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Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 1, January 2026

https://eurekaoa.com/index.php/5

CONTRIBUTION OF EDN1 AND COMT GENE VARIATIONS TO THE DEVELOPMENT OF CARDIOTOXIC COMPLICATIONS

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Abstract

Cardiac complications remain one of the leading causes of poor prognosis and decreased quality of life in patients receiving anticancer and combination therapy. Despite the active implementation of cardioprotective strategies, individual myocardial sensitivity to damaging factors varies significantly, indicating the significant role of genetic determinants in the development of cardiotoxicity. In recent years, increasing attention has been paid to the study of gene polymorphisms involved in the regulation of vascular tone, oxidative stress, and neurohumoral activity.

Keywords: Contribution, variations, gene, edn1, comt, occurrence, cardiotoxic, complications, cardiology.

ВКЛАД ВАРИАЦИЙ ГЕНОВ EDN1 И COMT В ВОЗНИКНОВЕНИЕ КАРДИОТОКСИЧЕСКИХ ОСЛОЖНЕНИЙ

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Кардиологические осложнения остаются одной из ведущих причин ухудшения прогноза и снижения качества жизни у пациентов, получающих противоопухолевую и комбинированную терапию. Несмотря на активное внедрение кардиопротективных стратегий, индивидуальная чувствительность миокарда к повреждающим факторам существенно варьирует, что указывает на значимую роль генетических детерминант в формировании кардиотоксичности. В последние годы всё большее внимание уделяется изучению полиморфизмов генов, вовлечённых в регуляцию сосудистого тонуса, оксидативного стресса и нейрогуморальной активности.

Ключевые слова: вклад, вариаций, ген, edn1, comt, возникновение, кардиотоксический, осложнений, кардиология.

KARDIOTOKSIK ASORATLARNING RIVOJLANISHIGA EDN1 VA COMT GEN VARIASIYALARINING QO'SHISH HISSASI

Kardiologik asoratlar o'smalarga qarshi va kombinatsiyalangan terapiya olayotgan bemorlarda yomon prognoz va hayot sifatining pasayishining asosiy sabablaridan biri bo'lib qolmoqda. Kardioprotektiv strategiyalarning faol qo'llanilishiga qaramay, miokardning zararli omillarga individual sezgirligi sezilarli darajada farq qiladi, bu esa kardiotoksiklik rivojlanishida genetik determinantlarning muhim rolini ko'rsatadi. So'nggi yillarda qon tomir tonusini, oksidlovchi stressni va neyrogumoral faollikni boshqarishda ishtirok etadigan gen polimorfizmlarini o'rganishga tobora ko'proq e'tibor qaratilmoqda.

Kalit so'zlar: Hissa, variatsiyalar, gen, edn1, comt, paydo bo'lishi, kardiotoksik, asoratlar, kardiologiya.

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Introduction

In recent years, increasing attention has been paid to the study of polymorphisms in genes involved in the regulation of vascular tone, oxidative stress, and neurohumoral activity.

Among these genes, EDN1, which encodes endothelin-1 – one of the most potent endogenous vasoconstrictors, is of particular interest. Increased expression of endothelin-1 is associated with endothelial dysfunction, vascular wall remodeling, and impairment of coronary microcirculation [7]. As shown in studies by Böhm et al. (2018) [8] and Schiffrin et al. (2019) [9], genetic variations in EDN1 can modify the risk of cardiovascular complications under the influence of stress factors, including drug load. Another important molecular regulator is the COMT gene, encoding catechol-O-methyltransferase – a key enzyme for catecholamine inactivation. The Val158Met polymorphism leads to reduced enzyme activity and, consequently, to increased catecholamine concentrations, enhanced oxidative stress, and metabolic overload of cardiomyocytes [10,11]. The role of COMT in cardiovascular pathology is described in detail in the works of Tunbridge et al. (2018) [10] and Männistö et al. (2020) [11], which demonstrate the association of the Met allele with adverse cardiometabolic effects.

Contemporary research emphasizes that isolated analysis of individual genes does not always allow for an adequate assessment of complication risk. According to Visscher et al. (2017) [12] and Torkamani et al. (2018) [13], clinically significant effects are more often realized through the combined action of several polymorphisms affecting different pathogenetic pathways. In this regard, the simultaneous study of EDN1 and COMT gene polymorphisms is of particular interest, since their functional effects potentially reinforce each other: endothelial dysfunction and vasoconstriction mediated by EDN1 may be exacerbated by neurohumoral and metabolic myocardial overload due to reduced COMT activity.

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However, data on the combined influence of these genes on the risk of cardiac complications remain limited and contradictory [5,12].

Objective

To study the association of EDN1 and COMT gene polymorphisms, as well as their combined influence, on the risk of developing cardiac complications in patients of the main group.

Materials and Methods

The study included 199 individuals, who were divided into a main group and a control group. The main group consisted of 102 patients, in whom the presence of cardiac complications was assessed during observation. Depending on the clinical course, patients in the main group were divided into two subgroups: a group with cardiac complications – 64 patients; a group without cardiac complications – 38 patients.

The control group consisted of 97 practically healthy individuals, comparable to the main group in terms of sex and age, with no history of clinically significant cardiovascular diseases.

Inclusion criteria: written informed consent; availability of complete clinical, laboratory, and genetic examination; possibility for dynamic cardiac follow-up.

Exclusion criteria: congenital heart defects; chronic heart failure of functional class III–IV; acute inflammatory diseases at the time of inclusion; refusal to participate in the study.

Cardiac complications were diagnosed based on clinical data, electrocardiographic and echocardiographic examination. Rhythm and conduction disorders, signs of systolic and diastolic dysfunction, as well as clinical manifestations of cardiovascular pathology that arose during observation were taken into account.

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For genetic analysis, peripheral venous blood samples were used. Genomic DNA extraction was performed using standard methods with commercial reagent kits. The following polymorphisms were investigated: the Lys198Asn polymorphism of the EDN1 gene; the Val158Met polymorphism of the COMT gene. Genotyping was performed using the polymerase chain reaction (PCR) method followed by analysis of amplification products. The quality of genotyping was controlled by re-analysis of randomly selected samples.

Statistical data processing was carried out using standard biostatistical methods. Allele and genotype frequencies are presented as absolute values and percentages. Comparison of allele and genotype distributions between groups was performed using Pearson's χ^2 test or Fisher's exact test for small expected values. The association of polymorphisms with the risk of developing cardiac complications was assessed by calculating the odds ratio (OR) with a 95% confidence interval (95% CI). Differences were considered statistically significant at a level of $p < 0.05$.

Results

Lys198Asn polymorphism of the EDN1 gene

In the group of patients with the Lys198Asn polymorphism of the EDN1 gene and with cardiac complications, the frequency of the Asn allele was 28.1%, whereas in the group without complications it was 22.4%. The Lys allele was detected in 71.9% and 77.6% of cases, respectively. The Asn allele was associated with an increased risk of developing cardiac complications; however, the differences did not reach the level of statistical significance (OR = 1.35; 95% CI 0.72–2.54; p = 0.34). The frequency of the Asn/Asn genotype was higher in the group with complications (7.8%) compared to the group without complications (5.3%). When combining carriers of Asn-containing genotypes (Lys/Asn + Asn/Asn), their proportion was 48.4% in the group with complications and 39.5% in the group without complications. Carriage of Asn-

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containing genotypes was associated with a trend towards an increased risk of cardiac complications (OR = 1.44; 95% CI 0.67–3.09; p = 0.35).

Val158Met polymorphism of the COMT gene

In the group with cardiac complications, the frequency of the Met allele was 60.9%, whereas in the group without complications it was 28.9%. The Val allele predominated in patients without complications (71.1%). The Met allele was statistically significantly associated with an increased risk of cardiac complications (OR = 3.82; 95% CI 2.01–7.25; p <0.001). Genotype analysis: the frequency of the Met/Met genotype in the group with complications was 34.4%, which was significantly higher compared to the group without complications (10.6%). The Val/Val genotype, on the contrary, predominated in patients without cardiac complications (52.6% versus 12.5%). Carriage of the Met/Met genotype was associated with a more than fourfold increase in the risk of developing cardiac complications (OR = 4.45; 95% CI 1.32–15.05; p = 0.01). Analysis of the dominant model (carriage of ≥1 Met allele: Val/Met + Met/Met) revealed a significant association with the development of complications (OR = 4.83; 95% CI 1.88–12.41; p = 0.001).

Comparative Analysis of EDN1 and COMT.

In contrast to the EDN1 gene polymorphism, for which only trends towards association with cardiac complications were found, the Val158Met polymorphism of the COMT gene demonstrated a pronounced and statistically significant association at both the allelic and genotypic levels. The highest risk of developing cardiac complications was observed in carriers of the COMT Met allele, especially with the homozygous Met/Met genotype, indicating the leading role of this gene in forming an unfavorable cardiac profile.

Thus, the Val158Met polymorphism of the COMT gene is a significant genetic risk factor for the development of cardiac complications, while the Lys198Asn

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polymorphism of the EDN1 gene demonstrates moderate, statistically non-significant associations that may be enhanced under combined genetic influence. The results of the combined analysis showed that in the group of patients with cardiac complications, the following were observed simultaneously: an increase in the frequency of Asn-containing genotypes of the EDN1 gene; and a statistically significant increase in the frequency of the Met allele and Met-containing genotypes of the COMT gene.

At the same time, the isolated effect of the EDN1 polymorphism was characterized by a moderate association with the development of cardiac complications (OR ≈ 1.3; $p > 0.05$), while the COMT polymorphism demonstrated a pronounced and statistically significant association (OR ≈ 3.8; $p < 0.001$). Considering the different directions and strengths of the effects of these genes, it can be assumed that the simultaneous carriage of the EDN1 Asn allele and the COMT Met allele forms an additive or synergistic genetic risk profile that contributes to the development of cardiac complications.

Genetic Profile	EDN1	COMT	Risk characteristics
Low Risk	Lys/Lys	Val/Val	Preserved endothelial function, efficient catecholamine inactivation.
Intermediate Risk	Asn+	Val/Val	Moderate endothelial dysfunction.
Intermediate Risk	Lys/Lys	Met+	Increased neurohumoral and metabolic load.
High Genetic Risk	Asn+	Met+	Combination of endothelial dysfunction and oxidative stress

The combined influence of the EDN1 and COMT polymorphisms affects different yet interrelated pathogenetic mechanisms: EDN1 — endothelial dysfunction, enhanced vasoconstriction, and impaired microcirculation; COMT — reduced catecholamine inactivation, increased oxidative stress, and metabolic overload of the myocardium.

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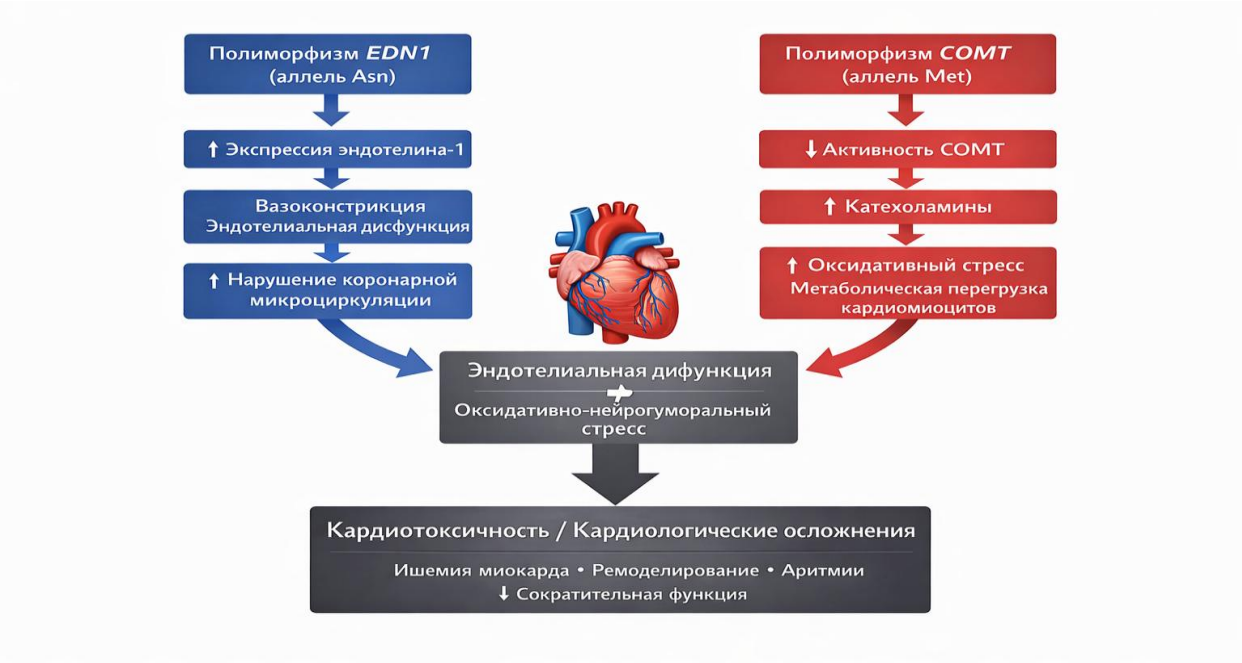
This combination can lead to cumulative damage to the cardiovascular system, especially under conditions of additional pharmacological or metabolic load.



Discussion

In the present study, the role of the EDN1 (Lys198Asn) and COMT (Val158Met) gene polymorphisms in the formation of cardiac complications was analyzed. The obtained results indicate the varying strength and direction of influence of the studied genes and point to their potential combined pathogenetic action.

In our study, the frequency of the EDN1 Asn allele was higher in patients with cardiac complications (28.1%) compared to patients without complications (22.4%) and the control group (18.0%). Allelic analysis showed a moderate increase in the risk of developing complications in carriers of the Asn allele (OR = 1.35; 95% CI 0.72–2.54; p = 0.34), but the differences did not reach statistical significance. At the genotype level, carriage of Asn-containing genotypes (Lys/Asn + Asn/Asn) was also more frequent in the complication group (48.4%

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vs. 39.5%), which was accompanied by a trend toward increased risk (OR = 1.44; 95% CI 0.67–3.09; p = 0.35).

The contribution of EDN1 to the development of cardiac complications is of a modulating nature, enhancing the action of other pathogenetic factors. Similar conclusions are presented in the works of Schiffrin et al. (2019) and Böhm et al. (2018), which show that EDN1 polymorphisms are associated primarily with endothelial dysfunction and vascular disorders but do not always demonstrate independent clinical significance.

In contrast to EDN1, the Val158Met polymorphism of the COMT gene in our study demonstrated a pronounced and statistically significant association with the development of cardiac complications. The frequency of the Met allele in the complication group reached 60.9%, while in the group without complications it was only 28.9%. The Met allele was associated with an almost fourfold increase in the risk of complications (OR = 3.82; 95% CI 2.01–7.25; p <0.001). Genotype analysis confirmed the dose-dependent effect of the Met allele: carriage of the Met/Met genotype increased the risk of developing cardiac complications more than fourfold (OR = 4.45; 95% CI 1.32–15.05; p = 0.01), whereas under the dominant model (Val/Met + Met/Met) the risk increased almost fivefold (OR = 4.83; 95% CI 1.88–12.41; p = 0.001). These findings are consistent with the results of studies by Männistö et al. (2020) and Tunbridge et al. (2018), which show that the Met allele is associated with reduced COMT activity, accumulation of catecholamines, and increased oxidative stress—key mechanisms of myocardial damage.

The results of our study indicate a possible enhancement of cardiotoxic risk with combined carriage of the EDN1 Asn allele and the COMT Met allele. The EDN1 polymorphism primarily affects the vascular component—endothelial dysfunction and impairment of coronary microcirculation, whereas COMT determines the level of neurohumoral and metabolic load on cardiomyocytes. Such complementarity of effects aligns with the concept of polygenic risk

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described by Torkamani et al. (2018) and Visscher et al. (2017), according to which clinically significant phenotypes are formed as a result of the interaction of several genetic variants with moderate individual effects. In this context, COMT can be considered a leading risk gene, whereas EDN1 can be seen as a modifier gene that enhances myocardial damage against an unfavorable neurohumoral background.

The results of the present study demonstrate the leading role of the Val158Met polymorphism of the COMT gene in the formation of cardiac complications and indicate the potential amplifying influence of the Lys198Asn polymorphism of the EDN1 gene. A joint analysis of these genes allows for a deeper understanding of the molecular mechanisms of cardiotoxicity and can be used to develop personalized approaches to risk assessment.

Conclusions

The combined analysis indicates a potentially unfavorable genetic profile with combined carriage of the EDN1 Asn allele and the COMT Met allele, reflecting an additive or synergistic impact of vascular and neurohumoral-metabolic mechanisms. The obtained data are consistent with modern concepts of the polygenic nature of cardiotoxicity and support the feasibility of comprehensive genetic analysis for assessing the individual risk of cardiac complications. The study results have potential practical significance for identifying high-risk groups and developing personalized preventive and monitoring strategies for patients with an unfavorable genetic profile.

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