Analysis in the Deciphering of Putative Mechanisms by Which Lipid-Associated GWAS Loci Contribute to Coronary Artery Disease. Biomedicines. 2022;10(2):259. DOI: 10.3390/biomedicines10020259
20. Weng L, Taylor KD, Chen Y-DI, Sopko G, Kelsey SF, Bairey Merz CN et al. Genetic loci associated with nonobstructive coronary artery disease in Caucasian women. Physiological Genomics. 2016;48(1):12–20. DOI: 10.1152/physiolgenomics.00067.2015
21. Solé X, Guinó E, Valls J, Iniesta R, Moreno V. SNPStats: a web tool for the analysis of association studies. Bioinformatics. 2006;22(15):1928–9. DOI: 10.1093/bioinformatics/btl268
22. Gaemperli O, Liga R, Bhamra-Ariza P, Rimoldi O. Nicotine Addiction and Coronary Artery Disease: Impact of Cessation Interventions. Current Pharmaceutical Design. 2010;16(23):2586–97. DOI: 10.2174/138161210792062894
23. Wei B-L, Yin R-X, Liu C-X, Deng G-X, Guan Y-Z, Zheng P-F. CYP17A1–*ATP2B1* SNPs and Gene–Gene and Gene–Environment Interactions on Essential Hypertension. Frontiers in Cardiovascular Medicine. 2021;8:720884. DOI: 10.3389/fcvm.2021.720884
24. Wang Y, Zhang Y, Li Y, Zhou X, Wang X, Gao P et al. Common variants in the *ATP2B1* gene are associated with hypertension and arterial stiffness in Chinese population. Molecular Biology Reports. 2013;40(2):1867–73. DOI: 10.1007/s11033-012-2242-3
25. Daily JW, Kim BC, Liu M, Park S. People with the major alleles of *ATP2B1* rs17249754 increases the risk of hypertension in high ratio of sodium and potassium, and low calcium intakes. Journal of Human Hypertension. 2017;31(12):787–94. DOI: 10.1038/jhh.2017.72
26. Võsa U, Claringbould A, Westra H-J, Bonder MJ, Deelen P, Zeng B et al. Unraveling the polygenic architecture of complex traits using blood eQTL meta-analysis. Genomics. 2018. DOI: 10.1101/447367.

ISSN 0022-9040. Kardiologiia. 2023;63(9). DOI: 10.18087/cardio.2023.9.n2252