DOI: https://doi.org/10.17816/KMJ607419

SERPINE-1 gene polymorphism in patients with cardiovascular diseases

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ABSTRACT

Currently, the issues of recurrent course of cardiovascular diseases are given great importance. Today, there is a search for more and more new factors and causes, including genetic ones, that contribute to the increase in the incidence of circulatory system diseases. The study of polymorphic variants of hemostasis system genes made it possible to study the molecular mechanisms underlying the causes of cardiovascular complications. Polymorphism of the *SERPINE-1* gene, encoding plasminogen activator inhibitor-1, is associated with the occurrence of cardiovascular diseases. This literature review examines the influence of *SERPINE-1* gene polymorphism and the concentration of the plasminogen activator inhibitor-1 it encodes on the development and severity of circulatory system diseases; as well as the role of plasminogen activator inhibitor-1 as one of the indicators reflecting the antifibrinolytic potential of the blood. Taking into account the opinion of most authors, we can conclude that the polymorphism of the *SERPINE-1* gene and its homozygous variant 4G/4G, due to which the synthesis of plasminogen activator inhibitor-1 is increased, is an unfavorable predictor of many pathological processes. However, most of the data have been obtained on the association of the *SERPINE-1* gene polymorphism with cardiovascular diseases, where, according to most authors, the 4G/4G genotype is a prognostically negative variant. However, a number of researchers believe that the heterozygous 5G/4G variant is likely associated with the occurrence of cerebral ischemia. The inconsistency of the data obtained, of course, requires further study of the characteristics of the *SERPINE-1* gene polymorphism in various pathological conditions, which is an important prerequisite for understanding the mechanisms of a number of diseases. To prepare the review, a literature search method in PubMed databases for the period 2013–2023 was used.

Keywords: gene polymorphism; *SERPINE-1*; plasminogen activator inhibitor-1 (PAI-1); cardiovascular diseases.

To cite this article:
Usmanova AF, Mayanskaya SD, Kravtsova OA. *SERPINE-1* gene polymorphism in patients with cardiovascular diseases. *Kazan Medical Journal*. 2024;105(2):272–283. DOI: https://doi.org/10.17816/KMJ607419

Received: 12.10.2023 **Accepted:** 26.10.2023 **Published:** 19.02.2024

DOI: https://doi.org/10.17816/KMJ607419
УДК 616.1

Полиморфизм гена *SERPINE-1* у пациентов с сердечно-сосудистыми заболеваниями

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АННОТАЦИЯ

В настоящее время вопросам рецидивирующего течения сердечно-сосудистых заболеваний придают большое значение. На сегодняшний день идёт поиск всё более новых факторов и причин, в том числе генетических, способствующих росту частоты болезней системы кровообращения. Исследование полиморфных вариантов генов системы гемостаза позволило изучить молекулярные механизмы, лежащие в основе причин сердечно-сосудистых осложнений. Полиморфизм гена *SERPINE-1*, кодирующего ингибитор активатора плазминогена-1, ассоциирован с возникновением сердечно-сосудистых заболеваний. В данном литературном обзоре рассмотрено влияние полиморфизма гена *SERPINE-1* и концентрации кодируемого им ингибитора активатора плазминогена-1 на развитие и тяжесть течения болезней системы кровообращения; а также роль ингибитора активатора плазминогена-1 как одного из показателей, отражающих антифибринолитический потенциал крови. Принимая во внимание мнение большинства авторов, можно сделать вывод о том, что полиморфизм гена *SERPINE-1* и его гомозиготный вариант 4G/4G, за счёт которого увеличен синтез ингибитора активатора плазминогена-1, — неблагоприятный предиктор многих патологических процессов. Однако больше всего данных получено по ассоциации полиморфизма гена *SERPINE-1* с сердечно-сосудистыми заболеваниями, где, по мнению большинства авторов, генотип 4G/4G представляет собой прогностически негативный вариант. Тем не менее, ряд исследователей считают, что гетерозиготный вариант 5G/4G, вероятно, связан с возникновением церебральной ишемии. Противоречивость полученных данных, безусловно, требует дальнейшего изучения особенностей полиморфизма гена *SERPINE-1* при различных патологических состояниях, что является важной предпосылкой к пониманию механизмов течения ряда заболеваний. При подготовке обзора был использован метод поиска литературы по базам данных PubMed за период 2013–2023 гг.

Ключевые слова: полиморфизм генов; *SERPINE-1*; ингибитор активатора плазминогена-1 (PAI-1); сердечно-сосудистые заболевания.

Как цитировать:
Усманова А.Ф., Маянская С.Д., Кравцова О.А. Полиморфизм гена *SERPINE-1* у пациентов с сердечно-сосудистыми заболеваниями. *Казанский медицинский журнал.* 2024;105(2):272–283. DOI: https://doi.org/10.17816/KMJ607419

Рукопись получена: 12.10.2023 **Рукопись одобрена:** 26.10.2023 **Опубликована:** 19.02.2024

ЭКО•ВЕКТОР

Despite ongoing treatment, preventive measures, and improvement of the urgent and emergency care system, cardiovascular diseases (CVDs) still retain their leading position as the main causes of mortality among adult populations in the Russian Federation [1]. Thus, predicting the development and severity of CVDs is important [2].

New factors, including genetic factors, associated with CVD progression are currently being sought [3]. In these pathological conditions, much attention has been paid to studying the role of polymorphisms in candidate genes encoding proteins activating the hemostasis system. Thus, in modern literature, evidence shows a rather close association of the *SERPINE-1* (serpin peptidase inhibitor, clade E), encoding plasminogen activator inhibitor-1 (PAI-1), with the severity and development of circulatory system diseases, as well as its value as an indicator of the antifibrinolytic potential of the blood [4, 5].

However, the inconsistency of data on the effect of different genotypes on a particular pathology, which is probably associated with the diversity of *SERPINE-1* mutations, inhibits us from drawing conclusions, particularly in further predicting disease course and outcomes.

The normal regulation of blood flow is a function, among other things, of the fibrinolysis system, whose main task is the breakdown of fibrin into small peptides and amino acids. This process occurs under the influence of the proteolytic enzyme plasmin. In turn, plasmin is formed in the liver from the circulating proenzyme plasminogen, with the involvement of urokinase and tissue plasminogen activator (tPA) [6]. In the blood, plasminogen activators are in a protein-bound state, among which PAI-1 is of major importance.

PAI-1 belongs to the family of serine protease inhibitors and has a molecular weight of 45 kDa. It is formed in endothelial and smooth muscle cells and megakaryocytes [7]. Moreover, it is deposited in platelets in an inactive (latent) form. In the case of substance-induced vessel injury, it is converted into its active form and released in large quantities, preventing the early destruction of fibrin. PAI-1 levels can increase in many pathological processes. Its increased synthesis is directly related to the polymorphism of *SERPINE-1* encoding it, which is located on chromosome 7q21.3–q22 [8]. The polymorphism of this gene is associated with a change in the number of guanine (G) repeats in its regulatory region. The 5G/4G genotype consists of five (5G) and four (4G) guanine nitrogenous bases. It is considered the most unfavorable mutation variant causing the weakening of the fibrinolysis system because of an increase in the blood PAI-1 concentration. This process occurs because if the regulatory region of the gene has five repeats of guanine (G) bases, both transcription activators and suppressors can bind to it; therefore, the regulation of this gene is considered correct. If the regulatory region of the gene has four repeats of guanine (G) bases, binding to the suppressor is impaired; therefore, PAI-1 synthesis is increased.

This gene has three genotype variants: 5G/5G, 5G/4G, and 4G/4G. The latter is associated with an increase in the concentration of PAI-1, which increases the risk of thrombogenesis, and in the case of meningococcal infection, it inhibits fibrinolysis, which is important in the development of meningococcal sepsis [9]. Patients homozygous for the 5G allele are at a higher risk of developing an abdominal aortic aneurysm [10]. This process is associated with less inhibition of the fibrinolysis system and therefore with increased activation of tissue proteases, which trigger chronic inflammation in the walls of blood vessels, primarily the aorta, leading to the impairment of its structural integrity [11, 12].

The PAI-1 level is one of the most important indicators of hemostatic system functioning; thus, it should be examined in blood plasma under various conditions [13–16].

To assess the quantitative indicator of PAI-1, an enzyme-linked immunosorbent assay is used. However, various forms of the inhibitor, both active and inactive, can interact with anti-PAI-1 antibodies. In this light, the determination of PAI-1 using specific test systems is more promising [17], which involves certain stages. At stage 1, blood plasma PAI-1 interacts with exogenous tPA. At stage 2, plasminogen is activated because of the residual amount of tPA with plasmin formation; simultaneously, it stimulates the activation reaction of the cleavage of the cyanogen bromide fragment of human fibrinogen. At stage 3, plasmin hydrolyzes the chromogenic substrate S-2403, and a colored substance is released, which is recorded using a spectrophotometer. The optical density value is directly proportional to the activity of residual tissue protease and inversely proportional to the activity of PAI-1 in a given sample [18].

Thus, PAI-1 exists in plasma in three forms:

1) Active form in complex with the protein vitronectin
2) Inactive form along with tPA and vitronectin
3) Inactive (latent) conformation outside the complex

Vitronectin is a glycoprotein that is synthesized in the liver. It serves as a PAI-1 stabilizer. In the absence of this protein, PAI-1 remains in an inactive form and does not deactivate the plasminogen activator [19]. In its latent form, the half-life of PAI-1 is 1–2 h. This time is increased because of its association with vitronectin. This modulation appears to play a significant role in two important processes: induction of the tumor process caused by angiogenic and antiapoptotic effects and maintenance of a balance between the rates of plasminogen activation and fibrin degradation [20].

In addition to PAI-1, blood plasma contains PAI-2 in very low concentrations, which is encoded by *SERPINE-2*. It also inhibits plasminogen activation but mainly through its effects on the urokinase plasminogen activator. It has two forms: free and associated with urokinase plasminogen activator [21]. The former is detected in placental tissue and the latter in the blood and ascitic fluid during pregnancy. The PAI-2 levels increase in the third trimester of pregnancy [22] and generally significantly in malignant neoplasms [23]. Both forms were also detected using enzyme immunoassay test systems.

Regarding its oncogenic role, PAI-1 is primarily associated with increased invasion and neoangiogenesis, which indicates

a poor prognosis [24]. Thus, according to R. Divella, the 4G/4G genotype of *SERPINE-1* was a prognostic marker of unfavorable outcomes in patients with hepatocellular carcinoma who underwent transcatheter chemoembolization. This gene variant in patients with hepatocellular carcinoma is associated with decreased overall survival [25]. Moreover, the PAI-1 level in patients with the 4G/4G genotype remained unchanged after transcatheter chemoembolization, whereas it decreased in patients with the 5G/4G genotype [25].

X. Zhang et al. investigated thrombosis, which is the most significant risk factor for high mortality in patients with myeloproliferative neoplasms, and found that the risk of thrombotic complications was most significant in patients with the 4G/4G genotype. Moreover, this factor is an independent predictor of mortality in patients with myeloproliferative neoplasms [26].

The influence of *SERPINE-1* polymorphisms on the course of pathological processes has been widely studied in obstetrics and gynecology [27, 28]. During a normal pregnancy, the mother's circulatory system is in a state of hypercoagulability because of hormones. Even minor changes in the fibrinolytic system can lead to hyper- or hypofibrinolysis, affecting placental formation and causing adverse pregnancy outcomes.

PAI-1 inhibitors inhibit the fibrinolysis cascade, which often leads to controversial PAI-1 relationships in various gynecological and obstetric diseases, such as recurrent miscarriage, preeclampsia, gestational diabetes mellitus, fetal growth retardation, recurrent implantation failure, polycystic ovary syndrome, and endometriosis [27].

N.V. Alexandrov et al. described the effects of PAI-1 on trophoblast invasion. They found that 5G/4G polymorphism of *SERPINE-1* was associated with the amount of the expressed PAI-1, whereas in the 4G/4G genotype, increased synthesis of PAI-1 reduced the depth of trophoblast invasion and disrupted implantation with subsequent placentation. They also found a direct association of the 4G allele of *SERPINE-1* with the risk of hematomas and/or blood-tinged discharge from the genital tract in the first trimester of pregnancy [29].

In another study, the homozygous 4G/4G genotype of *SERPINE-1* significantly increased the risk of severe preeclampsia caused by increased PAI-1 levels in the blood plasma [30]. However, other authors have different opinions, where the homozygous genotype 5G/5G of *SERPINE-1* is still considered a predictor of the early development of severe preeclampsia [31–33].

Two effective oral *SERPINE-1* inhibitors, tiplaxtinin and aleplazinin, were developed by Wyeth (NJ, USA) [34]. They have been used extensively in clinical trials in patients with Alzheimer's disease. Their activity depends on whether *SERPINE-1* i s bound to vitronectin, suggesting the presence of overlapping binding sites. These drugs selectively inactivate PAI-1, thereby preventing tPA inhibition.

Tahsin F. Kellici et al. analyzed the role of PAI-1 as a regulator of fibrinolysis in patients with viral pneumonia. They found that the blood plasma level of PAI-1 was higher in patients with pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1] than in those with infectious pneumonia of other origins. The level of vitronectin was also higher in patients with SARS-CoV-2 infection; as a result, PAI-1 was in an active state for a long time. These factors contributed to a decrease in fibrinolysis in patients with SARS-CoV-2 infection, thereby increasing the process of inflammation and thrombogenesis [35]. In addition, PAI-1 is a marker of endothelial damage, which allows it to be used as a prognostic marker of hospitalization and clinical outcomes associated with coronavirus disease 2019 (COVID-19) [36].

SERPINE-1 polymorphism is one of the most important predictors of CVD onset and progression because the associated increase in PAI-1 levels suppresses the activities of tPA and PAI-2 and creates a prothrombotic or hypofibrinolytic state [13, 37, 38].

Many studies have shown that PAI-1 gene polymorphisms, which possibly lead to higher levels of PAI-1, are independent risk factors for serious adverse cardiovascular events, including coronary heart disease [39], myocardial infarction [4, 40], ischemic stroke [41], venous thrombosis [42, 43], and atherosclerosis [44].

Thus, N. Abboud et al. (2010) assessed the association between polymorphisms in *SERPINE-1* encoding PAI-1 and myocardial infarction in Tunisians. The study included 305 patients with a history of acute myocardial infarction (AMI) and 328 healthy people unrelated to them as a control group. The majority of the patients with AMI had a homozygous variant of *SERPINE-1* 4G/4G, which contributed to an increase in the PAI-1 level and was associated with a low tPA value [4].

These results are comparable with those reported by Tarek A. Abd. El-Aziz et al. They reported that the 4G allele was associated with a significant increase in the PAI-1 level, which was also detected in the majority of patients with AMI and was directly associated with the risk of complications, including lethal outcomes [5].

Regarding the incidence of the 4G allele of *SERPINE* among residents of the south and east of the Mediterranean, a study assessed the possible risk of cardiovascular accidents associated with thrombosis, which included 160 healthy unrelated Lebanese residents. The most common genotype in the study cohort was 5G/4G. Moreover, the presence of the 4G allele in the study sample was associated with CVD development [45].

Similarly, a study examined a Chinese ethnic group, the Hans [46] and assessed the association of *SERPINE-1* polymorphism with an unfavorable prognosis of coronary heart disease. Patients were divided into two groups: 155 patients with coronary artery disease and 190 unrelated healthy controls. Moreover, the frequency of the 4G/4G genotype was higher in patients with coronary heart disease and multivessel disease than in those with single-vessel damage. Thus, the 5G/4G polymorphism of *SERPINE-1*, as well as the presence

[1] SARS-CoV-2: severe acute respiratory syndrome-related coronavirus-2.

of homozygous genotypes of this gene, can be considered important markers of vascular lesion severity [46].

Another study proposed performing an extended coagulation profile and genetic analysis to determine the dominant homozygous 4G/4G variant and high PAI-1 levels in patients with a genetic predisposition and a high risk of thromboembolic complications [47].

M. Jastrzebskal et al. examined the effects of perindopril and its relationship with tPA. They revealed that hypertension was associated with hyperfibrinogenemia and hypofibrinolysis. Perindopril accelerated fibrinolysis by increasing the tPA level, regardless of the *SERPINE-1* genotype polymorphism and the presence of the 4G allele [48].

According to a study from South Africa, the 4G/4G genotype of *SERPINE-1* increased the risk of hypertension development and progression. The study confirmed the hypothesis that PAI-1 promotes the development of hypertension and is not a consequence of it [49].

Researchers from the University Hospital Center of Zagreb (Croatia) conducted a combined study that assessed the association of polymorphisms in genes encoding prothrombotic and cardiovascular risk factors with disease severity in patients with COVID-19. Several polymorphisms, including *SERPINE-1* polymorphism, were considered markers. The study revealed that the combined effect of polymorphisms in genes encoding prothrombotic and cardiovascular risks worsens the disease course [50].

Each subsequent work revealed evidence that proves the important role of the association of *SERPINE-1* polymorphisms with the disturbance of hemostatic balance and development of severe complications in CVD [47–51]. Thus, a study established that the 4G allele of the 5G/4G polymorphism of *SERPINE-1* is associated with an increased risk of cerebral ischemia after aneurysmal subarachnoid hemorrhage, which is associated with changes in PAI-1 levels [51]. However, M. Stegnar et al. related the association of the 4G/4G genotype of SERPINE-1 with a decrease in stroke in older people. The authors suggested that the local increase in PAI-1 level associated with the 4G allele may stabilize plaques and thereby reduce the risk of cerebrovascular diseases [52].

Another study demonstrated the positive effect of the 4G/4G genotype of *SERPINE-1*. Accordingly, patients with the 4G/4G genotype of *SERPINE-1* had lower PAI-1 activity, whereas patients with the 5G/4G genotype had much higher PAI-1 inhibitor activity [53], which contradicted the above opinions and advocated as a counterargument in favor of the positive effect of the homozygous 4G/4G genotype of *SERPINE-1* [51–53].

Scientists from the Faculty of Medicine of the University of Padua revealed that the 4G/4G genotype is associated with a high thrombotic risk in patients with hereditary thrombophilia [54]. To confirm these data, they analyzed 149 patients with hereditary thrombophilia and assessed the possible prothrombotic contribution of *SERPINE-1* polymorphism and PAI-1 levels [54].

A recent study by a group of scientists from the Krakow Center for Medical Research and Technology revealed a direct association between low-density lipoprotein cholesterol and PAI-1 expression, which promoted hypofibrinolysis and in turn increased the degree of aortic valve stenosis. Moreover, aortic valve stenosis is considered the most common acquired heart defect in older patients [55].

Ci Song et al. reported a similar finding, where a high concentration of PAI-1, associated with *SERPINE-1* polymorphism, increased cardiovascular risks, including the subclinical risk of atherosclerosis [56]. However, in the study, a high concentration of PAI-1 affected the increase in the levels of glucose and low-density lipoprotein cholesterol, whereas in a previous study, high cholesterol levels increased the expression of PAI-1 [56].

Turkish colleagues from the Mersin Medical University examined patients with AMI with *ST*-segment elevation, who were initially divided into two groups: group 1 had a homozygous polymorphism genotype (4G/4G), and group 2 included patients with a more favorable heterozygous genotype of *SERPINE-1* polymorphism [57]. Both groups received thrombolytic therapy, followed by percutaneous coronary intervention within the first 24 h. The efficacy of thrombolytic therapy was assessed according to electrocardiography and coronary angiography, in accordance with the thrombolysis in myocardial infarction scale. Group 1 had the highest degree of ineffective thrombolytic therapy, and coronary angiography revealed the absence of anterograde blood flow in the infarct-related artery, regardless of the thrombolytic therapy. The authors concluded that the homozygous 4G/4G genotype of *SERPINE-1* was more associated with the lack of effectiveness of thrombolytic therapy in patients with AMI with *ST*-segment elevation [57].

Another study obtained similar results, in which the 4G allele of *SERPINE-1* was also associated with an increased risk of CVD [58]. After 3 months, a study revealed an association of another homozygous genotype, 5G/5G, with early spontaneous recanalization of the coronary arteries in patients with AMI and ST-segment elevation [59].

Considering the association of the effect of *SERPINE-1* polymorphism on the pathogenesis and early development of myocardial infarction in patients aged <35 years, L.S. Rallidis et al. demonstrated conflicting results because their data revealed that 4G carriage was more common in a healthy population and was associated with a low risk of AMI [60].

Researchers from Notre Dame University assessed the contribution of PAI-1 to the risk of cardiac fibrosis development [61]. They revealed that homozygous genetic deficiency of this enzyme contributes to the development of myocardial fibrosis. This finding provides evidence that PAI-1 deficiency may be an adverse predictor of cardiac remodeling [61].

Researchers from China investigated the contribution of *SERPINE-1* polymorphism and PAI-1 level to the development of venous thromboembolism and found that the homozygous 4G/4G variant and heterozygous 4G/5G variant

was associated with a high risk of thromboembolic conditions when compared with the 5G/5G genotype of this gene among Asian populations. This finding confirms the idea of most scientists. However, the authors recommended conducting a study among multiethnic groups to obtain more consistent results on the association of *SERPINE-1* polymorphism with venous thromboembolism [62].

Another group of researchers from China obtained similar results. They reported that patients with the 5G/5G genotype of *SERPINE-1* achieved complete recanalization with greater probability and had a relapse-free status compared with the 4G/4G or 4G/5G variants of *SERPINE-1* [63].

The above data were confirmed by a similar study by authors from India, where the 4G/4G genotype of *SERPINE-1* was considered a powerful risk factor for venous thrombosis and thromboembolic conditions; thus, the authors recommend its inclusion in the laboratory testing panel for thrombophilia [64].

CONCLUSIONS

At present, the influence of *SERPINE-1* polymorphism on the course of a heterogeneous group of diseases, such as malignant neoplasms, pneumonia caused by SARS-COV-2, and miscarriage, including some CVDs, is clearly defined, which is most relevant these days because the causes of recurrent CVDs remain underinvestigated. Moreover, such increasing studies demonstrate the obvious increasing interest of scientists in the influence of *SERPINE-1* polymorphisms on the development and severity of CVD.

Taking into account the opinion of most authors, the results indicate that the *SERPINE-1* polymorphism and its homozygous variant 4G/4G, which increases PAI-1 synthesis, are unfavorable predictors of various pathological processes. However, the small number of studies in which the 4G allele was considered a protective factor in relation to CVD and cerebrovascular diseases must be taken into account.

The inconsistency of the data obtained certainly requires further study of the characteristics of the polymorphism of *SERPINE-1* encoding PAI-1 under various pathological conditions. This is an important prerequisite for understanding the mechanisms of many diseases and their outcomes and for developing approaches to optimize the prognosis for the development of severe complications.

ADDITIONAL INFORMATION

Author contributions. S.D.M. — work management; O.A.K. — co-management of work; A.F.U. — literature review, analysis of results.
Funding. The study had no sponsorship.
Conflict of interest. The authors declare that there is no conflict of interest in the presented article.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. С.Д.М. — руководство работой; О.А.К. — соруководство работой; А.Ф.У. — обзор литературы, анализ результатов.
Источник финансирования. Исследование не имело спонсорской поддержки.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов по представленной статье.

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