Association of the COMT Gene Polymorphism rs4680 with Cognitive Impairment in Schizophrenia: A Narrative Review

Ассоциации функционального варианта гена COMT rs4680 с когнитивными нарушениями при шизофрении: нарративный обзор

doi: 10.17816/CP15603

Review

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ABSTRACT

BACKGROUND: Cognitive impairment in schizophrenia patients is characterized by decreased functioning, reduced quality of life, and is a predictor of a more severe course of the disease. The rs4680 variant of the *COMT* gene (Val158Met), which encodes catechol-O-methyltransferase, affects dopamine metabolism in the prefrontal cortex and is a key genetic modifier of cognitive endophenotypes. However, the associations of the rs4680 alleles with the severity of cognitive impairment remain unclear. This review summarizes and critically re-evaluates the evidence on the role of rs4680 in the development of cognitive deficits in schizophrenia.

AIM: To explore the associations of the rs4680 variant of the *COMT* gene with cognitive functions in schizophrenia.

METHODS: A literature search of the PubMed database for the last 10 years (2014–2024) was performed with the search query "rs4680 schizophrenia cognition". The review included 11 studies.

RESULTS: In the majority of studies (9 out of 11), carriers of the Met allele demonstrated better cognitive parameters, such as verbal and visual memory, information processing speed, and regulatory functions (especially in men). Individuals with the Val/Val genotype demonstrated worse attention. Women in the Russian population with Met allele had better conceptualization and inhibitory control results, and men in the Han population with Met allele had a better association with memory and attention.

CONCLUSION: The results of this review confirm the association between the rs4680 variant of the *COMT* gene and cognitive function. Although the quality of the studies included in this review was low, the overall results indicate that further investigation of this association is promising. The identification of a stable association between the *COMT* genotype and the severity of cognitive deficit provides the basis for a personalized approach in the management of patients with schizophrenia. Further studies on the validation of genetic markers in independent cohorts and the development of algorithms for the integration of genetic data with complex neurocognitive assessments and clinical endophenotypes are needed to make the clinical implementation of this approach successful.

АННОТАЦИЯ

ВВЕДЕНИЕ: Когнитивные нарушения при шизофрении приводят к снижению функционирования и ухудшению качества жизни, а также служат предикторами более тяжелого течения заболевания. Вариант rs4680 гена *COMT* (Val158Met), кодирующего катехол-О-метилтрансферазу, определяет метаболизм дофамина в префронтальной коре и является ключевым генетическим модификатором когнитивных эндофенотипов. Однако ассоциации аллелей rs4680 с выраженностью когнитивных нарушений остаются недостаточно ясными. В обзоре обобщены и критически переосмыслены сведения о роли rs4680 в формировании когнитивного дефицита при шизофрении.

ЦЕЛЬ: Изучить ассоциации варианта rs4680 гена *COMT* с когнитивными функциями при шизофрении.

МЕТОДЫ: Проведен поиск литературы по базе данных PubMed за последние 10 лет (2014–2024) по запросу «rs4680 schizophrenia cognitive». В обзор было включено 11 исследований.

РЕЗУЛЬТАТЫ: В большинстве исследований (в 9 из 11) носители аллеля Met демонстрировали лучшие когнитивные показатели, такие как вербальная и зрительная память, скорость обработки информации, регуляторные функции (особенно у мужчин). Для группы лиц с генотипом Val/Val наблюдалось снижение внимания. У женщин-носителей аллеля Met российской популяции были выше показатели концептуализации и тормозного контроля, а у мужчин-носителей аллеля Met популяции хань были выше показатели памяти и внимания.

ЗАКЛЮЧЕНИЕ: По результатам данного обзора подтверждена взаимосвязь между вариантом rs4680 гена *COMT* и когнитивными функциями. Несмотря на то что качество исследований, включенных в данный обзор, было низким, суммарный результат указывает на перспективность дальнейшего изучения данной связи. Выявление устойчивой связи между генотипом *COMT* и выраженностью когнитивного дефицита создает основу для персонализированного подхода в ведении пациентов с шизофренией. Для успешной клинической реализации этого подхода необходимы дальнейшие исследования по валидации генетических маркеров в независимых когортах и разработка алгоритмов интеграции генетических данных с комплексной нейрокогнитивной оценкой и клиническими эндофенотипами.

Keywords: *schizophrenia; COMT; Val158Met; cognitive functions; rs4680*
Ключевые слова: *шизофрения; COMT; Val158Met; когнитивные функции; rs4680*

INTRODUCTION

Schizophrenia leads to numerous negative social consequences, including impaired ability to work in the very first years of the disease and lifelong disability [1–3]. The main factors that decrease social activity, work capacity, and the possibility of independent life in patients are not only frequent psychotic exacerbations but also significant cognitive deficits, as well as increased negative symptoms [4, 5]. Schizophrenia is associated with impairments in cognitive domains, such as executive functions (impairment of planning, organization, flexibility of thinking, problem solving, and impulse control), difficulties with abstract thinking and multitasking, memory (working, verbal, and visual), attention (decreased concentration and attention span), information processing speed (understanding, slow perception, and response to information), social perception,

and emotion recognition [6]. It is believed that disorders are found in 85% of patients in this group [7]. After the onset of schizophrenia, the majority (98%) of patients demonstrate a decrease in cognitive function compared with the premorbid state, which leads to incomplete remission [7]. Cognitive impairment is observed both in patients on long-term treatment with neuroleptics and in those not receiving neuroleptics [1, 7, 8].

Dihydroxyphenylalanine (L-DOPA), is the precursor to the neurotransmitters dopamine, norepinephrine (noradrenaline), whose metabolism largely determines overall activity, attention control, and vigilance, as does a complex system of motivation and exploratory activities required to meet lower- and higher-level needs [9]. Increased or decreased activity of synaptic dopamine (DA) in the main functional regions helps regulate the cognitive activity and social interaction activity of a person under given circumstances (purposefulness, productivity) [9]. From the perspective of the implementation of cognitive function, maintaining DA activity and balance in the functional pathways from the striatum to the projections in the cortex and subcortical nuclei have been shown to be important [10]. Mesocortical pathways connect the associative regions of the striatum with the prefrontal cortex (PFC), regulating working memory, behavioral strategy assessment, and decision flexibility. The mesolimbic pathways connect the limbic striatum with the amygdala and the hippocampus and are responsible for declarative and state-dependent memory, memory recall from past experiences, motivation, and the reward system [11]. In addition, an important role is played by the feedback system of the sensorimotor striatum (sensory information processing speed, visual and motor functions, and the formation of habits) [9, 10, 11]. Optimal regulation of DA in the PFC is of key importance for cognitive functions, especially working memory, attention, and executive control [9, 12]. This regulation depends on the balanced stimulation of D1 (activating) and D2 (inhibiting) dopamine receptors. The DA imbalance in the PFC that is characteristic of schizophrenia is directly related to underlying cognitive impairment and negative symptoms [9]. The pathogenesis of this disease includes developmental disorders and dysfunctional interactions of DA with the glutamatergic and serotonergic systems [13, 14].

In most regions of the brain, the DA activity level is regulated by the reuptake transporter. Catechol-O-methyltransferase (*COMT*) is the main enzyme that metabolizes DA in the PFC, where the dopamine transporter (DAT) density is low [12]. *COMT* inactivates DA but more slowly than the reuptake transporter does, so the effects of DA can persist for much longer [12]. In humans, the *COMT* protein has two isoforms: 1) the soluble cytosolic S-COMT (221 amino acids), which is predominant in peripheral tissues, and 2) membrane-bound MB-COMT (271 amino acids), which are characteristic of nervous tissue. The MB isoform interacts more effectively with DA than the S isoform does [15]. The *COMT* gene is located in the q11 region of chromosome 22 and has 6 exons and 2 promoters. The P1 promoter initiates the synthesis of the transcript encoding the S-COMT isoform, whereas the P2 promoter initiates the synthesis of a transcript that can be translated into the MB-COMT or S-COMT isoform [16]. The best studied variant of the *COMT* gene is rs4680 in exon 4, a point mutation that leads to the substitution of methionine for valine in the amino acid sequence of the protein at position 158 of the MB-COMT isoform (Val158Met) and at position 108 of the S-COMT isoform (Val108Met). The *COMT* enzyme was shown to have higher activity in people with the Val 158 allele than in people with the Met allele, which is associated with accelerated removal of excess DA from the extracellular space [16].

The main factors regulating cognitive function in the PFC include the inactivation of DA activity by *COMT* [17]. Consequently, carriers of the Met allele have increased synaptic levels of DA in the PFC. Although this dual mechanism could be adaptive in theory, in the pathological context of schizophrenia, both excessive (Val/Val, low DA) and insufficient (Met/Met, high DA) *COMT* activity are associated with cognitive deficits, as they disrupt the precise regulation required for optimal prefrontal network function. [12]. Thus, the *COMT* rs4680 variant is a key genetic factor that modulates the dopaminergic tone of the PFC and, as a result, forms cognitive endophenotypes in schizophrenia.

According to the dopamine theory of the pathogenesis of schizophrenia, impaired cognitive function and social behavior may be associated with low levels of DA in the PFC and other essential regions of the brain. The rs4680 variant of the *COMT* gene can alter (slow down) the degradation of DA, increase its concentration in the PFC, and thus decrease the risk of cognitive impairment in schizophrenia patients.

Although the above has been known for many years and the genetic variant Val158Met has been studied in many aspects with regard to its association with schizophrenia, no studies have been conducted in the past 10 years to

analyse a possible relationship between variants of the *COMT* gene and the severity of cognitive impairment in schizophrenia.

The aim of this review is to explore the associations of the rs4680 variant of the *COMT* gene with cognitive functions in schizophrenia.

METHODS

Eligibility criteria

Inclusion criteria:

- systematic reviews, meta-analyses, and clinical studies;
- the study material included patients with schizophrenia and with schizoaffective disorders;
- cognitive functions were assessed using with standardized tests for cognitive impairment in patients with schizophrenia. In addition, several relative indicators of the Positive and Negative Syndrome Scale (PANSS) were included: N5 (abstract thinking disorders), P2 (thinking disorders), and G11 (attention disorders);
- the results present data on the impact of position 158 of the *COMT* gene.

Exclusion criteria: studies that failed to meet any of the listed inclusion criteria.

Information sources

A literature search was conducted in the PubMed database for articles published between 2014 and 2024. The search query "rs4680 schizophrenia cognitive" returned 32 articles.

Selection process

A total of 11 articles that met the inclusion criteria were selected for analysis. Furthermore, two relevant systematic reviews published in 2017 were identified [18, 19]. No statistical analysis was conducted.

Data analysis

The risk of bias in the included studies was assessed using the following methods:

1. testing for the Hardy-Weinberg equilibrium (for genetic studies);
2. analysis of the presence and comparability of control groups;
3. assessment of researcher blinding during testing;
4. assessment of the therapy's effects (neuroleptics, cognitive training);
5. analysis of systematic biases (absence of data on sex, age, and duration of the disorder).

The results were presented and summarized through the following approaches:

1. synthesis of data to identify the main trends;
2. comparison of the findings across individual studies;
3. discussion of consistency/contradictions between studies, including a comparison with the data from an earlier meta-analysis [18].

RESULTS

Analysis of systematic review data

Our analysis included the systematic review by Zai et al. [18], which was published in 2017 and included 12 original researches. The authors reported a significant correlation of the Val/Val allele with worse cognitive performance in healthy subjects in the control group than in carriers of the Met/Met allele. Compared with patients with the Val allele, patients with schizophrenia and the Met allele presented higher scores for verbal learning, false memory, prepulse inhibition, and abstract reasoning. Studies of the interaction between rs4680 and environmental factors revealed that carriers of the homozygous Val/Val genotype had improvements in executive functions only in the absence of a history of traumatic experience. However, cognitive deterioration was observed even in patients without traumatic experiences. These data suggest that the effect of *COMT* variants on cognitive function may not be specific to schizophrenia [18].

Another 2017 systematic review that employed a meta-analysis of 58 individual studies demonstrated no associations between *COMT* rs4680 and working memory or intelligence [19].

After that, we analysed and performed a quality assessment for each of the 11 researches. The included studies are presented in Table S1 in the Supplementary.

Tests used to assess cognitive impairment

The analysis of the systematic review data revealed that the study of cognitive impairment in schizophrenia patients was performed via standardized batteries and tests focused on key domains:

1. Regulatory functions (planning, control, and error monitoring): MATRICS Consensus Cognitive Battery (MCCB), Trail Making Test B (TMT-B), Wechsler Adult Intelligence Scale (WAIS), Stroop Color and

Word Test (SCWT), Wisconsin Card Sorting Test (WCST), and Frontal Assessment Battery (FAB) [20].

2. Attention (focus, stability, switching, inhibitory control): MCB, TMT-AB, SCWT, FMS, WAIS, Visual Working Memory (VWM), FAB, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), as well as the PANSS attention subscale and the FAB parameter "Inhibitory control" [20, 21].
3. Thinking (formation of concepts, reasoning, problem solving): MCCB, CNS Vital Signs, WCST, WAIS, FAB. Disorganization and impairment of abstract thinking were additionally assessed via the corresponding PANSS subscales (positive and negative symptoms).
4. Working memory (information retention and manipulation): MCCB, CNS Vital Signs, TMT-B, SCWT, WCST, WAIS, VWM, Keep Track, Letter Memory Task, FAB, RBANS.
5. Information processing speed: MCCB, CNS Vital Signs, TMT-A, SCWT, WAIS.

Analysis of original researches data

In the selected 11 original researches, we analysed the association between rs4680 and cognitive impairment in patients with schizophrenia (see Table S1 in the Supplementary). A quality assessment was performed for each study.

Among the 11 clinical and biological studies, three were conducted in outpatients with schizophrenia [22–24], seven were conducted with inpatients [21, 25–30], and one included both groups [31].

Different features of cognitive functioning in schizophrenia, depending on the rs4680 allele, were reported in 10 of the 11 articles. The authors reported better cognitive performance in patients with schizophrenia with the Met allele in the vast majority of the studies (9 out of 11) [21, 22, 24, 25, 27–31]. However, the conclusions of the two studies were opposite [23, 26]. Most often, cognitive impairment in schizophrenia patients manifests as deterioration of verbal and visual working memory, attention switching, information processing speed, cognitive activity, regulatory functions, and social cognition.

The analysis of cognitive phenotypes revealed a number of strong associations. Two studies [22, 24] demonstrated better preserved executive functions in carriers of the Met allele, but data from one paper suggest the opposite result [23]. A previous study [28] revealed an association with impaired attention; a decrease in attention was observed in men with the Val/Val genotype [29]. According to the analysis, the Met allele was associated with significantly higher scores in tests for verbal and visual learning and memory [27, 29, 31], as well as with other memory domains in men [29]. In another publication [30], the authors reported that carriers of the Met allele have a faster processing speed. In another study [27], carriers of the Met allele were found to have had higher scores on the VWM and Keep Track tests, whereas impaired information processing speed in patients with schizophrenia was associated with a decrease in working memory. The authors of one study [28] identified a tendency toward shorter TMT-A and TMT-B test performance times in carriers of the Met allele, assuming its contribution to the speed of information processing. Two studies have identified associations between thinking and the rs4680 genetic variants [22, 26]. Carriers of the Met allele made fewer perseverative errors [22] but had worse results in the assessment of abstract thinking [26], i.e., the results from different studies were contradictory in terms of this domain. In another study [21], women with the Met allele had better "conceptualization" and "inhibitory control" results, as assessed by the FAB scale, which can also be considered in the context of thinking tests. The results of the analysis are in good agreement with the data of a meta-analysis [18], which included earlier (conducted more than 10 years prior) studies and demonstrated better executive functions, working memory, and abstract thinking in carriers of the Met allele. Despite the difference in methodologies and time intervals (the meta-analysis data include studies conducted more than 10 years prior), the revealed pattern persists, which confirms the reliability of this genetic association. Decreased activity of the *COMT* enzyme in carriers of the Met allele leads to an increase in DA in the PFC, optimizing functions dependent on this region (executive functions, working memory, and abstract thinking) [12]. Thus, most studies confirm the association of the Met allele with better cognitive function in patients with schizophrenia in terms of cognitive control, thinking, working memory, and, to a lesser extent, attention and information processing speed.

There were no significant genetic differences for rs4680 when comparing European, South African, and South American populations: the frequency of the A allele is approximately 0.5 (according to information from the PubMed database). For the African and Asian populations, the frequency of the A allele is lower, at approximately 0.3,

based on the data from the PubMed database. No overall Russian data on the prevalence of the A allele were found. According to our own data, the frequency of the A allele was 0.507 for patients with early-onset schizophrenia and 0.53 for healthy volunteers [21].

Two studies [21, 29] reported a sex-specific dependence of cognitive functions on the genotype among women in the Russian population [21] and men in the Han population [29]. Another study [29] reported a difference in the frequency of rs4680 genotypes between men and women with schizophrenia. It was previously shown that male patients have more severe negative symptoms, a greater decrease in social functioning, and an earlier age of disease onset [32]. A previous study [33] demonstrated sex-specific effects of the *COMT* gene on the predisposition to mental disorders and personality traits. Intersex differences have not been investigated in other studies or populations. The impacts of education, the nature of work and other factors were practically not studied in the studies we considered; therefore, they were not taken into account in our review.

Psychopharmacotherapy was not described in 4 studies [21, 24, 26, 27]. Patients received atypical neuroleptics in 2 studies [22, 31] and only risperidone in one study [28]. Another publication [23] described patients who received not only neuroleptics but also other psychotropic drugs, although their proportion was relatively small. Thus, assessing the effects of drug therapy on cognitive functions in relation to the *COMT* genotype appears challenging.

DISCUSSION

In the psychiatric genetics of schizophrenia, associations with the disease or disease endophenotypes (which may include a decrease in certain cognitive domains) are ambiguous, and the manifestation of genetic factors depends on many other factors. Studies indicate that several factors may influence the assessment of the association of gene variants with cognitive functions, including ethnicity, sex, age, environmental factors, education and work during one's lifetime, and other sample characteristics that affect cognitive functions.

The main limitations of our review are the quality of the included papers and the small number of published studies available. We detected several sources of systematic biases, such as the absence of a control group, significant sociodemographic differences between the experimental and control groups, the absence of blinding among the researches who conducted the testsing, the absence of information about the prescribed treatment and the duration of antipsychotic therapy, and a failure to analyze the association between genetic variants and cognitive deficits in connection with sex and age. Only a few studies were conducted with minimal systematic errors [21, 27, 29].

Five studies did not have a control group [24–26, 30, 31]. Two studies evaluated cognitive function after cognitive training [24, 31]; these studies included neither a control group nor a group without cognitive training. No testing for the Hardy-Weinberg equilibrium was reported in five studies [22, 25, 28, 30, 31]. The testing for the Hardy-Weinberg equilibrium is a principle in population genetics that describes the distribution of alleles in a population and their frequencies in the absence of factors that disrupt the genetic balance [34]. Deviations from the testing for the Hardy-Weinberg equilibrium indicate bias in the study (incorrect sampling or methodological errors) rather than a mutational process or genetic drift. Thus, the absence of a testing for the Hardy-Weinberg equilibrium in medical genetics studies is a factor that significantly compromises their quality. The study results may also be affected by the occurrence of certain alleles and genotypes in the study population. The quality of the studies was greater when the sex of the subjects was taken into consideration in the data analysis. Sex differences in the role of rs4680 polymorphism in cognitive impairment were demonstrated in two publications we analysed [21, 29]. Difficulties arose due to the need to compare the cognitive functions of patients with schizophrenia during an exacerbation/psychosis (inpatient monitoring) and remission (outpatient monitoring). The results of studies combining longitudinal and cross-sectional designs and showing a similar degree of cognitive impairment in patients after the first episode of schizophrenia and in cases of stable clinical presentation of the disease were taken into account [35]. However, some cognitive disorders, such as executive dysfunctions, may be less common in the early stages of the disease. Antipsychotics of different classes, which are used for the treatment of schizophrenia, could have direct and indirect effects on cognitive functions, including a negative impact, which was difficult to assess within the framework of our review [36].

In the future, investigators should also aim to compare homogeneous groups of patients in terms of sex, age, education level, disease stage, and the nature and duration of the psychotropic agents used, which will increase the reliability of the results.

CONCLUSION

To improve the quality of research on genetic predisposition to cognitive impairment in schizophrenia, particularly the impact of rs4680 it is essential to refine assessment protocols. This refinement should include the adoption of a minimum set of validated tests and the development of combined tools that allow precise characterization of cognitive endophenotypes, intermediate phenotypes, and behavioral indicators in conditions close to real-world practice. Our data highlight the importance of a comprehensive approach combining clinical assessment with quantitative analyses of executive functions, attention, working memory, information processing speed, and verbal fluency, as well as operational and motivational aspects of thinking, for accurate phenotypic characterization.

Analysis of the available data suggests a significant association of rs4680 with cognitive functioning in schizophrenia. Carriers of the Met allele demonstrate less pronounced cognitive deficits, especially in terms of working memory and executive functions, which is consistent with the results of a systematic review that included studies conducted more than 10 years ago [18]. Despite the limited number and heterogeneity of the methodological quality of available studies, the identified patterns indicate the potential for using this genetic marker to predict the severity of cognitive impairment and develop personalized rehabilitation programs. Further studies with unified protocols for neurocognitive assessment, taking into account potential modifying factors (age of onset, duration of the disease, drug therapy), are needed to clarify the role of rs4680 in the development of cognitive endophenotypes and optimize strategies for the cognitive rehabilitation of patients with schizophrenia.

Article history

Submitted: 9 Dec. 2024
Accepted: 25 Aug. 2025
Published Online: 17 Sep. 2025

Authors' contribution: Tatiana Maksimenko: formal analysis, conceptualization, data curation, writing — original draft, writing — review & editing. Yana Zorkina: conceptualization, methodology, data curation, formal analysis, resources, writing — original draft, writing — review & editing, data administration. Olga Efimova: methodology, data administration. Alisa Andriushchenko: conceptualization, methodology, resources, writing — original draft, writing — review & editing. George Kostyuk: resources, project administration, supervision.

Funding: This work was supported by the Russian Science Foundation (Grant Number 22-15-00474).

Conflict of interest: The authors declare no conflicts of interest.

Generative AI use statement: Nothing to disclosure.

Supplementary data

Supplementary material to this article can be found in the online version:
Table S1: 10.17816/CP15603-145727

For citation:

Maksimenko TV, Zorkina YA, Efimova OI, Andriushchenko AV, Kostyuk GP. Association of the COMT Gene Polymorphism rs4680 with Cognitive Impairment in Schizophrenia: A Narrative Review. *Consortium PSYCHIATRICUM*. 2025;6(3):CP15603. doi: 10.17816/CP15603

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