UDC: 796.08:612.897-899:616-074

GENETIC MARKERS ASSOCIATED WITH VEGETATIVE DYSFUNCTIONS IN ATHLETES

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СПОРТЧИЛАРДА ВЕГЕТАТИВ ДИСФУНКЦИЯЛАР БИЛАН БОҒЛИҚ ГЕНЕТИК БЕЛГИЛАР

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ГЕНЕТИЧЕСКИЕ МАРКЕРЫ, АССОЦИИРОВАННЫЕ С ВЕГЕТАТИВНЫМИ ДИСФУНКЦИЯМИ У СПОРТСМЕНОВ

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Резюме. *Мақолада катехоламинлар метаболизмининг генетик жиҳатларини ўрганиш бўйича таҳлилий маълумотлар келтирилган бўлиб, улар инсон танасидаги кўплаб физиологик ва психологик жараёнларни тушунишда муҳим рол ўйнайди. Допамин ва унинг ҳосилалари метаболизми билан боғлиқ бўлган энг муҳим генлардан бири COMT (catechol-O-methyltransferase) гени эканлиги кўрсатилган. Ушбу ген катехоламинлар алмашинувида иштирок этадиган ферментни, шу жумладан допамин, адреналин ва норепинефринни кодлайди, бу кўплаб физиологик жараёнларни, шу жумладан стрессга жавоб, кайфиятни тартибга солиш ва юрак-қон томир динамикасини тартибга солишда муҳим рол ўйнайди COMT генининг полиморфизмлари дунёнинг турли популяцияларида сезиларли ўзгаришларни кўрсатиши ва руҳий саломатлик ва когнитив функцияларни шакллантиришда муҳим рол ўйнаши аниқланди.*

Калит сўзлар: *катехоламинлар, метаболизм, COMT гени, вегетатив дисфункция, когнитив функция, стресс, юрак-қон томир тизими.*

Abstract. *The article presents analytical data on the study of the genetic aspects of catecholamine metabolism, which play a key role in understanding many physiological and psychological processes in the human body. It has been shown that one of the most important genes related to dopamine metabolism and its derivatives is the COMT (catechol-O-methyltransferase) gene. This gene encodes an enzyme involved in the metabolism of catecholamines, including dopamine, adrenaline, and norepinephrine, which play a crucial role in regulating many physiological processes, including stress response, mood regulation, and cardiovascular system dynamics. It has been determined that COMT gene polymorphisms exhibit significant variations across different populations worldwide and play an important role in shaping mental health and cognitive functions.*

Keywords: *catecholamines, metabolism, COMT gene, vegetative dysfunction, cognitive functions, stress, cardiovascular system.*

The genetic aspects of catecholamine metabolism play a key role in understanding many physiological and psychological processes in the human body. One of the most important genes involved in the metabolism of dopamine and its derivatives is the COMT (catechol-O-methyltransferase) gene, which encodes an enzyme involved in the metabolism of catecholamines, including dopamine, adrenaline, and norepinephrine.

The COMT gene is located on the long arm of human chromosome 22 (22q11.21). It is an alpha-gene that encodes the enzyme catechol-O-methyltransferase. COMT consists of 5 exons and 4 introns and encodes a polypeptide approximately 271 amino acids long, which catalyzes the methylation of catecholamines, leading to their inactivation [10]. The full designation of the gene is COMT (OMIM 116790). The COMT gene contains several alleles, with the most well-known being Val158Met (rs4680), representing a polymorphism where valine (Val) is replaced by methionine (Met) at position 158 [6]. The Val158Met (rs4680) polymorphism is a single nucleotide substitution in the COMT gene, where adenine (A) is replaced by guanine (G) at position 158, resulting in the substitution of valine (Val) with methionine (Met) [24]. This change affects the enzyme's thermostability and catalytic activity.

The location of the COMT gene on chromosome 22 also makes it a subject of research in genetics and psychiatry. Polymorphisms in the COMT gene may interact with other genes and environmental factors, making the study of its functions and associations particularly significant [14].

The Val158Met polymorphism is associated with the substitution of valine (Val) with methionine (Met) at the 158th amino acid residue of the COMT enzyme. This substitution results in two allelic variants: Val/Val (homozygous valine) and Met/Met (homozygous methionine), as well as the heterozygous Val/Met variant. The A allele, which encodes the amino acid Val (valine), is associated with high enzyme activity, while the G allele, which encodes Met (methionine), leads to reduced COMT activity. There is significant variability in the distribution of these alleles among different populations. A comparative analysis of CC, CG, and GG genotypes shows that the AA genotype predominates in Central Asian populations, while in other regions, such as Western Europe, there may be a more even distribution of alleles [33]. This indicates complex interactions between genetic factors and ecosystems.

According to allele distribution in populations, in European populations, particularly in Northern and Central Europe, the methionine allele (Met) is found in about 20-30% of carriers, whereas the valine allele (Val) is much more prevalent [26]. This may be related to differences in selection and adaptation to the environment. Among people of East Asian descent (e.g., Chinese and Japanese), the Met allele is also common but to a lesser extent than in European populations [5]. In some groups, Met carriers account for about 18%. Studies show that the Val allele dominates in African populations, reaching 90% or more, which may reflect evolutionary adaptation to conditions potentially related to stress levels and cognitive demands [28].

Among indigenous Americans, research shows a much higher level of polymorphism, where the frequency of the Met allele can vary significantly depending on the specific group [11]. In some tribes, the frequency of the Met allele reaches 25%.

It can be concluded that COMT gene polymorphisms exhibit significant variations in populations around the world, opening new horizons for understanding their role in mental health and cognitive functions. Adaptive changes in polymorphism patterns may indicate complex interactions between genetics and the environment.

The enzyme encoded by the COMT gene (catechol-O-methyltransferase) plays a key role in the metabolism of neurotransmitters such as dopamine, adrenaline, and norepinephrine, as well as in the detoxification of xenobiotics and catecholamines. It catalyzes the transfer of a methyl group to catechols, leading to their inactivation. The primary function of the enzyme is the metabolism of dopamine, which is critical for cognitive functions, mood regulation, and motor activity [17,30].

Catechol-O-methyltransferase is a cytosolic enzyme consisting of a single polypeptide chain with a molecular weight of approximately 28 kDa [31]. It contains an active site where the catalytic methylation reaction occurs. The enzyme's active site includes a histidine residue, which participates in substrate binding, and a methionine residue involved in methyl group transfer. COMT requires the cofactor S-adenosylmethionine (SAM), which serves as a methyl donor for its activity [2].

Catechol-O-methyltransferase has two main isoenzymes: peripheral (mainly expressed in the liver and other tissues) and central (present in the brain). The isoenzymes differ in activity: a high-activity variant (Val) and a low-activity variant (Met), which are associated with polymorphism in the gene's coding region [15].

As mentioned, the enzyme encoded by the COMT gene plays a key role in the metabolism of catecholamines, including dopamine, adrenaline, and norepinephrine. Methylation of catecholamines by COMT leads to the formation of less active metabolites, which is critical for regulating the levels of these neurotransmitters in synapses [3]. Deviations in COMT activity can lead to various disorders, including changes in cognitive functions and emotional states.

Catecholamines, including dopamine, adrenaline, and norepinephrine, play a crucial role in regulating many physiological processes, such as stress response, mood regulation, and cardiovascular dynamics [20]. They are involved in mood regulation, motivation, emotional learning, and memory.

The components of the reaction involving COMT differ depending on the allelic variant. The enzyme encoded by the G allele has a lower maximum reaction rate and a higher KM, indicating lower substrate affinity [7]. This suggests that individuals with this allele may be more sensitive to changes in catecholamine levels, which could lead to various consequences for their mental state and overall physiological stress response.

Dopamine, in turn, is a key neurotransmitter involved in regulating many physiological processes, including mood, motivation, and motor activity. The COMT gene metabolizes dopamine by attaching a methyl group to the hydroxyl groups on its molecule. This process occurs primarily in the brain and liver. The metabolism of dopamine by COMT is crucial for its inactivation and maintaining normal levels of this neurotransmitter in the central nervous system [16].

Dopamine is a catecholamine that acts as a neurotransmitter in the human central nervous system. It is synthesized from the amino acid tyrosine in neurons and plays a significant role in regulating various bodily functions such as motivation, attention, memory, learning, movement, mood, and the regulation of the hormonal system [1,32]. Dopamine consists of a catechol group (a benzene ring with two hydroxyl groups) and ethylamine. Dopamine synthesis in neurons occurs from tyrosine through the following steps: 1. Tyrosine hydroxylation: The enzyme tyrosine hydroxylase (TH) catalyzes the conversion of tyrosine into L-DOPA (dihydroxyphenylalanine); 2. Decarboxylation of L-DOPA: The enzyme DOPA decarboxylase converts L-DOPA into dopamine [19]. Dopamine is metabolized by the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) [12].

Considering the two main variants of the COMT gene (Val) and (Met), it is noteworthy that the Val variant leads to higher enzyme activity, which results in faster dopamine metabolism. In contrast, the Met variant leads to slower dopamine metabolism, which may affect its concentration in the brain and peripheral tissues [4,8].

It is also known that dopamine directly participates in the regulation of cognitive processes, including learning, attention, and memory. Disruptions in the dopaminergic system may lead to cognitive disorders, such as memory

impairment and inability to concentrate [29]. The COMT Val158Met polymorphism may be considered a risk factor for developing such disorders, particularly in individuals with the G allele.

Dopamine also has a direct effect on the cardiovascular system. It can increase cardiac output and dilate blood vessels, reducing peripheral resistance, and thereby affecting blood pressure. Dopamine metabolism, regulated by the COMT gene, can influence these processes. For example, insufficient dopamine levels due to high COMT activity may lead to decreased cardiac function and increased blood pressure [23].

Differences in COMT genotypes may also lead to varying susceptibility to cardiovascular diseases. Studies have shown that polymorphisms in the COMT gene may be linked to the risk of developing hypertension and other cardiovascular diseases [22]. For example, carriers of the Met variant may have an increased risk of developing diseases due to slower dopamine metabolism and, consequently, its higher concentration in the brain and body overall [25].

Research shows that Val (G) allele carriers may have a lower risk of developing hypertension and other cardiovascular diseases due to efficient catecholamine metabolism, while Met (A) allele carriers may exhibit higher levels of stress and anxiety, potentially contributing to cardiovascular system dysfunction [9]. High dopamine levels may increase sympathetic nervous system activity, which correlates with hypertension risk [18].

In this context, it is important to recall that the COMT gene plays a crucial role in dopamine metabolism, and its polymorphisms can significantly influence cardiovascular function. Understanding the mechanism of the COMT gene's action may help develop strategies for treating cardiovascular diseases and other disorders associated with dopamine deficiency.

The COMT Val158Met polymorphism is also associated with stress response. Individuals with the A allele exhibit greater stress resilience due to more efficient catecholamine metabolism, whereas G allele carriers are more prone to stress and may develop autonomic dysfunctions, such as increased anxiety, depression, and other disorders [13].

The impact of COMT polymorphisms on autonomic dysfunction is equally significant. Carriers of the Met (A) allele show more pronounced symptoms of autonomic dysfunction, such as increased fatigue, impaired thermoregulation, and altered heart rhythm. This is due to the system's high sensitivity to stress factors and changes in dopamine levels, which affect autonomic tone [27]. For example, studies indicate that people with the Met (A) allele have a heightened stress response and are more prone to diseases related to autonomic dysfunction, such as irritable bowel syndrome and autonomic neurosis [34].

To gain a deeper understanding of the functional consequences and biological mechanisms of variations in the COMT gene, as well as their effects on behavior and psychological state, it is essential to consider both genetic and environmental contexts in which these variations act [21]. It should be noted that COMT gene functioning may be subject to epigenetic changes, such as DNA methylation, which can influence autonomic dysfunction [35].

DNA methylation is the process of adding a methyl group to cytosine in regions rich in guanine and cytosine (CpG islands), leading to changes in gene activity without altering its sequence. High methylation of the COMT gene region may inhibit its expression, which could result in elevated dopamine levels in the brain, and this is associated with various psycho-emotional states and autonomic dysfunctions, such as anxiety and depression [36]. Autonomic dysfunction may manifest through various symptoms, including heart rhythm disturbances, digestive issues, and changes in blood pressure. Epigenetic factors such as stress, nutrition, and environment can trigger changes in DNA methylation, which in turn affects COMT gene expression and thus catecholamine levels. For example, stress can cause hypermethylation of the COMT gene, leading to decreased activity and, consequently, impairments in dopamine regulation [37].

The relationship between COMT gene methylation and autonomic dysfunction opens new avenues for understanding the mechanisms underlying psycho-emotional disorders. Further research in this area could help identify potential therapeutic targets and strategies for preventing diseases associated with autonomic nervous system dysfunction.

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ГЕНЕТИЧЕСКИЕ МАРКЕРЫ, АССОЦИИРОВАННЫЕ С ВЕГЕТАТИВНЫМИ ДИСФУНКЦИЯМИ У СПОРТСМЕНОВ

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Резюме. *В статье приводятся аналитические данные по изучению генетических аспектов метаболизма катехоламинов, которые играют ключевую роль в понимании множества физиологических и психологических процессов в организме человека. Показано, что одним из важнейших генов, связанных с метаболизмом дофамина и его производных, является ген COMT (catechol-O-methyltransferase). Данный ген кодирует фермент, участвующий в метаболизме катехоламинов, включая дофамин, адреналин и норэпинефрин, играющих важную роль в регуляции многих физиологических процессов, включая реакцию на стресс, регуляцию настроения и динамику сердечно-сосудистой системы Определено, что полиморфизмы гена COMT демонстрируют значительные вариации в различных популяциях мира и играют важную роль в формировании психического здоровья и когнитивных функциях*

Ключевые слова: *катехоламины, метаболизм, ген COMT, вегетативная дисфункция, когнитивные функции, стресс, сердечно-сосудистая система.*