УДК 616.136-007.64-056.7
DOI: https://doi.org/10.17816/PAVLOVJ108311

Роль и значение ряда полиморфизмов генов у пациентов с аневризмой брюшной аорты

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АННОТАЦИЯ

Введение. До настоящего времени многие факторы, влияющие на риск и течение развития аневризмы брюшной аорты (АБА), являются неизученными. Все большее значение в этиологии и развитии АБА придается наличию некоторых генетических полиморфизмов, роль многих из которых также не изучена.

Цель. Проанализировать наличие ассоциации аневризмы брюшной аорты с рядом полиморфизмов генов (ПГ).

Материалы и методы. Проанализированы ПГ у 20 пациентов с АБА (исследуемая группа, ИГ; 18 мужчин (90%) и 2 женщины (10%), средний возраст — 68,1 ± 7,3 года) и у 5 пациентов без АБА (контрольная группа, КГ; 4 мужчины (80%) и 1 женщина (20%), средний возраст — 64,2 ± 7,2 года). Определялась частота сопутствующих заболеваний и факторов риска АБА. Изучены ПГ: Lys198Asn в гене *EDN1*; C-786T в гене *NOS3*; Leu28Pro в гене *APOE*; Val174Ala в гене *SLC01B1*; Thr715Pro в гене *SELP*; C807T в гене *ITGA2*; Ser447Ter в гене *LpL*; Thr174Met в гене *AGT*; Met235Thr в гене *AGT*. Статистический анализ проводили с помощью «IBM SPSS Statistics 21», корреляционный анализ проводили по Пирсону. Результаты считали статистически значимыми при $p < 0,05$.

Результаты. В ИГ корреляционные связи были выявлены при полиморфизме Ser447Ter в гене *LpL*: прямые связи с полиморфизмами Lys198Asn ($r = 0,63$; $p < 0,001$) в гене *EDN1*, Leu28Pro ($r = 0,70$; $p < 0,001$) в гене *APOE* и Thr715Pro ($r = 0,63$; $p < 0,001$) в гене *SELP*; обратная связь с полиморфизмом C786T ($r = -0,35$; $p = 0,006$) в гене *NOS3*. Столько же связей у полиморфизма Leu28Pro в гене *APOE*: наряду с Ser447Ter в гене *LpL* ещё имеются прямая связь с Lys198Asn ($r = 0,70$; $p < 0,001$) в гене *EDN1* и Thr715Pro ($r = 0,63$; $p < 0,001$) в гене *SELP*; обратная связь с C786T ($r = -0,35$; $p = 0,006$) в гене *NOS3*. У полиморфизма Thr715Pro в гене *SELP* также наряду со связями Ser447Ter ($r = 0,63$; $p < 0,001$) в гене *LpL* и Leu28Pro в гене *APOE* имеется дополнительно прямая связь с Lys198Asn ($r = 0,55$; $p < 0,001$) в гене *EDN1*. У полиморфизма Thr174Met в гене *AGT* имеется обратная связь с Leu28Pro ($r = -0,35$; $p = 0,006$) в гене *APOE* и прямая связь с Val174Ala ($r = 0,40$; $p = 0,002$) в гене *SLC01B1*. При этом у полиморфизма Met235Thr в гене *AGT* имеется прямая связь с Val174Ala ($r = 0,33$; $p = 0,011$) в гене *SLC01B1* и обратная связь с C807T в гене *ITGA2*.

Заключение. Установлено наличие прямых корреляций некоторых полиморфизмов генов у пациентов с аневризмой брюшной аорты, что указывает на их возможную роль в развитии данной патологии и может являться скрининговым тестом для определения вероятности ее развития.

Ключевые слова: *аневризма брюшной аорты; полиморфизмы генов; корреляция полиморфизмов; генетика аневризмы брюшной аорты*

Для цитирования:
Kalmykov E.L., Сучков И.А., Калинин Р.Е., Неъматзода О., Додхоев Д.С. Роль и значение ряда полиморфизмов генов у пациентов с аневризмой брюшной аорты // Российский медико-биологический вестник имени академика И.П. Павлова. 2022. Т. 30, № 4. С. 437–445. DOI: https://doi.org/10.17816/PAVLOVJ108311

Рукопись получена: 29.05.2022 **Рукопись одобрена:** 14.09.2022 **Опубликована:** 31.12.2022

ЭКО•ВЕКТОР

DOI: https://doi.org/10.17816/PAVLOVJ108311

The Role and Significance of Polymorphisms of Certain Genes in Patients with Abdominal Aortic Aneurysm

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ABSTRACT

INTRODUCTION: To date, many factors that influence the risk and course of abdominal aortic aneurysm (AAA) are not studied. Increasing significance in the etiology and development of AAA is assigned to the existence of some genetic polymorphisms, the role of many of them is not studied either.

AIM: To analyze the existence of association of the abdominal aortic aneurysm with some gene polymorphisms (GPs).

MATERIALS AND METHODS: Gene polymorphisms were analyzed in 20 patients with AAA (study group, SG); 18 men (90%) and 2 women (10%), the mean age 68.1 ± 7.3 years), and in 5 patients without AAA (control group, CG; 4 men (80%) and 1 woman (20%), the mean age 64.2 ± 7.2 years). The frequency of concomitant diseases and risk factors for AAA were determined. The following GPs were studied: : Lys198Asn in the *EDN1* gene; C-786T in the *NOS3* gene; Leu28Pro in the *APOE* gene; Val174Ala in the *SLC01B1* gene; Thr715Pro in the *SELP* gene; C807T in the *ITGA2* gene; Ser447Ter in the *LpL* gene; Thr174Met in the *AGT* gene; Met235Thr in the *AGT* gene. Statistical analysis was performed using IBM SPSS Statistics 21, correlation analysis — according to Pearson. The results were considered statistically significant at $p < 0.05$.

RESULTS: In the SG, correlation relationships were identified in Ser447Ter polymorphism in the *LpL* gene: direct relationships with Lys198Asn polymorphism ($r = 0.63$; $p < 0.001$) in the *EDN1* gene, Leu28Pro ($r = 0.70$; $p < 0.001$) in the *APOE* gene and Thr715Pro ($r = 0.63$; $p < 0.001$) in the *SELP* gene; a reverse relationship with C786T polymorphism ($r = -0.35$; $p = 0.006$) in the *NOS3* gene. The same amount of relationships were found in Leu28Pro polymorphism in the *APOE* gene: besides with Ser447Ter in the *LpL* gene, there is also a direct relationship with Lys198Asn ($r = 0.70$; $p < 0.001$) in the *EDN1* gene and Thr715Pro ($r = 0.63$; $p < 0.001$) in the *SELP* gene; a reverse relationship with C786T ($r = -0.35$; $p = 0.006$) in the *NOS3* gene. Thr715Pro polymorphism in the *SELP* gene, along with relationships with Ser447Ter ($r = 0.63$; $p < 0.001$) in the *LpL* gene and Leu28Pro in the *APOE* gene, has an additional direct relationship with Lys198Asn ($r = 0.55$; $p < 0.001$) in the *EDN1* gene. Thr174Met polymorphism in the *AGT* gene has a reverse relationship with Leu28Pro ($r = -0.35$; $p = 0.006$) in the *APOE* gene and direct relationship with Val174Ala ($r = 0.40$; $p = 0.002$) in the *SLC01B1* gene. With this, Met235Thr polymorphism in the *AGT* gene has a direct relationship with Val174Ala ($r = 0.33$; $p = 0.011$) in the *SLC01B1* gene and reverse relationship with C807T in the *ITGA2* gene.

CONCLUSION: The existence of direct correlations of some gene polymorphisms in patients with abdominal aortic aneurysm has been established, which indicates their probable role in the development of this pathology and may be used as a screening test for determination of the likelihood for its development.

Keywords: *abdominal aortic aneurysm; gene polymorphism; correlation of polymorphisms; genetics of abdominal aortic aneurysm*

For citation:
Kalmykov EL, Suchkov IA, Kalinin RE, Ne'matzoda O, Dodkhoyev DS. The Role and Significance of Polymorphisms of Certain Genes in Patients with Abdominal Aortic Aneurysm. *I.P. Pavlov Russian Medical Biological Herald*. 2022;30(4):437–445. DOI: https://doi.org/10.17816/PAVLOVJ108311

Received: 29.05.2022 **Accepted:** 14.09.2022 **Published:** 31.12.2022

ECO•VECTOR

LIST OF ABBREVIATIONS

AAA — abdominal aortic aneurysm
ACE — angiotensin converting enzyme
AGT — angiotensin
AH — arterial hypertension
Ala — alanin
APOE — apolipoprotein E
Asn — asparagine
CHD — coronary heart disease
CI — confidence interval
COPD — chronic obstructive pulmonary disease
EDN1 — endothelin-1
GPs — gene polymorphisms
ITGA2 — integrin alpha-2
Leu — leucine
LpL — lipoprotein lipase
Lys — lysine
Met — methionine
NOS3 — nitric oxide synthase 3
OATP1B1 — organic anion transporting polypeptide, 1B1
OR — odds ratio
Pro — proline
SELP — P-selectin
Ser — serin
SLC01B1 — solute carrier organic anion transporter family member 1B1
Ter — termination codon
Thr — tryptophan
Val — valin

INTRODUCTION

Despite a long history of investigation of the etiopathogenesis of the abdominal aortic aneurysm (AAA), many factors that influence the risk and course of the disease, have not been studied up to the present moment. It has been shown in some works that patients with AAA have a number of concomitant diseases mostly associated with disorders of lipid metabolism, vascular endothelial dysfunction, arterial hypertension, diabetes mellitus [1, 2]. However, their role in the pathogenesis of AAA is still being studied, and the results are controversial. Besides, increasing significance in the etiology and pathogenesis of AAA is assigned to some genetic polymorphisms, especially to the risk factors of the development of AAA [3–12]. With this, very few scientific works are devoted to study of gene polymorphisms (GPs) playing a definite role in the development of a number of concomitant pathologies in AAA. In this context, we studied some GPs in patients with AAA in the aspect of their probable influence on the pathogenesis of the disease.

The **aim** of this study was analyze the existence of association of the abdominal aortic aneurysm with some gene polymorphisms.

MATERIALS AND METHODS

The study was approved by the local Ethics Committee of Pavlov Ryazan State Medical University (Protocol No. 11 of 2021, May 11) and registered on ClinicalTrials.gov platform. All the patients signed a written informed consent to participate in this study.

GPs were analyzed in 20 patients with AAA (***study group***) and in 5 patients without AAA (***control group***). Of the total number of patients with AAA (study group) there were 18 (90%) of men, 2 (10%) women. The control group included 4 (80%) men and 1 (20%) woman. The mean age was 68.1 ± 7.3 and 64.2 ± 7.2 years in the study group and the control group, respectively.

In the study group there were 17 (85%) smokers, the *main concomitant diseases* were:

- coronary heart disease (CHD) in 11 (55%) patients;
- diabetes mellitus in 1 (5%) patient;
- carotid artery atherosclerosis/stroke in 4 (20%) patients;
- peripheral artery diseases in 9 (45%) patients;
- arterial hypertension (AH) in 18 (90%) patients;
- aneurysms of other locations in 6 (30%) patients;
- chronic obstructive pulmonary disease in 1 (5%) patient;
- arrhythmia in 4 (20%) patients.

In the control group of 5 volunteers, there was only one case of AH, no other concomitant diseases were identified.

The genetic status of the patients was studied by a molecular genetic method. Blood was taken from the peripheral vein. The genomic DNA was isolated from the whole blood leukocytes using 'DNA-ekspresskrov' reagent (Litekh, Russian Federation) and was analyzed. With the sample of isolated DNA two amplification reactions were performed with two pairs of allele-specific primers, and three conclusions were made: homozygosity for allele1, heterozygosity, homozygosity for allele 2. The choice of genes was based on the integral approach used in the analysis of the etiology and pathogenesis of AAA [3–14].

Polymorphisms of the following genes were analyzed:

- lysine198asparagine (Lys198Asn) in the endothelin 1 (*DN1*) gene;
- C-786T in the nitric oxide synthase 3 (*NOS3*) gene;
- leucine28proline (Leu28Pro) in the apolipoprotein E (*APOE*) gene;
- valin174alanin (Val174Ala) in the gene of solute carrier organic anion transporter family member 1B1 (*SLC01B1*);

DOI: https://doi.org/10.17816/PAVLOVJ108311

- tryptophan715 proline (Thr715Pro) in the P-selectin (*SELP*) gene;
- C807T in the integrin alpha-2 (*ITGA2*) gene;
- serin 447 termination codon (serin447Ter) in the lipoprotein lipase (*LpL*) gene;
- tryptophan174methionine (Thr174Met) in the angiotensin 1 (*AGT*) gene;
- Met235Thr in the *AGT* gene.

Statistical analysis was performed on a PC using IBM SPSS Statistics 21 (IBM Corp., 1989–2012, USA). In the work, qualitative parameters (risk factors and alleles) are presented as fractions. Qualitative parameters were compared using the chi square ($\chi 2$) test for arbitrary tables. Method of logistic regression (the results are given in the form of odds ratio (OR) with confidence interval (CI)), and Pearson correlation analysis (the result is presented as correlation coefficient, r) were used. The differences between the groups were considered statistically significant at $p < 0.05$.

RESULTS

Comparison of the frequency of occurrence of homo- and heterozygotes in the study groups are given in Table 1.

On the basis of the results of Table 1, no statistically significant differences in GPs and their frequency were found by us between the study and control groups.

Table 2 presents the results of the analysis of the existence of homozygous and heterozygous alleles in the study and control groups.

At the next stage of the study, a probable influence of GPs on the development of AAA was analyzed (Table 3).

Table 1. Frequency of Homozygous and Heterozygous Alleles in the Study and Control Groups

Polymorphism in Gene	Group	Homozygote for Allele 1, % (n)	Heterozygote, % (n)	Homozygote for Allele 2, % (n)
Lys198Asn in the *EDN1* gene	Study group, n = 20	80 (16)	15 (3)	5 (1)
	Control group, n = 5	60 (3)	40 (2)	0
	p	> 0.05 (df = 2; $\chi 2$ = 1.71)		
C-786T in the *NOS3* gene	Study group, n = 20	10 (2)	55 (11)	35 (7)
	Control group, n = 5	0	100 (5)	0
	p	> 0.05 (df = 2; $\chi 2$ = 3.52)		
Leu28Pro in the *APOE* gene	Study group, n = 20	100 (20)	0	0
	Control group, n = 5	100 (5)	0	0
	p	> 0.05 (df = 2; $\chi 2$ = NaN)		
Val174Ala in the *SLC01B1* gene	Study group, n = 20	40 (8)	60 (12)	0
	Control group, n = 5	60 (3)	40 (2)	0
	p	> 0.05 (df =2; $\chi 2$ = NaN)		
Thr715Pro in the *SELP* gene	Study group, n = 20	75 (15)	20 (4)	5 (1)
	Control group, n =5	60 (3)	40 (2)	0
	p	> 0.05 (df =2; $\chi 2$ =1.04)		
C807T in the *ITGA2* gene	Study group, n = 20	25 (5)	55 (11)	20 (4)
	Control group, n = 5	40 (2)	60 (3)	0
	p	> 0.05 (df = 2; $\chi 2$ = 1.34)		
Ser447Ter in the *LpL* gene	Study group, n = 20	80 (16)	20 (4)	0
	Control group, n = 5	100 (5)	0	0
	p	> 0.05 (df = 2; $\chi 2$ = NaN)		
Thr174Met in the *AGT* gene	Study group, n = 20	10 (2)	90 (18)	0
	Control group, n = 5	0	100 (5)	0
	p	> 0.05 (df = 2; $\chi 2$ = NaN)		
Met235Thr in the *AGT* gene	Study group, n = 20	40 (8)	40 (8)	20 (4)
	Control group, n = 5	60 (3)	20 (1)	20 (1)
	p	> 0.05 (df = 2; $\chi 2$ = 0.81)		

Table 2. Presence of Homozygous and Heterozygous Alleles in Study and Control Groups

Allele	Study Group, % (n)	Control Group, % (n)	p
Homozygous 1	100 (9)	77.8 (7)	< 0.001 (df = 2; $\chi 2$ = 16.7)
Heterozygous	88.9 (8)	77.8 (7)	
Homozygous 2	55.6 (5)	11.1 (1)	

Table 3. Influence of Gene Polymorphisms on Development of Abdominal Aortic Aneurysm

Allele	OR	95% CI for OR		p
		lower	upper	
Lys198Asn in the *EDN1* gene				
Homozygote for allele 1	2.667	0.327	21.733	> 0.05
Heterozygote	0.265	0.030	2.318	> 0.05
Homozygote for allele 2	–	–	–	–
Val174Ala in the *SLC01B1* gene				
Homozygote for allele 1	0.444	0.060	3.285	> 0.05
Heterozygote	2.250	0.304	16.632	> 0.05
Homozygote for allele 2	–	–	–	–
Thr715Pro in the *SELP* gene				
Homozygote for allele 1	2.000	0.256	15.623	> 0.05
Heterozygote	0.375	0.046	3.056	> 0.05
Homozygote for allele 2	–	–	–	–
C807T in the *ITGA2* gene				
Homozygote for allele 1	0.500	0.064	3.906	> 0.05
Heterozygote	0.815	0.111	5.987	> 0.05
Homozygote for allele 2	–	–	–	–
Met235Thr in the *AGT* gene				
Homozygote for allele 1	0.444	0.060	3.285	> 0.05
Heterozygote	2.667	0.250	28.438	> 0.05
Homozygote for allele 2	1.000	0.086	11.588	> 0.05

Note: OR — odds ratio CI — confidence interval. Influence of the parameters was determined by OR calculated by logistic regression method, and the dependence between parameters — by Pearson correlation analysis

Interesting data were obtained in the correlation analysis (Figures 1, 2).

From the data presented in Figures 1 and 2 it follows that significant correlations of GPs coincided in the study and control groups for the interrelation of Ser447Ter in the *LpL* gene and Leu28Pro (r = 0.70; p < 0.001) in the *APOE* gene.

In the study group of patients, the correlation relationships were identified with Ser447Ter polymorphism in the LpL gene:

- *direct correlation* with Lys198Asn (r = 0.63; p < 0.001) polymorphism in the *EDN1* gene, Leu28Pro (r = 0.70; p < 0.001) in the *APOE* gene and Thr715Pro (r = 0.63; p < 0.001) in the *SELP* gene;

- *inverse correlation* with C786T polymorphism (r = -0.35; p = 0.006) in the *NOS3* gene.

Similar results were obtained for Leu28Pro polymorphism in the *APOE* gene:

- *direct correlation* with Ser447Ter in the *LpL* gene, Lys198Asn (r = 0.70; p < 0.001) in the *EDN1* gene and Thr715Pro (r = 0.63; p < 0.001) in the *SELP* gene;

- *inverse correlation* with C786T (r = -0.35; p = 0.006) in the *NOS3* gene.

Thr715Pro polymorphism in the *SELP* gene, along with correlations with Ser447Ter (r = 0.63; p < 0.001) in the *LpL* gene and Leu28Pro in the *APOE* gene, has an a*dditional direct correlation* with Lys198Asn (r = 0.55; p < 0.001) in the *EDN1* gene.

For Thr174Met polymorphism in the *AGT* gene there were obtained:

- *direct correlation* with Val174Ala (r = 0.40; p = 0.002)

	Lys198	C786	Leu28	Val174	Thr715	C807	Ser447	Thr174	Met235
Lys198									
C786	-0.20 > 0.05								
Leu28	0.70 < 0.001	-0.35 = 0.006							
Val174	0.25 > 0.05	-0.05 > 0.05	0.10 > 0.05						
Thr715	0.55 < 0.001	-0.05 > 0.05	0.63 < 0.001	0.25 > 0.05					
C807	0.02 > 0.05	0.02 > 0.05	-0.13 > 0.05	-0.05 > 0.05	-0.05 > 0.05				
Ser447	0.63 < 0.001	-0.35 = 0.006	0.70 < 0.001	0.10 > 0.05	0.63 < 0.001	-0.05 > 0.05			
Thr174	-0.13 > 0.05	0.18 > 0.05	-0.35 = 0.006	0.40 = 0.002	-0.20 > 0.05	0.18 > 0.05	-0.05 > 0.05		
Met235	0.10 > 0.05	-0.05 > 0.05	0.10 > 0.05	0.33 = 0.011	0.02 > 0.05	-0.28 = 0.033	0.18 > 0.05	0.25 > 0.05	

Fig. 1. Results of Pearson correlation analysis of gene polymorphisms in patients with abdominal aortic aneurysm (study group).
Note: the first number — correlation coefficient (r), the second number — statistical significance (p).

	Lys198	C786	Leu28	Val174	Thr715	C807	Ser447	Thr174	Met235
Lys198									
C786	0.10 > 0.05								
Leu28	0.40 > 0.05	-0.50 > 0.05							
Val174	0.40 > 0.05	0.10 > 0.05	0.40 > 0.05						
Thr715	0.40 > 0.05	0.10 > 0.05	0.40 > 0.05	-0.20 > 0.05					
C807	0.70 = 0.004	0.40 > 0.05	0.10 > 0.05	0.70 = 0.004	0.10 > 0.05				
Ser447	0.40 > 0.05	-0.50 > 0.05	1.00 < 0.001	0.40 > 0.05	0.40 > 0.05	0.10 > 0.05			
Thr174	0.10 > 0.05	1.00 < 0.001	-0.50 > 0.05	0.10 > 0.05	0.10 > 0.05	0.40 > 0.05	-0.50 > 0.05		
Met235	-0.20 > 0.05	-0.20 > 0.05	0.40 > 0.05	0.40 > 0.05	0.10 > 0.05	0.10 > 0.05	0.40 > 0.05	-0.20 > 0.05	

Fig. 2. Results of Pearson correlation analysis of gene polymorphisms in patients without abdominal aortic aneurysm (control group).
Note: the first number — correlation coefficient (r), the second number — statistical significance (p).

in the *SLC01B1* gene;

- *inverse correlation* with Leu28Pro (r = -0,35; p = 0,006) in the *APOE* gene.

To note, polymorphism Met235Thr in the *AGT* gene is:

- *in direct correlation* with Val174Ala (r = 0.33; p = 0.011) in the *SLC01B1* gene;

- *in inverse correlation* with C807T in the *ITGA2* gene.

In the control group, the following correlation relationships were identified:

- C807T polymorphism in the *ITGA2* gene directly correlates with Lys198Asn (r = 0.70; p = 0.004) in the *EDN1* gene and Val174Ala in the *SLC01B1* gene.

- Thr174Met polymorphism in the *AGT* gene directly correlates with C786T (r = 1.00; p < 0.001) in the *NOS3* gene, Ser447Ter in the *LpL* gene and Leu28Pro (r = 1.00; p < 0.001) in the *APOE* gene.

DISCUSSION

The analysis of the presented data revealed statistically significant differences in the dominance of homozygous and heterozygous alleles in the main and control groups, which probably influences the occurrence of AAA. There was also found the absence of polymorphism for the 2nd allele in the control group except for the *AGT* gene (Met235Thr polymorphism). In the meantime, there is little information in the literature about dominance of alleles, their role in the development of AAA and related risk factors.

A. Sethi, et al. found mutations of Thr235 and Met174 among 9100 women and men of the general population of Denmark (54% had AH) in 41% and 12% of cases, respectively; mutation of Met174 always occurred on the same allele as mutation of Thr235. In the multifactorial logistic regression analysis it was found that in women homozygous for Thr235, in comparison with women who are not carriers, OR for AH was 1.29 (95% CI 1.05–1.58); in women homozygous also for Thr174 (and non-carriers of Met174), OR increased to 1.5 (from 1,15 to 1.96). Women, homozygous for Thr235, also had an increased risk of isolated elevation of systolic arterial pressure (OR 1.37; 95% CI 1.02–1.84) and moderate elevation of arterial pressure (OR 40; 95% CI 1.10–1.77). Here, the authors did not reveal any statistically significant correlation between the elevated arterial pressure and genotype in men or between genotype and systolic arterial pressure, diastolic arterial pressure or pulse pressure in both genders. Homozygosity both for Thr235 and Thr174 was associated with 10% increase in the level of angiotensin in plasma in both genders compared to homozygosity for Met235 and Thr174 [6].

J. A. Staessen, et al. showed in their work that, compared to MM homozygotes, TT homozygotes and M heterozygotes had excessive risk for AH in 31% and 11% of cases, respectively [7]. As noted in the work of J. C. Bis, et al., in patients with AH receiving pharmacological therapy, angiotensinogen genotype modified relationship of angiotensin converting enzyme (ACE) inhibitors with the development of stroke, and the risk of stroke associated with use of ACE inhibitor in participants with ThrThr genotype (OR 0.37; 95% CI 0.14–0.99), was about a quarter lower than in participants with a copy of Met235 allele (OR 1.44; 95% CI 0.88–2.35). The risk of myocardial infarction associated with the use of ACE inhibitor, did not depend on Met235Thr genotype of angiotensinogen [8]. This aspect has a very important role, in a multicenter study earlier published by us, is was established that the frequency of AH and CHD in patients with AAA reached 80% and 77%, while the optimal drug therapy was given to less than half the patients [2], and only a part of them received combined therapy including ACE inhibitors.

Statistically significant correlations of polymorphisms in the gene between the study and control groups coincided in the dependence of Ser447Ter in the *LpL* gene and Leu28Pro in the *APOE* gene. Besides, in the study group of patients, the greatest relationships were found with Ser447Ter polymorphism in *LpL* gene: direct relationships with Lys198Asn polymorphisms in the *EDN1* gene. Meta-analysis of C. Wang, et al. showed that *LPL* Ser447Ter polymorphism was associated with a considerably lower risk of ischemic stroke, especially of atherosclerotic stroke subtype, both in the representatives of the Caucasian race and in the population of East Asia. Nevertheless, the authors made a suggestion about the association of Lys198Asn polymorphism of the *EDN1* gene with increased risk of ischemic stroke [9].

Correlation of these parameters in our study in the patients with AAA may evidence increased risk of cardiovascular complications, but requires further study. To add, in patients of the main group atherosclerosis of brachiocephalic arteries/stroke was found in 20% of cases.

An important direct correlation of Leu28Pro in the *APOE* gene and Thr715Pro in the *SELP* gene was obtained. Here it is necessary to mention the results of meta-analysis by G. Herrera–Maya, et al. [10], which provide empirical evidence that genetic polymorphisms of *SELP* may promote development of CHD, in particular, myocardial infarction. Thus, genetic polymorphisms of *SELP* may be potential and practical biomarkers for early diagnosis of CHD and myocardial infarction. In this connection it should be noted that in the group with the obtained correlations, CHD was diagnosed in 11 (55%) cases.

The data obtained by us demonstrate that along with Ser447Ter in the *LpL* gene there is also a direct correlation with Lys198Asn in the *EDN1* gene and Thr715Pro in the *SELP* gene, which, according to some studies, is associated with diabetes mellitus and development of stroke [10, 11]. At the same time, there exist rather contraversial data on the influence of diabetes on the pathogenesis of AAA [2].

Thr174Met polymorphism in the *AGT* gene directly correlates with Val174Ala in the *SLC01B1* gene. According to A. Kalliokoski, et al., genetic variability of genes can lead to the interindividual differences in the pharmacokinetics. In particular, single-nucleotide polymorphism (c.521T > C, p.Val174Ala) in the *SLCO1B1* gene encoding the organic anion transporting polypeptide, 1B1 (OATP1B1), reduces the ability of OATP1B1 to transport the active simvastatin acid to the liver leading to increase in its concentration in plasma, which, in turn, increases the risk of development of simvastatin-induced myopathy. Besides, it is shown in the same review that *SLCO1B1* polymorphism also affects pharmacokinetics of many statins and of repaglinide antidiabetic drug, that are used in treatment of atherosclerosis and diabetes in patients with AAA to reduce the risk of cardiovascular complications. With that, Met235Thr polymorphism in the *AGT* gene has a direct relationship with Val174Ala in the *SLC01B1* gene [12].

CONCLUSION

Based on the results of our study, statistically significant differences in the dominance of homozygous and heterozygous alleles in the main and control groups were established. The existence of direct correlations of some polymorphisms of a number of genes in patients with abdominal aortic aneurysm has been established, which shows their probable role in the development of this pathology and may be a screening test for determination of the probability for its development.

ADDITIONAL INFORMATION

Funding. This study was not supported by any external sources of funding.
Conflict of interests. The authors declare no conflicts of interests.
Contribution of the authors: *E. L. Kalmykov* — study concept and design, statistical analysis, data analysis and interpretation, text writing; *I. A. Suchkov* — the concept and design of the study, checking the critical intellectual content of the work, final approval for publication of the manuscript; *R. E. Kalinin* — concept and design of the study, verification of the critical intellectual content of the work, final approval for publication of the manuscript; *O. Ne'matzoda* — analysis and interpretation of data; *D. S. Dodkhoyev* — statistical analysis, analysis and interpretation of data.. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Вклад авторов: *Калмыков Е. Л.* — концепция и дизайн исследования, статистический анализ, анализ и интерпретация данных, написание текста; *Сучков И. А.* — концепция и дизайн исследования, проверка критически важного интеллектуального содержания работы; *Калинин Р. Е.* — концепция и дизайн исследования, проверка критически важного интеллектуального содержания работы, окончательное утверждение для публикации рукописи; *Неъматзода О.* — анализ и интерпретация данных; *Додхоев Д. С.* — статистический анализ, анализ и интерпретация данных. Авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

СПИСОК ИСТОЧНИКОВ

1. Kobeissi E., Hibino M., Pan H., et al. Blood pressure, hypertension and the risk of abdominal aortic aneurysms: a systematic review and meta-analysis of cohort studies // European Journal of Epidemiology. 2019. Vol. 34 № 6. P. 547–555. doi: 10.1007/s10654-019-00510-9
2. Kalmykov E.L., Ahmad W., Suchkov I.A., et al. Demographic differences in patients with abdominal aortic aneurysm in different countries: Germany, Tajikistan and Russian Federation // Novosti Khirurgii. 2021. Vol. 29, № 5. P. 535–541. doi: 10.18484/2305-0047.2021.5.535
3. Бебякова Н.А., Левицкий С.Н., Шабалина И.А., и др. Полиморфизм LYS198ASN гена эндотелина-1 и развитие сердечно-сосудистой патологии (обзор) // Современная наука: актуальные проблемы теории и практики. Серия: Естественные и технические науки. 2020. № 3. С. 12–16.
4. Калинин Р.Е., Сучков И.А., Чобанян А.А. Перспективы прогнозирования течения облитерирующего атеросклероза артерий нижних конечностей // Наука молодых (Eruditio Juvenium). 2019. Т. 7, № 2. С. 274–282. doi: 10.23888/HMJ201972274-282
5. Калинин Р.Е., Сучков И.А., Чобанян А.А., и др. Генетические предикторы неблагоприятного течения облитерирующего атеросклероза артерий нижних конечностей // Российский медико-биологический вестник имени академика И.П. Павлова. 2021. Т. 29, № 2. С. 251–256. doi: 10.17816/PAVLOVJ65383
6. Sethi A.A., Nordestgaard B.G., Agerholm–Larsen B., et al. Angiotensinogen polymorphisms and elevated blood pressure in the general population: the Copenhagen City Heart Study // Hypertension. 2001. Vol. 37, № 3. P. 875–881. doi: 10.1161/01.hyp.37.3.875
7. Staessen J.A., Kuznetsova T., Wang J.G., et al. M235T angiotensinogen gene polymorphism and cardiovascular renal risk // Journal of Hypertension. 1999. Vol. 17, № 1. P. 9–17. doi: 10.1097/00004872-199917010-00003
8. Bis J.C., Smith N.L., Psaty B.M., et al. Angiotensinogen Met235Thr polymorphism, angiotensin-converting enzyme inhibitor therapy, and the risk of nonfatal stroke or myocardial infarction in hypertensive patients // American Journal of Hypertension. 2003. Vol. 16, № 12. P. 1011–1017. doi: 10.1016/j.amjhyper.2003.07.018
9. Wang C., Sun T., Li H., et al. Lipoprotein lipase Ser447Ter polymorphism associated with the risk of ischemic stroke: a meta-analysis // Thrombosis Research. 2011. Vol. 128, № 5. P. e107–e112. doi: 10.1016/j.thromres.2011.07.016
10. Herrera–Maya G., Vargas–Alarcón G., Pérez–Méndez O., et al. The Ser290Asn and Thr715Pro Polymorphisms of the SELP Gene Are Associated with A Lower Risk of Developing Acute Coronary Syndrome and Low Soluble P-Selectin Levels in A Mexican Population // Biomolecules. 2020. Vol. 10, № 2. P. 270. doi: 10.3390/biom10020270
11. Nepal G., Ojha R., Dulal H.P., et al. Association between Lys198Asn polymorphism of endothelin-1 gene and ischemic stroke: A meta-analysis // Brain and Behavior. 2019. Vol. 9, № 10. P. e01424. doi: 10.1002/brb3.1424
12. Kalliokoski A., Niemi M. Impact of OATP transporters on pharmacokinetics // British Journal of Pharmacology. 2009. Vol. 158, № 3. P. 693–705. doi: 10.1111/j.1476-5381.2009.00430.x

REFERENCES

1. Kobeissi E, Hibino M, Pan H, et al. Blood pressure, hypertension and the risk of abdominal aortic aneurysms: a systematic review and meta-analysis of cohort studies. *European Journal of Epidemiology.* 2019;34(6):547–55. doi: 10.1007/s10654-019-00510-9
2. Kalmykov EL, Ahmad W, Suchkov IA, et al. Demographic differences in patients with abdominal aortic aneurysm in different countries: Germany, Tajikistan and Russian Federation. *Novosti Khirurgii.* 2021;29(5):535–41. doi: 10.18484/2305-0047.2021.5.535
3. Bebyakova NA, Levitsky SN, Shabalina IA, et al. Endothelin-1 gene Lys198Asn polymorphism and development of cardiovascular

pathology (review). *Sovremennaya Nauka: Aktual'nyye Problemy Teorii i Praktiki. Seriya: Estestvennyye i Tekhnicheskiye Nauki.* 2020;(3):12–6. (In Russ).
4. Kalinin RE, Suchkov IA, Chobanyan AA. Prospects for forecasting the course of obliterating atherosclerosis of lower limb arteries. *Nauka Molodykh (Eruditio Juvenium).* 2019;7(2):274–82. (In Russ). doi: 10.23888/HMJ201972274-282
5. Kalinin RE, Suchkov IA, Chobanyan AA, et al. Genetic predictors of an unfavorable course of obliterating atherosclerosis of lower limb arteries. *I.P. Pavlov Russian Medical Biological Herald.* 2021;29(2):251–6. (In Russ). doi: 10.17816/PAVLOVJ65383
6. Sethi AA, Nordestgaard BG, Agerholm–Larsen B, et al. Angiotensinogen polymorphisms and elevated blood pressure in the general population: the Copenhagen City Heart Studyю. *Hypertension.* 2001;37(3):875–81. doi: 10.1161/01.hyp.37.3.875
7. Staessen JA, Kuznetsova T, Wang JG, et al. M235T angiotensinogen gene polymorphism and cardiovascular renal risk. *Journal of Hypertension.* 1999;17(1):9–17. doi: 10.1097/00004872-199917010-00003
8. Bis JC, Smith NL, Psaty BM, et al. Angiotensinogen Met235Thr polymorphism, angiotensin-converting enzyme inhibitor therapy, and the risk of nonfatal stroke or myocardial infarction in hypertensive patients. *American Journal of Hypertension.* 2003;16(12):1011–7. doi: 10.1016/j.amjhyper.2003.07.018
9. Wang C, Sun T, Li H, et al. Lipoprotein lipase Ser447Ter polymorphism associated with the risk of ischemic stroke: a meta-analysis. *Thrombosis Research.* 2011;128(5):e107–12. doi: 10.1016/j.thromres.2011.07.016
10. Herrera–Maya G, Vargas–Alarcón G, Pérez–Méndez O, et al. The Ser290Asn and Thr715Pro Polymorphisms of the SELP Gene Are Associated with A Lower Risk of Developing Acute Coronary Syndrome and Low Soluble P-Selectin Levels in A Mexican Population. *Biomolecules.* 2020;10(2):270. doi: 10.3390/biom10020270
11. Nepal G, Ojha R, Dulal HP, et al. Association between Lys198Asn polymorphism of endothelin-1 gene and ischemic stroke: A meta-analysis. *Brain and Behavior.* 2019;9(10):e01424. doi: 10.1002/brb3.1424
12. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *British Journal of Pharmacology*. 2009;158(3):693–705. doi: 10.1111/j.1476-5381.2009.00430.x

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