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Association Analysis of Polymorphism rs386000 of the LILRA3 Gene and the Risk of Atherosclerosis Obliterans: a Pilot Study

Aim	To study the association of the rs386000 polymorphic variant in the LILRA3 gene with the risk of developing obliterating atherosclerosis of the lower extremity arteries (OALEA).
Material and methods	1277 individuals of Slavic origin were examined (629 patients with OALEA and 648 healthy volunteers). Genotyping of the LILRA3 gene rs386000 was performed with a MassARRAY-4 genomic mass spectrometer. Polymorphic variants of the LILRA3 gene, that encodes the leukocyte immunoglobulin-like receptor A3, may be attractive objects for studying the mechanisms of atherosclerosis.
Results	The study showed that the rs386000 polymorphic variant in the LILRA3 gene was associated with the risk of developing OALEA. However, this association was characterized by sexual dimorphism: in men, carriage of the rs386000-C allele (p=0.03) and the rs386000-C/C genotype (p=0.01) was protective against the risk of developing OALEA, while in women, this polymorphism did not influence the susceptibility to the disease. Single nucleotide polymorphism (SNP) annotation showed that carriage of the rs386000-C allele was associated with an increased expression of the LILRA2, LILRB5, LILRA6, LILRP1 and TSEN34 genes and a decreased expression of the LILRA3 and LILRA5 genes in the blood.
Conclusion	The present study revealed for the first time an association of the rs386000-C allele of the LILRA3 gene with a reduced risk of developing OALEA. Further studies, including experimental studies, will determine the specific mechanisms mediating the involvement of the LILRA3 gene rs386000 polymorphism in the molecular mechanisms for the development of obliterating atherosclerosis, as well as the nature of the sex-specific association of the polymorphism.

Keywords	Obliterating atherosclerosis of the lower extremity arteries; genetic predisposition; LILRA3 gene; single nucleotide polymorphism; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol
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Introduction

Atherosclerosis of the peripheral and major arteries currently represents the primary etiology of cardiovascular morbidity and mortality. The search for pathogenetic links in the development and progression of atherosclerosis based on the study of genome variability has contributed to a greater understanding of the molecular nature of atherogenesis, the causes of thrombotic complications, and the mechanisms of vascular inflammation [1, 2]. The recognition of atherosclerosis as a complex and polyetiological disease has enabled the formulation of the concept that its principal pathological process is inflammation, the activity of which is largely determined by genetic factors [3, 4].

Scientific evidence suggests that the LILRA3 gene, which encodes the leukocyte immunoglobulin-like receptor A3 (a member of the leukocyte receptor family), may play a role in inflammatory processes. LILRA3 is a soluble protein that is predominantly expressed by peripheral blood monocytes. The LILRA3 gene functions as a soluble receptor for major histocompatibility complex (MHC) class I antigens and binds to the surface of monocytes with high affinity, thereby inhibiting lipopolysaccharide-induced production of tumor necrosis factor alpha (TNF-α) by monocytes [5].

Given the described function of the LILRA3 gene, polymorphic variants of this gene represent an attractive target for the study of the molecular mechanisms underlying the development and progression of atherosclerosis. In a previous study, we demonstrated the association between the single nucleotide polymorphism (SNP) rs386000 of the LILRA3 gene and the development of coronary artery disease and blood plasma lipid composition [6]. Furthermore, the literature indicates that this SNP is associated with plasma

high-density lipoprotein cholesterol (HDL–C) levels [7–11], as well as the risk of developing age-dependent macular degeneration of the eye [12] and autoimmune diseases [13]. However, investigations into the potential association between this polymorphism and the risk of lower extremity arteriosclerosis obliterans (LEASO) have yet to be undertaken in Russia or abroad.

Objective

The objective of this pilot study was to investigate the potential association between the rs386000 polymorphic variant of the LILRA3 gene and the risk of developing LEASO.

Material and Methods

The study protocol was approved by the Regional Ethics Committee of the Kursk State Medical University (minutes no. 9 dated December 10, 2019). The study was conducted using DNA samples from 1,277 unrelated individuals of Slavic origin from the biobank of the Research Institute of Genetic and Molecular Epidemiology of the Kursk State Medical University.

The study group comprised 629 patients with LEASO, while the control group consisted of 648 patients without chronic diseases who were examined in the context of previous studies [14, 15]. The clinical base for the examination of the patients was the Departments of Surgery of the Kursk Regional Multidisciplinary Clinical Hospital. A questionnaire was utilized to gather anamnestic data concerning the presence of cardiovascular and metabolic diseases and information regarding smoking habits from the patients. Duplex scanning and angiography of the lower extremities were employed to evaluate the condition of the arteries and veins of the lower extremities. The coronary and brachiocephalic arteries were not examined in patients with LEASO. Genotyping of the rs386000 polymorphism of the LILRA3 gene was conducted at the Research Institute of Genetic and Molecular Epidemiology utilizing the MassARRAY-4 time-of-flight mass spectrometer.

The statistical power of polymorphism associations with the risk of developing LEASO was calculated using the online Genetic Association Study Power Calculator (ttps://csg.sph.umich.edu/abecasis/gas_power_calculator/). The analysis of the association between SNPs (recessive model)

Central illustration. Association Analysis of Polymorphism rs386000 of the LILRA3 Gene and the Risk of Atherosclerosis Obliterans: a Pilot Study

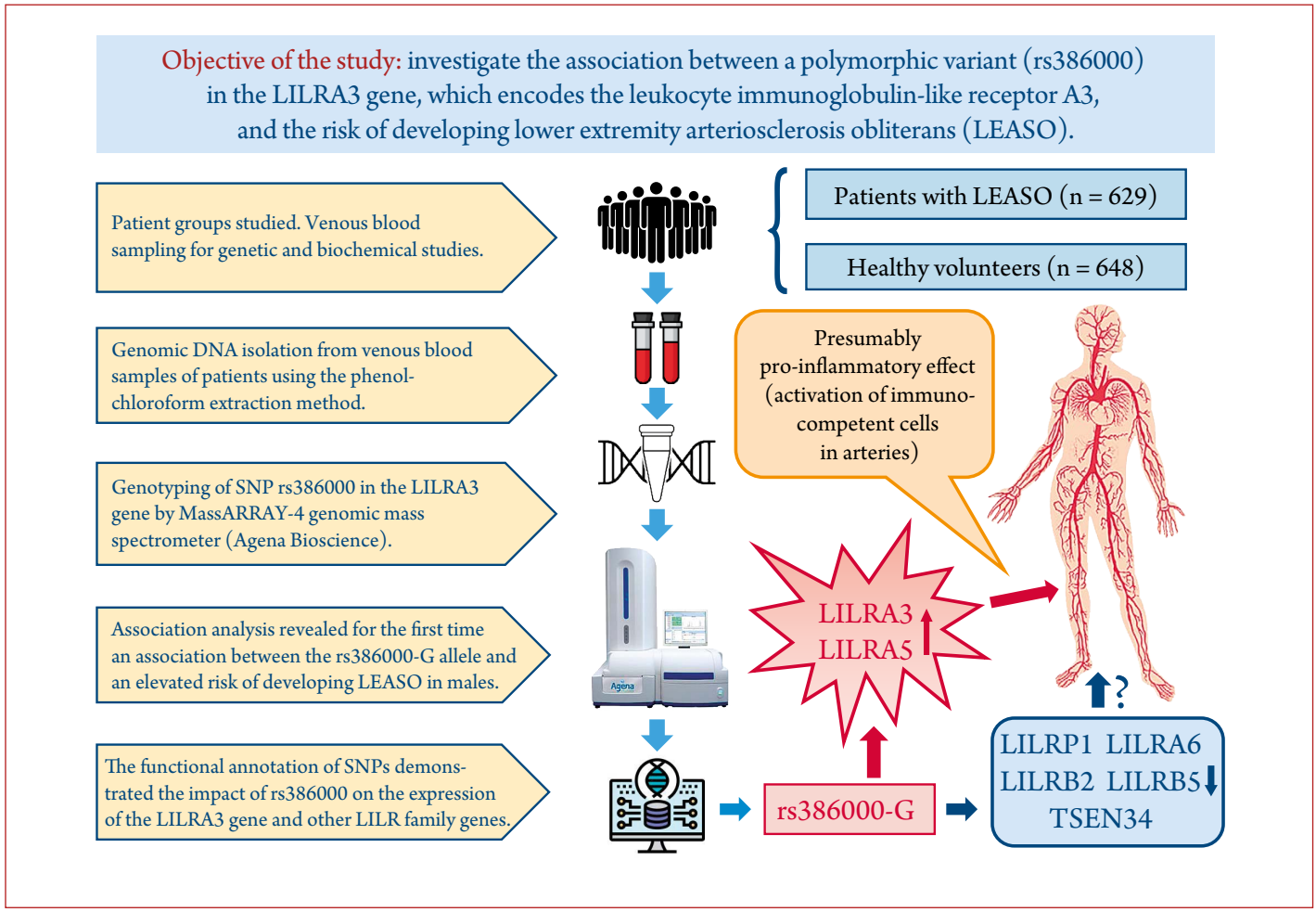

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Table 1. Demographic and clinical characteristics of the subjects examined

Parameter		LEASO group (n = 629)	Control group (n = 648)	p
Age, years*		62.2 ± 9.1	60.7 ± 7.9	0.001
Sex	Male, n (%)	540 (85.9)	394 (60.8)	<0.001
	Female, n (%)	89 (14.1)	254 (39.2)	—
Body mass index, kg/m2		26.84 ± 6.1	27.02 ± 4.5	0.56
Hypertensive heart disease, n (%)		368 (58.5)	—	—
Coronary artery disease, n (%)		193 (30.7)	—	—
Diabetes mellitus, n (%)		109 (17.3)	—	—
Non-smokers**, n (%)		299 (47.5)	332 (52.7)	0,07
Smokers, n (%)		330 (52.5)	298 (47.3)	

* The data are expressed as M ± SD; ** Smoking status was unknown in 18 patients in the control group. LEASO, lower extremity arteriosclerosis obliterans.

Table 2. Association between polymorphic variant rs386000 of the LILRA3 gene and the development of lower extremity arteriosclerosis obliterans in the general group and sex-stratified groups

SNP ID	Genotype, allele	Frequencies of genotypes N (%), alleles		p*	OR (95 %CI)**
		Control group	LEASO group		
General groups					
rs386000	G/G	416 (64.2)	409 (65.1)	0.01	1.00
	G/C	206 (31.8)	209 (33.3)		0.38 (0.18–0.82)
	C/C	26 (4.0)	10 (1.6)		
	C	0.199	0.182	0.28	0.90 (0.44–1.09)
Males					
rs386000	G/G	231 (58.6)	346 (64.1)	0.01	1.00
	G/C	147 (37.3)	186 (34.4)		0.34 (0.14–0.81)
	C/C	16 (4.1)	8 (1.5)		
	C	0.227	0.187	0.03	0.78 (0.62–0.98)
Females					
rs386000	G/G	185 (72.8)	63 (71.6)	0.62	1.00
	G/C	59 (23.2)	23 (26.1)		0.68 (0.14–3.27)
	C/C	10 (3.9)	2 (2.3)		
	C	0.156	0.153	0.95	0.98 (0.61–1.58)

LEASO, lower extremity arteriosclerosis obliterans; OR, odds ratio; CI, confidence interval;
* Significance level of association between LILRB3 allele/genotype and the risk of developing LEASO (recessive genetic model);
** Odds ratio and 95 % confidence interval of the association with age-adjusted risk of developing LEASO..

and the risk of developing LEASO revealed a genotype relative risk (GRR) ranging from 2.6 to 2.9 with a statistical power of 78–89% based on the available sample sizes of 629 patients and 648 healthy individuals and taking into account the false positive rate of 5%. Thus, the studied populations are representative of a larger population, allowing for the generation of statistically reliable estimates when analyzing gene-phenotypic relationships. The associations between LILRA3 alleles and genotypes and the risk of developing LEASO were investigated using SNPStats (https://www.snpstats.net/start.htm). The functional annotation of SNPs was conducted using the eQTLGen service (https://www.eqtlgen.org). The associations between alleles and genotypes and the risk of LEASO development were analyzed using logistic regression methods, with adjustments made for the patients' age and sex. For replication analysis of the identified associations, we utilized data from summary statistics of full-genome studies presented on the Cardiovascular Disease Knowledge portal (https://cvd.hugeamp.org). The threshold for statistical significance was set at $p < 0.05$.

Results

Table 1 presents a summary of the demographic and clinical characteristics of the subjects examined. As evidenced by the presented data, the LEASO group comprised more male subjects compared to the control group. Additionally, the mean age of the LEASO patients was approximately two years higher. Consequently, a statistical analysis was conducted, incorporating adjustments for sex and age.

The frequencies of the rs386000 genotypes of the LILRA3 gene were found to be at Hardy-Weinberg equilibrium. Table 2 illustrates the results of the association analysis between

the polymorphic variant rs386000 of the LILRA3 gene and the development of LEASO in the general group and the sex-stratified groups. The rs386000-C/C genotype and the rs386000-C allele were found to be statistically significantly associated with a reduced risk of LEASO development in the male cohort (p=0.01 and p=0.03, respectively). The correlation between this SNP and the risk of developing LEASO has not been established in female subjects.

The replication analysis of newly detected associations in independent populations worldwide represents the gold standard for genetic and epidemiological studies of multifactorial diseases. It allows for the confirmation or exclusion of the association between the studied polymorphism and the development of pathology [16].

Our analysis of summary statistics from genomic studies sourced from the Cardiovascular Disease Knowledge Portal revealed that the rs386000 C LILRA3 allele was associated with a reduced risk of peripheral artery disease in the 9,560-person European Peripheral Artery Disease 2021 GWAS cohort. However, this trend was observed at a borderline significance level (p=0.056).

The functional annotation of SNPs was conducted. The analysis of genomic and transcriptomic data from the eQTLGen portal (https://www.eqtlgen.org) enabled the establishment of associations between the rs386000 C allele and the expression of multiple genes situated within the 19q13.4 chromosomal segment, namely elevated levels of LILRA2 (P=9.72·10-14), LILRB5 (P=3.20· 10 -10), LILRA6 (P=3.38·10-7), LILRP1 (P=2.49·10-18), and TSEN34 (P=3.63·10-15), as well as a reduced levels of LILRA3 (P=3.27·10-310) and LILRA5 (P=1.02·10-74) in the blood plasma.

Discussion

The human leukocyte immunoglobulin-like receptors (LILR) constitute a family of 11 functional genes, which encode five activating forms (LILRA1, 2, 4–6) and five inhibitory forms (LILRB1–5), as well as a soluble form (LILRA3) [17]. LILRs serve a multitude of functions, including the regulation of inflammatory processes, immune tolerance, cell differentiation, and nervous system plasticity [17]. LILRA3 is the sole soluble member of the LILR family to be secreted by monocytes, B cells, and T cell subpopulations and not detectable on the cell surface [18]. It is noteworthy that the LILRA3 gene is activated by IL-10 and IFN-γ, while TNF-α inhibits its expression [18]. It is hypothesized that LILRA3 functions as an antagonist or negative regulator of other LILRs [17]. The prevalence of LILRA3 deficiency in East Asians was found to exceed 50%, which suggests that LILRA3 does not influence survival [19]. The LILR family of genes was linked to the onset of autoimmune and infectious diseases, including rheumatoid arthritis and cytomegalovirus infection [13, 17]. Furthermore, plasma LILRA3 concentration was demonstrated to be positively correlated with the active phase of rheumatoid arthritis [18] and multiple sclerosis [20], thereby indicating pro-inflammatory effects of elevated LILRA3 levels.

The results of a family study indicate that mutations in the LILRA3 gene are associated with elevated levels of HDL–C in family members who carry these mutations [21]. Moreover, the results of extensive whole-genome association studies suggest that this polymorphism is highly correlated with HDL–C and TC levels [7–11]. In other words, loss-of-function mutations in the LILRA3 gene exhibit antiatherogenic properties by increasing HDL–C production [21]. Concurrently, the rs386000 C allele is linked to elevated levels of TC [22], a discovery that lacks an evident rationale.

This study is the first to ascertain the correlation between the rs386000 polymorphic variant of the LILRA3 gene and the onset of LEASO. The identified associations exhibited sexual dimorphism, with the rs386000 C allele conferring a protective effect against LEASO development in males, whereas this SNP had no impact on the susceptibility to the disease in females.

The present study was limited by the insufficient number of LEASO patients with measured blood lipid parameters, which precluded the establishment of their relationship with the rs386000 polymorphism of the LILRA3 gene. Consequently, we were unable to interpret the potential mechanisms through which polymorphism influences lipid metabolism, as previously identified in large international studies.

A review of the genomic and transcriptomic data from the eQTLgen portal revealed that the rs386000 C allele, which is associated with a reduced risk of developing LEASO, is linked to a reduction in the expression of the LILRA3 gene and is also associated with coordinated alterations in the expression of other LILR family genes clustered on chromosome 19 [17]. The data suggest that the atherogenic effect may be associated with the presence of the rs386000 G allele and, consequently, elevated expression of LILRA3 in the blood. As previously discussed, this correlates with the activity of inflammatory processes [18]. It is therefore possible that the atherogenic effect of the rs386000 G allelic variant of the LILRA3 gene may be realized through proinflammatory changes in the vascular wall induced by activated immunocompetent cells. Such a possibility was demonstrated by Wu et al. (2021) [23], who observed that LILRA3-treated monocytic dendritic cells exhibited pronounced proliferative activity of allogeneic CD4+ T-lymphocytes and a polarization of the Th0 to Th1 phenotype. This assumption is corroborated by the data, which indicate that T-lymphocytes play a significant pathogenic role in the development and progression of atherosclerosis [24]. It should be noted that LILRA3 targets not only T lymphocytes and macrophages, but also natural killer cells, which contribute to the inflammatory changes in vessels observed in atherosclerosis [25, 26]. It is established that the LILRA3 gene is activated by the

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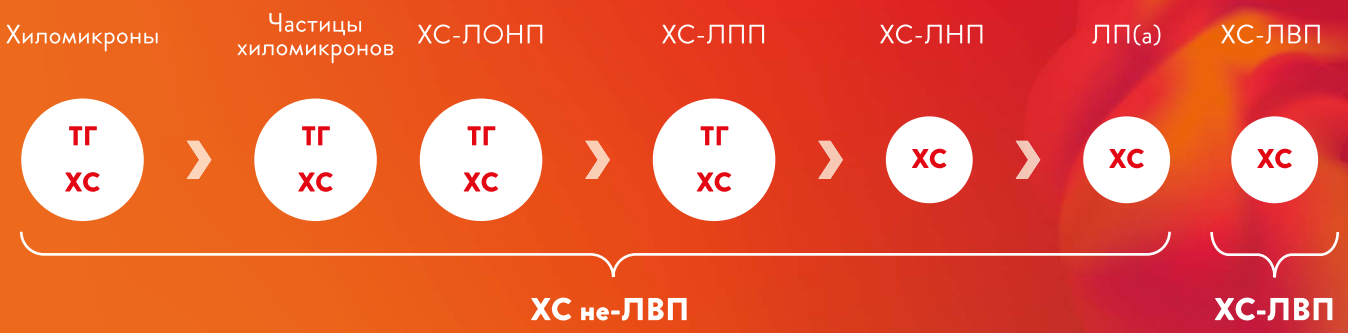
ХОЛЕСТЕРИН НЕ-ЛВП — МИШЕНЬ ДЛЯ СНИЖЕНИЯ СЕРДЕЧНО-СОСУДИСТОГО РИСКА[1]

ХС не-ЛВП включает в себя все атерогенные классы липопротеинов[1]



ДЛЯ СНИЖЕНИЯ УРОВНЯ ХС НЕ-ЛВП ТРЕБУЕТСЯ КОНТРОЛЬ ВСЕХ АТЕРОГЕННЫХ ЧАСТИЦ

Целевые значения ХС не-ЛВП для пациентов с различным уровнем сердечно-сосудистого риска[2]

Основа SCORE-2

ХС не-ЛВП	
< 2,6 ммоль/л	желателен для лиц с высоким риском
< 2,2 ммоль/л	у лиц с очень высоким риском
< 1,8 ммоль/л	для лиц с экстремально высоким риском

Оценка ХС не-ЛВП не требует дополнительных затрат

Формула определения ХС не-ЛВП

Холестерин Не-ЛВП = ОХС - ХС-ЛВП

ХС не-ЛВП — достоверный индикатор сердечно-сосудистой смертности у пациентов:

- с ожирением и метаболическим синдромом
- с ССЗ (ИБС, перенесенный инфаркт миокарда)
- с СД 2-го типа
- с гипертриглицеридемией
- с низким уровнем ХС-ЛНП

ХС — холестерин, ТГ — триглицериды; ХС-ЛОНП — холестерин липопротеинов очень низкой плотности; ХС-ЛПП — холестерин липопротеинов промежуточной плотности; ЛП (а) — липопротеин (а); ХС-ЛНП — холестерин липопротеинов низкой плотности; ХС-ЛВП — холестерин липопротеинов высокой плотности; ССЗ — сердечно-сосудистые заболевания, ИБС — ишемическая болезнь сердца; СД — сахарный диабет; ОХС — общий холестерин.

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2. Клинические рекомендации МЗ РФ Нарушения липидного обмена 2023 г. Рубрикатор КР (minzdrav.gov.ru) Дата доступа: 31.05.2023.

RUS2280609 (v1.3)

anti-inflammatory cytokine IL-10 and IFN-γ, and suppressed by the pro-inflammatory cytokine TNF-α [18]. This indicates that LILRA3 represents a negative feedback regulation loop of immune response and inflammation.

Conclusion

This is the first instance in which the rs386000 polymorphism of the LILRA3 gene has been identified as a potential risk factor for lower extremity arteriosclerosis obliterans in males. The data on the functional annotation of this variant suggest that the rs386000 C allele is associated with reduced transcriptional activity of the LILRA3 gene in response to the action of regulatory cytokines. This results in a reduction in gene expression and a weakening of the transmission of activating signals to immunocompetent cells. It is evident that this assumption requires experimental confirmation. Further studies, including experimental studies, should be conducted to determine the specific mechanisms through which the rs386000 polymorphism of the LILRA3 gene is involved in the molecular mechanisms of the development of lower extremity arteriosclerosis obliterans and atherosclerosis of other localizations.

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No conflict of interest is reported.

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