ORIGINAL ARTICLE

Catechol-O-methyltransferase (COMT) polymorphisms modulate working memory in individuals with schizophrenia and healthy controls

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Objective: Cognitive impairment is a core feature of schizophrenia, related to dopaminergic dysfunction in the prefrontal cortex (PFC). It is hypothesized that functional single nucleotide polymorphism (SNP) rs4680 of the catechol-O-methyltransferase (COMT) gene could mediate the relationship between cognition and dopamine activity in the PFC. Other COMT SNPs could also play a role.

Methods: We evaluated the role of three COMT SNPs (rs737865, rs165599, and rs4680) in schizophrenia and their impact on three working memory tasks. For genetic association analyses, 212 individuals with schizophrenia and 257 healthy controls (HCs) were selected. The Visual Working Memory (VWM) Task, Keep Track Task, and Letter Memory Task were administered to 133 schizophrenics and 93 HCs.

Results: We found a significant association of rs737865, with the GG genotype exerting a protective effect and the GA haplotype (rs4680/rs165599) exerting a risk effect for schizophrenia. COMT rs4680 AA carriers and rs737865 AA carriers scored lowest on the Keep Track Task. When the genotype*group interaction effect was evaluated, rs165599 exerted opposite effects for VWM and Keep Track task performance in patients and controls, with AA carriers scoring lowest on both tests among controls, but highest among patients.

Conclusion: These data support the hypothesis that COMT polymorphisms may be associated with schizophrenia and modulate cognition in patients and controls.

Keywords: Cognition; dopamine; gene

Introduction

Schizophrenia is a multifactorial and debilitating disease with a high heritability rate (approximately 80%).1 It affects four to seven people per 1,000 worldwide.2 Despite broad phenotypic heterogeneity, cognitive impairments have been considered profound and clinically relevant since the original descriptions.3 Deficits usually described in patients involve several cognitive functions, such as memory, attention, working memory (WM), problem solving, processing speed, and social cognition.4 Cognitive dysfunction in schizophrenia has been widely studied in recent decades, prompted by evidence that it is a determinant of quality of life and everyday functioning in patients.5 Reduced cognitive performance is already evident at the first episode of psychosis, which implies that cognitive dysfunction is a likely neurobiological marker of schizophrenia even before the onset of illness.5,7

The dopamine hypothesis, based on evidence from pharmacological and in vivo imaging studies, is considered the final common pathway for psychotic symptoms in schizophrenia.8 The enzyme catechol-O-methyltransferase (COMT) metabolizes several catecholamines, but is especially relevant to dopaminergic transmission in the prefrontal cortex (PFC), in which it is a key element to dopamine availability.9 COMT is encoded by a single gene (also COMT) located on chromosome 22q11.2, a region that is commonly missing in 22q11.2 microdeletion syndrome, which has long been associated with predisposition for schizophrenia.10 The enzymatic activity of COMT is altered by a guanine (G) to adenine (A) single nucleotide polymorphism (SNP) known as Val158Met or rs4680 in the COMT gene sequence, resulting in a trimodal distribution (high activity in the Val/Val genotype, intermediate activity in Val/Met, and low activity in Met/Met) and a three- to four-fold difference in COMT activity (Val/Val vs. Met/Met).11 Studies on the COMT Val158Met polymorphism and vulnerability to schizophrenia have produced
conflicting results. Previous meta-analyses do not support an association between COMT Val158Met and schizophrenia,\textsuperscript{13-14} whereas one meta-analysis found a small but significant effect for homozygotes as the risk variant over heterozygotes in both mixed and Caucasian cohorts.\textsuperscript{15} Nevertheless, Gatt et al.,\textsuperscript{16} in a recent review of meta-analyses, highlights that Val vs. Met comparisons were null when considering larger samples and mixed or Asian samples.

Cognitive abilities related to the functional integrity of the frontal lobe and its neural networks throughout the brain (WM and executive functioning) might be related to hypodopaminergia in the PFC. Manipulation of dopaminergic tone in the PFC is crucial for executive and WM performance.\textsuperscript{17} Thus, genetically determined variations in COMT activity might affect the availability of dopamine in prefrontal synapses, and, thus, affect cognitive abilities, including WM performance, independently from proneness to schizophrenia.

COMT is one of the most investigated genes in schizophrenia, and its role in cognition has also been studied. Samples of healthy individuals showed associations, either positive\textsuperscript{18,19} or negative, between COMT genotypes and cognition.\textsuperscript{20} In schizophrenia samples, there have also been reports of positive\textsuperscript{21-23} and negative associations.\textsuperscript{24} In studies that showed positive associations, schizophrenia patients demonstrated a similar pattern to healthy controls (HCs): Met (G) homozygotes seem to have better cognitive performance relative to Val (A) carriers. A meta-analysis of the cognitive effects of COMT Val158Met,\textsuperscript{25} however, concluded that there is weak evidence of association between this polymorphism and cognitive function.

Notably, functional variation in the COMT gene is not limited to the rs4680 SNP, but rather includes other polymorphisms, such as a P2 promoter region SNP (rs2097603) and a 3’ region SNP (rs165599). These three SNPs show nonlinear interacting effects on prefrontal efficiency during WM task performance, in agreement with predictions of resultant cortical dopaminergic cataleptic rates, and highlight the complexity of genetic contributions to functional neuroimaging phenotypes, even within a single gene.\textsuperscript{26} Many studies have focused on the Val158Met polymorphism, neglecting other SNPs in the gene. Studies assessing thousands of SNPs at once, such as genome-wide association studies (GWAS), need a large sample size, which is limited by the time-consuming nature of neuropsychological tests.

Within this context, the aim of this study was to further investigate the role of three COMT SNPs (rs737865, rs165599, and rs4680) in schizophrenia and on performance in WM tasks in a sample of patients and controls.

**Methods**

**Subjects**

A total of 212 patients and 257 HCs were recruited from Programa de Esquizofrenia (PROESQ) and Laboratório Interdisciplinar de Neurociências Clínicas (LINC), Universidade Federal de São Paulo (UNIFESP), Brazil. The diagnosis of schizophrenia was confirmed by the Structured Clinical Interview for DSM-IV applied by trained psychiatrists. HCs had no family history of severe psychiatric illness and no current or previous psychiatric disorders.

All subjects underwent blood collection for genetic analyses and a sample of 124 patients was assessed with the Positive and Negative Syndrome Scale (PANSS). Psychopathological dimensions (negative, positive, excited, and anxiety/depression) were classified according to PANSS ratings.\textsuperscript{27} These individuals had no history of a diagnosed neurological disorder or medical condition known to be associated with neuropsychological impairment (e.g., epilepsy, stroke). The UNIFESP Ethics Committee approved the research protocol, and participants entered the study only after giving written informed consent.

**DNA isolation and COMT genotyping**

Whole blood was collected into tubes containing 0.1% ethylenediaminetetraacetic acid (EDTA), and genomic DNA isolation was performed using the Gentra Puregene Kit (Qiagen, Germantown, United States) according to the manufacturer’s protocol.

All three COMT polymorphisms (rs737865, rs165599, and rs4680) were genotyped by TaqMan probe-based real-time polymerase chain reaction (PCR) assays (Life Technologies, Foster City, United States) performed under standard conditions. For each reaction, at least one positive control for each genotype was included.

**Neuropsychological tests**

Three tests assessing the ability to update information, part of WM function, were administered by trained psychologists to 133 patients and 93 controls. Previous studies have shown that these tasks are sensible choices for discriminating the cognitive performance of subjects with schizophrenia and healthy comparators.\textsuperscript{28} The IQ of each participant was also assessed.

In the Visual Working Memory (VWM) task,\textsuperscript{29} a subject is asked to pay attention to a computer screen where one to four 3 × 3 matrices are displayed. A stimulus appears within each matrix for 2 seconds and arrows then start indicating special manipulations that the subject will be asked to perform with the stimuli within each matrix. For example, an arrow pointing to the upward position followed by an arrow pointing to the left indicates that the stimulus should be displaced one row above and one column to the left from its original position. There is no time limit for each answer, but the test stops after consecutive errors. This test was based on the experimental tasks designed by Salthouse et al.\textsuperscript{30}

The Keep Track task, adapted from Yntema,\textsuperscript{31} first shows several target categories (animals, colors, countries, distances, metals, and relatives) on the computer screen. Then, 15 words are presented verbally in random order for 1,500 milliseconds each. The target categories remain on the screen. Each list had two or three exemplars
from each of the six possible categories. Participants had to remember the last word presented belonging to the remaining target categories (the first three trials had four categories and the last three had five).

The Letter Memory task, adapted from Morris & Jones, was the third updating measure. In this task, letters are presented serially and individually. Participants had to recall the last two letters presented in each presented list. However, they had to rehearse the last two letters out loud by mentally adding the most recent letter, dropping the third letter back, and then saying the new string of two letters out loud. This instruction was given to ensure that participants were performing continuous updating. Although previous studies have used sequences ranging from four to nine words, we had to define this length because most of the patients could not start performance with larger sequences.

For all three tests, higher values denote better performance.

Statistical analysis

First, Hardy-Weinberg equilibrium (HWE) was verified using the chi-squared test. For cognitive analysis, we used square root transformation. To associate each genotype and allele to schizophrenia, we used logistic regression. Then, we constructed a general linear model (GLM) using each cognitive variable as a dependent variable, genotypes of each SNP and group (patient or control) as independent variables, and IQ as covariate to explore SNP and group effects on cognitive variables individually or their interaction (genotype*group), investigating whether the association of each genotype with the relevant dependent variable differed between cases and controls. Linkage disequilibrium (LD) was assessed with SNP Stats (http://bioinfo.iconcologia.net/snpstats/start.htm?) and haplotypes were estimated using PLINK. To test for association between haplotypes and schizophrenia, we performed logistic regression, and for association between haplotypes and cognitive variables, we used a GLM, considering haplotypes and groups as independent variables and IQ as covariate, with the Bonferroni post-hoc procedure. We also investigated the haplotype*group interaction effect on cognitive variables.

Results

The clinical and demographic characteristics of the study population are described in Tables 1 and 2. No differences in gender, age, ethnicity, handedness, or education were found between cases and controls.

Association between COMT SNPs and schizophrenia

Allele and genotype frequencies for each group, as well as p-values for HWE, are described in Supplementary Table 1 (online-only). Only rs737865 genotype distribution in the patient group deviated from HWE (p = 0.001). However, when combining schizophrenia and control...
Table 3: Association between each single nucleotide polymorphism and cognitive variables

| Group | rs165599 | rs4680 | rs737865 |
|-------|----------|--------|----------|
| Group |          |        |          |
|        | n = 4680 | n = 165599 | n = 737865 |
| Patients: | 2.31 (0.82) | p = 0.001 | p = 0.033 |
| Controls: | 2.48 (0.85) | p = 0.214 | p = 0.467 |

The main effects when comparing cognitive variables and groups or genotypes are described in Table 3. We found a significant decrease in all three WM task scores (VWM, Keep Track, and Letter Memory) in patients when compared to controls (Table 3). Analyzing the association between SNPs and cognitive variables, we found a significant association between rs4680 and Keep Track task scores (Table 3), with AA (Val/Val) subjects performing worse than GG (Met/Met) subjects (post-hoc Bonferroni p = 0.042). The same association was identified for rs737865, with AA carriers performing worse than GG (Met/Met) subjects (post-hoc Bonferroni p = 0.043). However, when the interaction between these SNPs and group (genotype*group) was analyzed, we did not find a significant association (Table 3).

Although rs165599 was not associated with any of the cognitive variables, considering the interaction genotype*group, there was a significant difference (Table 3 and Figure 1), with AA carriers performing worse in the control group and GG carriers performing worse in the patient group for both the VWM and Keep Track tasks.

Comparing haplotypes and cognitive variables, we found a significant association with Keep Track Task performance (p = 0.017), showing that G-A (rs4680/rs165599) (mean = 3.89; standard deviation [SD] = 0.49) subjects had higher scores than A-A carriers (mean = 3.74; SD = 0.51) (post-hoc Bonferroni p = 0.043). Moreover, haplotype blocks with rs737865 and rs4680 were also associated with Keep Track Task performance (p = 0.040), with A-A (rs737865/rs4680) carriers performing worse.
(mean = 3.76; SD = 0.51) than G-G haplotype carriers (mean = 3.92; SD = 0.53) (post-hoc Bonferroni p = 0.034). All p-values comparing haplotypes and each cognitive variable are described in Supplementary Table 3 (online-only).

Discussion

In this study, we evaluated the association between three COMT SNPs and the diagnosis of schizophrenia and cognitive performance on WM tasks. We found a significant association between rs737865 genotypes and schizophrenia, with the GG genotype exerting a protective effect and GA a risk effect. In a large study of an Israeli Ashkenazi Jewish population, Shifman et al. reported that the polymorphisms rs737865 and rs165599 were highly associated with the disease, suggesting that more than one functional polymorphism should affect susceptibility to schizophrenia at the COMT locus. For the other SNPs, we did not find associations on comparisons of genotypes and alleles individually, similarly to previous studies in Brazilian35 and Greek36 populations.

When analyzing the haplotypes constructed with rs4680 and rs165599 SNPs, we did find a significant association, with the G-A haplotype (rs4680/rs165599) being a risk factor for schizophrenia when compared to the G-G haplotype. According to the literature, several haplotypes instead of individual alleles may be associated with schizophrenia due to differences in LD among populations.37 Previous studies have implicated associations of the rs4680/rs165599 haplotypes with schizophrenia and reported an effect opposite from that observed in our sample. With G-G (rs4680/rs165599) and A-G-G (rs737865/rs4680/rs165599) being the risk haplotypes and G-G-A (rs737865/rs4680/rs165599) the protective haplotype. Both SNPs seem to exert a functional effect, since rs4680 has an effect on COMT activity and rs165599 has an impact on COMT expression.39 Clinical studies of COMT have revealed that the Met allele (G) was associated with better performance on tests of prefrontally mediated cognition.22,23,40-42 Moreover, in a postmortem human brain study, Chen et al. demonstrated that Val (A) is a predominant factor that determines higher COMT activity, which results in lower prefrontal dopamine signaling and, by this mechanism, leads to relatively impaired prefrontal cortical function. Hence, we could hypothesize that the G/Met-allele (rs4680), which induces a low activity, in combination with the G-allele (rs165599), which leads to reduced expression of COMT, might exert a protective effect, explaining the higher frequency of the G-G haplotype in controls than in patients in our sample.

Regarding the cognitive variables, patients performed worse in all three WM tests (VWM, Keep Track Task and Letter Memory Task), and COMT SNPs might be influencing cognitive performance. We found that both rs4680 and rs737865 seem to be associated with Keep Track Task performance, independently of group status (i.e., schizophrenia or HC), with AA carriers (for either rs4680 or rs737865) scoring lowest. This result is in line with previous studies that reported positive results in both healthy and schizophrenia samples.16,19,21-23 This association seems to be even stronger in the haplotype analysis, with a similar effect, i.e., A-A carriers (A allele of rs4680; A allele of rs165599) scoring lower than G-A carriers (G allele of rs4680; A allele of rs165599). A similar effect was found for haplotypes constructed with rs737865 and rs4680, with A-A haplotype carriers (A allele of rs737865; A allele of rs4680) scoring lower than G-G carriers (G allele of rs737865; G allele of rs4680). Our results are consistent with those of Meyer-Lindenberg et al., who demonstrated how haplotype analysis should be superior in predicting WM task performance and prefrontal function. When we evaluated the genotype*group interaction, rs165599 exerted opposite effects for VWM and Keep Track Task performance in patients and controls: AA carrier status was associated with the lowest scores for both tests in controls, but the highest scores in patients (Figure 1).

Our study has limitations that must be considered. First, the sample size was small and statistical power was weak, especially for a genetic association study; however, we analyzed cognitive data, which limited the number of participants assessed. Despite selecting 212 patients with schizophrenia and 257 HCs, only 133 patients and 93 HCs underwent cognitive testing, due to logistic issues. Nevertheless, our sample has power to support that the COMT polymorphisms may be associated to schizophrenia.

![Figure 1](image.png) Interaction effect between group and rs165599, which was significant for both Visual Working Memory (VWM) Task and Keep Track Task. Scores presented as square roots.
diagnosis and modulate cognitive performance in both, people with schizophrenia and healthy subjects. Second, the effect sizes were small, which is a common limitation of gene association studies. Further studies should be performed with larger samples. Finally, we acknowledge that the role of COMT in schizophrenia has been widely investigated in past decades, and that the heterogeneity of past research and complexity of schizophrenia phenotypes must be taken into consideration for our conclusions.

Our results are consistent with the major role of COMT in modulating dopamine flux in the PFC and its association with schizophrenia and cognitive function. Regarding this association with the disorder, we found a significant effect of rs737865 genotypes in schizophrenia and of rs4680/rs165599 haplotypes, with an effect opposite to that observed in European populations. The effect of individual SNPs on cognition was supported by previous studies, indicating a worse performance of A-allele genotypes and haplotypes of rs4680 on WM tasks. In addition, the GG genotype and G-allele haplotypes of rs737865 seemed to exert a protective effect on risk of schizophrenia and be associated with higher scores on the Keep Track Task. An interaction effect was also found for group rs165599, showing the importance of investigating both patients and healthy subjects.

This was the first association study to analyze COMT haplotypes and cognition in a Brazilian sample of patients with schizophrenia. The significance of our positive findings encourages further investigations.

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Disclosure

The authors report no conflicts of interest.

References

1 Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 2000;157:514-20.
2 Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005;2:e141.
3 Kraepelin E. Dementia praecox and paraphrenia. New York: Krieger; 1919.
4 Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. Schizophr Res. 2004;72:29-39.
5 Tolman AW, Kurtz MM. Neurocognitive predictors of objective and subjective quality of life in individuals with schizophrenia: a meta-analytic investigation. Schizophr Bull. 2012;38:304-15.
6 Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraoe SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology. 2008;22:315-36.
7 Szoke A, Tranafar A, Dupont ME, Meary A, Schurhoff F, Leboyer M. Longitudinal studies of cognition in schizophrenia: meta-analysis. Br J Psychiatry. 2008;192:248-57.
8 Bowes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. J Psychopharmacol. 2015;29:97-115.
9 Karoum F, Chrapusta SJ, Egan MF. 3-Methoxytyramine is the major metabolite of released dopamine in the rat frontal cortex: reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex; nucleus accumbens, and striatum by a simple two pool model. J Neurochem. 1994;63:972-9.
10 Christofolini DM, Bellucco FT, Ota VK, Belangero SI, Cernach MC, Gadelha A, et al. Assessment of 22q11.2 copy number variations in a sample of Brazilian schizophrenia patients. Schizophr Res. 2011;132:99-100.
11 Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics. 1996;6:243-50.
12 Fan JB, Zhang CS, Gu NF, Li RX, Sun WW, Wang HY, et al. Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. Biol Psychiatry. 2005;57:139-44.
13 Okochi T, Ikeda M, Kishi T, Kawashima K, Kinoshita Y, Kitajima T, et al. Meta-analysis of association between genetic variants in COMT and schizophrenia: an update. Schizophr Res. 2009;110:140-8.
14 Munafò MR, Bowes L, Flint J. Lack of association of the COMT (Val158/108 Met) gene and schizophrenia: a meta-analysis of case-control studies. Mol Psychiatry. 2005;10:765-70.
15 Costas J, Sanjuan J, Ramos-Rios R, Paz E, Agra S, Ivorra JL, et al. Heterozygosity at catechol-O-methyltransferase Val158Met and schizophrenia: new data and meta-analysis. J Psychiatr Res. 2011;45:7-14.
16 Gatt JM, Burton KL, Williams LM, Schofield PR. Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. J Psychiatr Res. 2015;60:1-13.
17 Brozoski TJ, Brown RM, Rosvold HE, Goldman PS. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science. 1979;205:929-32.
18 Blasi G, Mattay VS, Bertolino A, Elvevag B, Callicott JH, Das S, et al. Effect of catechol-O-methyltransferase val158met genotype on attentional control. J Neurosci. 2005;25:5038-45.
19 Bruder GE, Keilp JG, Xu H, Shihkman M, Schori E, Gorman JM, et al. Catechol-O-methyltransferase (COMT) genotypes and working memory: associations with differing cognitive operations. Biol Psychiatry. 2005;58:901-7.
20 Stefanis NC, Van Os J, Aramopoulos D, Smyrnis N, Evdokimidis I, Hantoumi I, et al. Variation in catechol-o-methyltransferase val158met genotype associated with schizotypy but not cognition: a population study in 543 young men. Biol Psychiatry. 2004;56:510-5.
21 Wirgenes KV, Djurovic S, Sundet K, Agartz I, Mattingdal M, Athanasiu L, et al. COMT (Val158/108 Met) gene association in schizophrenia and bipolar disorder versus controls. Schizophr Res. 2010;122:31-7.
22 Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A. 2001;98:9197-22.
23 Goldberg TE, Egan MF, Gasheide T, Cippolla R, Weickert T, Kolachana BS, et al. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch Gen Psychiatry. 2003;60:889-96.
24 Mata I, Perez-Iglesias R, Pelayo-Teran JM, Rodriguez-Sanchez JM, Gonzalez-Blanch C, Carrasco-Marín E, et al. Lack of influence of COMT Val158Met genotype on cognition in first-episode non-affective psychosis. Schizophr Res. 2008;102:206-9.
25 Barnett JH, Scoriels L, Munafò MR. Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108 Met polymorphism. Biol Psychiatry. 2008;64:137-44.
26 Meyer-Lindenberg A, Nichols T, Callicott JH, Ding J, Kolachana B, Buchholz J, et al. Impact of complex genetic variants in COMT on human brain function. Mol Psychiatry. 2006;11:867–77, 797.
27 Levine SZ, Rabinowitz J. Revisiting the 5 dimensions of the Positive and Negative Syndrome Scale. J Clin Psychopharmacol. 2007;27:431-6.
28 Barberian AA, Trevisan BT, Moriyama TS, Montiel JM, Oliveira JA, Seabra AG. Working memory assessment in schizophrenia and its correlation with executive functions ability. Rev Bras Psiquiatr. 2009;31:219-26.

29 Primi R. Bateria informatizada de capacidades cognitivasItatiba: LabAPE; 2002.

30 Salthouse TA, Babcock RL, Shaw RJ. Effects of adult age on structural and operational capacities in working memory. Psychol Aging. 1991;6:118-27.

31 Yntema DB. Keeping track of several things at once. Hum Factors. 1963;5:7-17.

32 Morris N, Jones DM. Memory updating in working memory: the role of the central executive. Br J Psychol. 1990;81:111-21.

33 Sole X, Guino E, Valls J, Iniesta R, Moreno V. SNP Stats: a web tool for the analysis of association studies. Bioinformatics. 2006;22:1928-9.

34 Shifman S, Bronstein M, Stermfeld M, Pisante-Shalom A, Lev-Lehman E, Weizman A, et al. A highly significant association between a COMT haplotype and schizophrenia. Am J Hum Genet. 2002;71:1296-302.

35 Cordeiro Q, Silva RT, Vallada H. Association study between the rs165599 catechol-O-methyltransferase genetic polymorphism and schizophrenia in a Brazilian sample. Arq Neuropsiquiatr. 2012;70:913-6.

36 Maria K, Charalampous T, Vassilakopoulou D, Stavroula S, Vasiliki K, Nikolaos D. Frequency distribution of COMT polymorphisms in Greek patients with schizophrenia and controls: a study of SNPs rs737865, rs4880, and rs165599. ISRN Psychiatry. 2012;2012:651613.

37 Mukherjee N, Kidd KK, Pakstis AJ, Speed WC, Li H, Tamok Z, et al. The complex global pattern of genetic variation and linkage disequilibrium at catechol-O-methyltransferase. Mol Psychiatry. 2010;15:216-25.

38 Handoko HY, Nyholt DR, Hayward NK, Nestney DA, Hannah DE, Windus LC, et al. Separate and interacting effects within the catechol-O-methyltransferase (COMT) are associated with schizophrenia. Mol Psychiatry. 2005;10:589-97.

39 Bray NJ, Buckland PR, Williams NM, Williams HJ, Norton N, Owen MJ, et al. A haplotype implicated in schizophrenia susceptibility is associated with reduced COMT expression in human brain. Am J Hum Genet. 2003;73:152-61.

40 Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A. 2003;100:6186-91.

41 Diamond A, Briand L, Fossella J, Gehlbach L. Genetic and neurochemical modulation of prefrontal cognitive functions in children. Am J Psychiatry. 2004;161:125-32.

42 Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol O-methyltransferase Val158Met polymorphism in schizophrenia: differential effects of Val and Met alleles on cognitive stability and flexibility. Am J Psychiatry. 2004;161:359-61.

43 Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet. 2004;75:807-21.