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# The role of polymorphism of genes related to atherogenesis in development of stable coronary artery disease

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**ABSTRACT**

**Objective.** To study the role of polymorphisms of cell adhesion genes *SELE*, *SELP*, *SELPLG*, endothelin *EDN1* gene and endothelial nitric oxide synthase *NOS3* gene in individual risk of coronary artery disease.

**Material and methods.** The study enrolled 560 patients including 260 ones with stable coronary artery disease and 300 healthy donors. Mean age of patients in both groups was 58 and 53 years, respectively.

**Results.** Protective (C/A genotype in the *SELE* rs1805193 gene) and risk (G/T genotype in the *EDN1* rs5370 gene and T/T genotype in the *NOS3* rs1799983 gene) variants were discovered. In addition, we observed the AGCT haplotype of the *EDN1* and *NOS3* genes (rs3087459-rs5370-rs2070744-rs1799983) associated with a 2-fold increased risk of coronary artery disease. It was found that carriers of the T/T and G/G genotypes in the *SELP* rs6136 gene are characterized by higher levels of soluble form of P-selectin compared to carriers of the heterozygous G/T genotype.

***Keywords:*** *coronary artery disease, atherosclerosis, E-selectin, P-selectin, endothelin, endothelial nitric oxide synthase, SELE, SELP, NOS3, EDN1.*

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## Introduction

Cardiovascular diseases are one of the leading causes of mortality. Among them, atherosclerosis accounts for 28.6% of mortality in women and 26.5% in men. The main risk group usually includes women over 70 years old and men over 60 years old [1]. Among all cardiovascular diseases, the leading pathology is coronary artery disease (CAD) and underlying atherosclerosis of coronary arteries [2].

Analysis of the causes of atherosclerosis is currently one of the most common scientific directions around the world. It is known that atherosclerotic damage is multifactorial and accompanied by a cascade of processes controlled at the genetic level. According to modern ideas about the causes of atherosclerosis, three main theories are distinguished: endothelial dysfunction, lipid metabolism disorders and theory of inflammation [3].

It is known that damage to endothelial layer is accompanied by active expression of various molecules [4]. These molecules include E- and P-selectins, VCAM, ICAM, and others. In addition to the generally accepted risk factors of atherosclerosis, much attention is currently paid to genetic component. Modern literature data indicate a significant role of selectins in atherogenesis [4–7]. In addition to selectins, endothelial NO synthase is also involved in atherogenesis. This enzyme catalyzes formation of nitric oxide (NO) from L-arginine. Endothelial NO synthase is important for regulation of blood vessel tone, functioning of vascular smooth muscles, processes of thrombosis and atherogenesis. This enzyme is encoded by the NOS3 gene. There is a clear relationship between the level of NO and severity of oxidative stress in vascular diseases [8]. In addition, the role of endothelin peptide (encoded by the EDN1 gene) as important element of vascular homeostasis was described in pathogenesis of CAD [9].

Considering the above-mentioned data, we can assume that structural variability of gene loci encoding proteins of cell adhesion molecules, NO synthase and endothelin can affect activation of endothelium, severity of inflammatory response in endothelium and increase the risk of development and progression of atherosclerosis and coronary artery disease.

Thus, the purpose was to study the role of polymorphisms of cell adhesion genes SELE, SELP, SELPG, endothelin EDN1 gene and endothelial nitric oxide synthase NOS3 gene in individual risk of coronary artery disease.

***Table 1.*** **Characteristics of study genes**

| *SNP* | Nucleotide substitution | Chromosomal position | Functional value |
|---|---|---|---|
| *SELE* | | | |
| rs5361 | T>G | 1:169731919 | Missense Variant |
| rs1805193 | C>A | 1:169733631 | 5 Prime UTR Variant |
| *SELP* | | | |
| rs6136 | T>G | 1:169594713 | Missense Variant |
| *SELPLG* | | | |
| rs2228315 | C>T | 12:108624122 | Missense Variant |
| *EDN1* | | | |
| rs3087459 | A>C | 6:12289406 | Intron Variant |
| rs5370 | G>T | 6:12296022 | Missense Variant |
| *NOS3* | | | |
| rs2070744 | C>T | 7:150992991 | Intron Variant |
| rs1799983 | G>T | 7:150999023 | Missense Variant |

## Material and methods

The study was performed at the Research Institute for Complex Issues of Cardiovascular Diseases (Kemerovo). Local ethical committee approved the study. There were 560 patients including 260 ones with stable coronary artery disease and 300 healthy donors. Mean age of patients in the study group was 58 years, in the control group — 53 years.

Venous blood samples were taken from cubital vein in all participants (test tube with K3EDTA) for further phenol-chloroform extraction of genomic DNA. In addition, blood samples were also harvested in a test tube with a coagulation activator to analyze serum proteins (enzyme-linked immunosorbent assay). All samples were labeled and stored at a low temperature until the study.

We studied 8 polymorphic variants of 5 genes: SELE (rs5361, rs1805193), SELP (rs6136), SELPG (rs2228315), EDN1 (rs3087459, rs5370), NOS3 (rs2070744, rs1799989). Their characteristics are shown in **Table 1**.

Genotyping was carried out using real-time polymerase chain reaction (TaqMan technology, ViiATM 7, LifeTechnologies, USA). We harvested the control samples with known genotypes to assess the quality of molecular genetic analysis; 10% of samples were genotyped again.

***Table 2.*** **Incidence of various genotypes of polymorphic variants**

| Gene | Patients with CAD | Control group | OR (95% CI) | *p*-value | HWE |
|---|---|---|---|---|---|
| *SELE* rs5361 | | | | | |
| T/T | 226 (87.3%) | 248 (82.7%) | 1.00 | 0.3 | 0.19 |
| G/T | 31 (12%) | 48 (16%) | 0.71 (0.44—1.15) | | |
| G/G | 2 (0.8%) | 4 (1.3%) | 0.55 (0.10—3.02) | | |
| *SELE* rs1805193 | | | | | |
| C/C | 228 (88%) | 242 (80.7%) | 1.00 | 0.019 | 0.56 |
| C/A | 29 (11.2%) | 55 (18.3%) | 0.56 (0.34—0.91)* | | |
| A/A | 2 (0.8%) | 3 (1%) | 0.71 (0.12—4.27) | | |
| *SELP* rs6136 | | | | | |
| T/T | 207 (79.9%) | 235 (78.3%) | 1.00 | 0.9 | 0.95 |
| G/T | 49 (18.9%) | 61 (20.3%) | 0.91 (0.60—1.39) | | |
| G/G | 3 (1.2%) | 4 (1.3%) | 0.85 (0.19—3.85) | | |
| *SELPLG* rs2228315 | | | | | |
| C/C | 230 (88.8%) | 268 (89.3%) | 1.00 | 0.98 | 0.10 |
| C/T | 27 (10.4%) | 30 (10%) | 1.05 (0.61—1.82) | | |
| T/T | 2 (0.8%) | 2 (0.7%) | 1.17 (0.16—8.34) | | |
| *EDN1* rs3087459 | | | | | |
| A/A | 171 (66%) | 220 (73.3%) | 1.00 | 0.15 | 0.80 |
| A/C | 80 (30.9%) | 74 (24.7%) | 1.47 (0.96—2.25) | | |
| C/C | 8 (3.1%) | 6 (2%) | 1.75 (0.52—5.86) | | |
| *EDN* rs5370 | | | | | |
| G/G | 153 (59.1%) | 221 (73.7%) | 1.00 | 0.011 | 0.21 |
| G/T | 95 (36.7%) | 66 (22%) | 1.90 (1.24—2.91)* | | |
| T/T | 11 (4.2%) | 13 (4.3%) | 1.19 (0.47—2.98) | | |
| *NOS3* rs2070744 | | | | | |
| T/T | 111 (42.9%) | 107 (35.7%) | 1.00 | 0.067 | 0.17 |
| C/T | 101 (39%) | 149 (49.7%) | 0.71 (0.47—1.08) | | |
| C/C | 47 (18.1%) | 44 (14.7%) | 1.30 (0.74—2.28) | | |
| *NOS3* rs1799983 | | | | | |
| G/G | 99 (38.2%) | 174 (58%) | 1.00 | 0.0001 | 0.01 |
| G/T | 112 (43.2%) | 106 (35.3%) | 1.97 (1.30—2.98)* | | |
| T/T | 48 (18.5%) | 20 (6.7%) | 4.00 (2.10—7.62)* | | |

*Note.* * — significant differences compared to the control group ($p < 0.05$).

Quantitative analysis of serum concentrations was performed using the commercial kits sE-selectin (BMS205), sP-selectin (BMS219-4), Endothelin (DET100) and eNOS (DY950-05) for researches in accordance with the manufacturer's protocol and detection of results depending on optical density (Multiskan Sky Microplate Spectrophotometer, Thermo Scientific, USA).

Statistical analysis was carried out using th GraphPad Prism 8 (GraphPad Software, USA) and SNPstats software. Distribution normality was tested using the Kolmogorov-Smirnov test. Between-group analysis of qualitative variables was performed using the non-parametric Mann-Whitney and Kruskal-Wallis tests. We analyzed the frequencies of qualitative and nominal data using the $\chi 2$ test with Yates correction. Quantitative data are presented as median (Me), $25^{th}$ and $75^{th}$ percentiles. The odds ratio (OR) and 95% confidence interval were calculated for risk assessment. Differences were significant at *p*-value <0.05.

## Results

### *Analysis of associations of genotypes with predisposition to stable coronary artery disease*

Distribution of genotype frequencies of various polymorphic variants corresponded to the Hardy-Weinberg equilibrium. Analysis of genotypes and their association with predisposition to CAD revealed several significant differences. For example, heterozygous genotype C/A of the polymorphic variant rs1805193 of the SELE gene encoding E-selectin was more common in the control group and had a protective effect (OR 0.56, 95% CI 0.34-0.91) against coronary artery disease. In addition, there were 2 associations increasing the risk of coronary artery disease. One of them was obtained for heterozygous G/T genotype of the rs5370 EDN1 polymorphism (OR 1.90, 95% CI 1.24-2.91) that almost doubled the predisposition to CAD. Another relationship was obtained for the NOS3 gene and its polymorphic variant rs1799983. Regarding this variant, it was found that homozygous T/T genotype was almost 2 times more common in the study group and increased the risk of CAD by 4 times (OR 4.00, 95% CI 2.10 — 7.62). No significant differences were obtained with other polymorphic variants **(Table 2)**.

In addition to analysis of certain genotypes and predisposition to CAD, we assessed the role of haplotypes of the SELE, SELP and SELPG genes and their relationship with the risk of CAD **(Table 3)**. This analysis found no significant differences.

Comparison of haplotypes of polymorphic variants of the EDN and NOS3 genes revealed one AGCT haplotype (rs3087459–rs5370–rs2070744–rs1799983) doubling predisposition to CAD (OR 2.09, 95% CI 1.21-3.62) **(Table 4)**.

It is hypothesized that genetic component can influence the levels of serum proteins. To test this hypothesis, we compared the concentrations of soluble forms of E-selectin, P-selectin, endothelin and endothelial nitrogen synthase (eNOS) with carriage of alleles of polymorphic variants in patients with coronary artery disease **(Figure)**. Data analysis showed that carriers of homozygous T/T and G/G genotypes of the rs6136 SELP polymorphic variant have higher levels of soluble form of P-selectin (136.4 ng/mL [106.8; 184.2]) compared with the carriers of heterozygous genotype G/T (104.8 ng/ml [77.8–130.9]) ($p = 0.02$). However, no significant results were obtained regarding other polymorphic variants.

***Table 3.*** **Analysis of associations of haplotypes of polymorphic variants of the SELE, SELP, and SELPLG genes and risk of coronary artery disease**

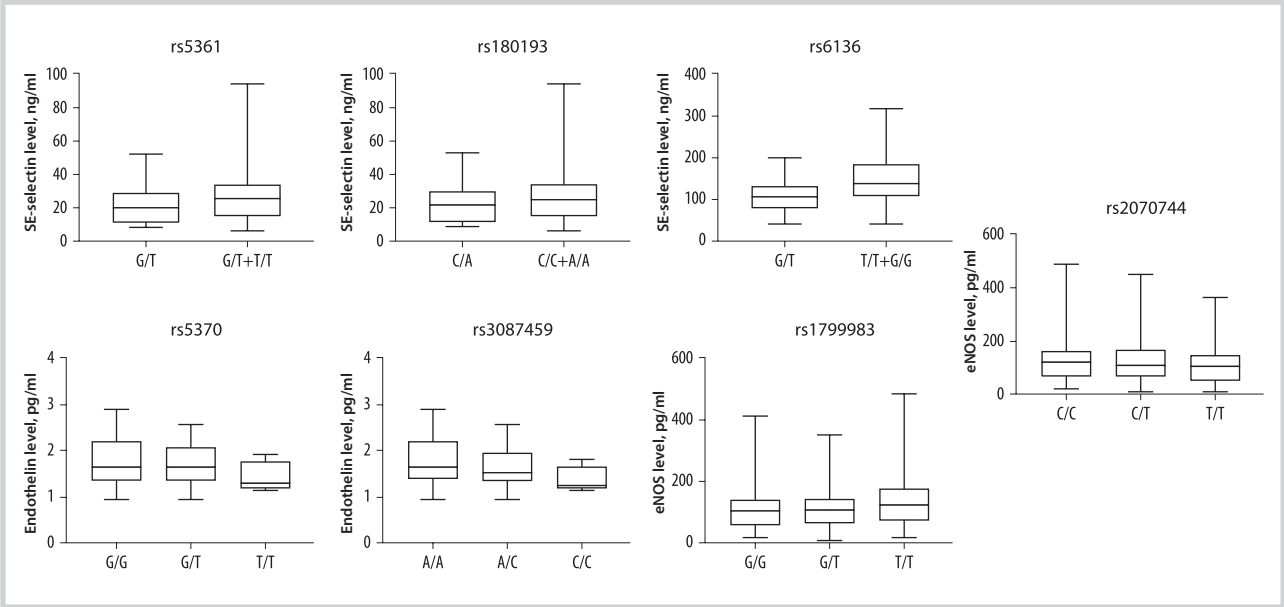
| No. | rs5361 | rs1805193 | rs6136 | rs2228315 | Incidence, % | OR (95% CI) | *p*-value |
|---|---|---|---|---|---|---|---|
| 1 | T | C | T | C | 0.77 | 1.00 | — |
| 2 | T | C | G | C | 0.09 | 0.85 (0.55—1.30) | 0.45 |
| 3 | G | A | T | C | 0.06 | 0.69 (0.41—1.18) | 0.18 |
| 4 | T | C | T | T | 0.04 | 0.99 (0.50—1.94) | 0.97 |
| 5 | T | C | G | T | 0.01 | 1.53 (0.38—6.12) | 0.54 |

*Note.* * — significant differences compared to the control group ($p < 0.05$).

***Table 4.*** **Analysis of associations of haplotype of polymorphic variants of the EDN and NOS3 genes and risk of coronary artery disease**

| No. | rs3087459 | rs5370 | rs2070744 | rs1799983 | Incidence, % | OR (95% CI) | *p*-value |
|---|---|---|---|---|---|---|---|
| 1 | A | G | T | G | 0.35 | 1.00 | — |
| 2 | A | G | C | G | 0.19 | 0.38 (0.22—0.65) | 0.001* |
| 3 | A | G | T | T | 0.13 | 0.89 (0.51—1.55) | 0.69 |
| 4 | A | G | C | T | 0.11 | 2.09 (1.21—3.62) | 0.01* |
| 5 | C | T | T | G | 0.06 | 0.82 (0.40—1.67) | 0.58 |
| 6 | C | T | C | T | 0.04 | 2.94 (1.00—8.65) | 0.05 |
| 7 | A | T | T | G | 0.03 | 0.93 (0.36—2.40) | 0.88 |
| 8 | C | T | C | G | 0.02 | 2.55 (0.57—11.29) | 0.22 |
| 9 | C | T | T | T | 0.02 | 2.67 (0.38—18.84) | 0.32 |
| 10 | C | G | T | G | 0.01 | 0.10 (0.00—4.35) | 0.23 |
| 11 | A | T | T | T | 0.01 | 0.55 (0.11—2.73) | 0.46 |

*Note.* * — significant differences compared to the control group ($p < 0.05$).




**Serum concentration of various molecules depending on the carriage of specific genotypes.**

## Discussion

The main molecules of cell adhesion are P-selectin and E-selectin. These molecules are directly related to vascular inflammation. Surface markers include E-selectin [4], while P-selectin enhances procoagulant activity and activation of leukocyte integrins [10]. Thus, we can say that proteins of adhesion molecules are potentially activators of atherosclerotic process in early stages.

E-selectin is a protein encoded by the SELE gene. Its expression is usually observed in activated endothelial cells. This protein promotes the binding and adhesion of leukocytes to endothelial cells. E-selectin is also involved in leukocyte migration by activating intracellular signaling pathways. Its expression requires promoter activation. Translation of this protein in endothelial cells is accompanied by its modification with addition of oligosaccharides. Then, E-selectin moves from Golgi complex to cell surface. E-selectin is removed from the surface of endothelial cells by endocytosis [11]. SELE gene is associated with such cardiovascular diseases as arterial hypertension [12], myocardial infarction [13], and atherosclerosis [14].

P-selectin (molecular weight 140 kDa) is stored in platelet α-granules and Weibel-Palade bodies of endothelial cells. This protein is redistributed to cell membrane during platelet activation and degranulation and mediates interaction of activated endothelial cells or platelets with leukocytes. P-selectin is encoded by the SELP gene. The last one is associated with such cardiovascular diseases as chronic heart failure [15], atherosclerosis [16], and myocardial infarction [17].

The SELPLG (P-selectin ligand) gene encodes a glycoprotein functioning as a counter-receptor for P, E, and L-selectin cell adhesion molecules expressed on myeloid cells and stimulated T-lymphocytes. This protein is essential in inflammation due to its ability to bind leukocytes with activated platelets or endothelium expressing these selectins.

Various studies confirmed significance of variability of cell adhesion molecule genes in pathogenesis of cardiovascular diseases, including coronary artery disease. One of the early meta-analyses investigated significance of the SELE polymorphism in pathogenesis of CAD and myocardial infarction. The following databases were used: PubMed, CISCOM, CINAHL, Web of Science, Google Scholar, EBSCO, Cochrane Library, and CBM. The authors systematized the data until November 1, 2013. They reviewed a total of 20 manuscripts describing 6 SELE polymorphic sites (554 L/F, 98 G/T, 128 S/R, 2692G/A, 1901 C/T and 1856A/G). These data suggest that SELE polymorphism is directly associated with higher risk of CAD. At the same time, no correlation with the risk of myocardial infarction was confirmed [18].

Another review considered P-selectin as one of the factors of cardiovascular diseases, in particular, atherosclerosis. Experimental analysis revealed that deficiency of P-selectin in mice leads to delayed recruitment of neutrophils. Moreover, injection of monoclonal antibodies to P-selectin reduced adhesion of leukocytes to endothelial cells stimulated by thrombin and histamine [19].

Another study was conducted on the territory of the Republic of Adygea and included 44 people (8 patients with coronary artery atherosclerosis, 9 ones with peripheral arterial atherosclerosis, and 10 healthy people) regardless ethnicity of subjects. Genotyping of the rs5361 SELE and rs6136 SELP polymorphic sites was performed. It was found that carriage of homozygous genotype and rs5361 SELE allele was associated mainly with peripheral arterial atherosclerosis and, to a lesser extent, coronary artery atherosclerosis. Carriage of minor allele G of the SELP gene (rs6136) predisposed to peripheral arterial atherosclerosis. This allele was a molecular genetic predictor of vascular brain lesions (ischemic and hemorrhagic stroke). The authors concluded a relationship between individual variations in polymorphic sites with atherogenesis and their possible use for early diagnosis of atherosclerosis in residents of the Republic of Adygea [20].

Another study comprising 208 patients and 300 healthy residents of the large industrial region of Western Siberia (Kemerovo) analyzed the genes EDN1 (rs3087459, rs5370), SELE (rs1805193, rs5361), SELP (rs6136) and SELPLG (rs2228315). There was no relationship between the carriage of variant al-

leles in polymorphic sites and serum concentration of adhesion molecules [21].

Association of SELE gene polymorphisms (G98T rs1805193, A561C rs5361, C1880T rs5355) with atherosclerosis has been recently analyzed using logistic regression analysis. In codominant, dominant and additive inheritance patterns, G98T (rs1805193) and A561C (rs5361) variants were associated with higher risk of this pathology. The authors reported association of C/T rs5355 genotype with higher risk of atherosclerosis compared to C/C genotype. In addition, CT haplotype of variants G98T and A561C was associated with higher risk of atherosclerosis, while AG haplotype was much less common in people with this pathology [6].

Association of SELP gene polymorphism with the risk of atherosclerosis and coronary artery disease was also shown in 2020 [22].

Thus, the available data on the role of polymorphisms of cell adhesion genes SELE, SELP and SELPG, endothelin gene EDN1 and endothelial nitric oxide synthase NOS3 in the risk of coronary artery disease are quite contradictory and vary depending on population. Further research is required.

## Conclusion

We established protective (C/A genotype of the SELE rs1805193 gene) and risk (G/T genotype of the EDN1 rs5370 gene and T/T genotype of the NOS3 rs1799983 gene) variants regarding coronary artery disease. In addition, AGCT haplotype of the EDN1 and NOS3 genes (rs3087459-rs5370-rs2070744-rs1799983) associated with a 2-fold increase of the risk of this pathology was found. Carriers of T/T and G/G genotypes of the rs6136 polymorphic variant of the SELP gene have higher levels of soluble form of P-selectin compared to carriers of heterozygous G/T genotype.

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**The authors declare no conflicts of interest.**

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