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ORIGINAL ARTICLE

COMT rs4680 and DRD2 rs6275 variants and their association with YMRS scores in children with early-onset bipolar disorder



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KEYWORDS
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DRD2 rs6275 variants

Abstract
Background and objectives: Bipolar disorder (BD) is a clinical status with at least one manic, hypomanic or mixed attacks. Genetic factors take part significantly in early-onset BD (EOBD). Dopamine receptors (DRD) act in neurological mechanisms like motivation, learning, memory, and, control of neuroendocrine signaling. DRD2 receptor has been reported to influence the stability of *DRD2* transcript. Catechol-O-Methyl transferase (COMT) inactivates catecholamines and Val158Met variation on *COMT* has effects on COMT activity. This study aims to explore *DRD2* and *COMT* variants in the clinical development of EOBD.
Methods: In this case-control study, 102 EOBD patients and 168 healthy control subjects were used. *DRD2* rs6275 and *COMT* Val158Met variations were detected by real-time polymerase chain reaction (RT-PCR). Young Mania Rating Scale (YMRS) was utilized to determine the EOBD severity.
Results: For *DRD2* rs6275 and *COMT* Val158Met polymorphisms, no significant relationship was observed in the genotype and allele frequencies between patient and control groups. Nevertheless, TT genotype carriers of *DRD2* rs6275 polymorphism demonstrated significantly increased YMRS scores when compared with CC and CT genotype carriers (p = 0.039). Nevertheless, no significant difference was observed between *COMT* Val158Met genotypes and YMRS scores.
Conclusions: We suggest that the *DRD2* rs6275 TT variant can be associated with symptom severity in children with EOBD and can have a clinical significance in EOBD pathogenesis. However, these results need to be confirmed with larger samples of patient and control groups.

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Introduction

Bipolar Disorder (BD) is a common, severe disease and affects approximately 60 million people worldwide.[1] Bipolar disorders have multifactorial, complex, and heterogeneous characters.[2] There is a genetic tendency to BD and the rate of heritability is approximately 70% in twin studies of BD patients.[3] Early-onset bipolar disorder (EOBD) is considered if BD becomes clinically manifested before the ages of 18-22 years. Familial penetrance of EOBD has been found at a higher rate than adult-onset and has been shown in several studies.[4—7] Therefore, genetic studies in EOBD have been of interest, and have been conducted with many candidate genes to investigate the underlying mechanisms. However, the results are inconsistent.[8]

Catechol-O-methyltransferase (COMT) encodes the catechol-O-methyltransferase enzyme and has a functional polymorphism known as rs4680 or Val158Met. A nucleotide change in codon 158 from guanine to adenine (G to A) results in methionine to valine substitution. G (Val) allele composes higher enzyme activity than the A (Met) allele.[9] The enzyme that catalyzes catecholamines is expressed in the prefrontal cortex and hippocampus region of the brain.[10] While the Met allele provides higher dopamine concentrations, the Val allele causes a decrease in dopamine. Heterozygous (Val/Met) carriers present an intermediate phenotype.[11]

Since the dopamine level in the prefrontal cortex can influence cognitive functions such as working memory, executive functions, and attention, it has gained importance in various psychiatric disorders.[12,13] In addition, it has been reported that the basal dopamine level in the prefrontal cortex may interact with mood swings.[14,15] Nevertheless, only a few studies have evaluated the role of *COMT* in the etiology of BD. In a study, rs4680 polymorphism was associated with EOBD.[16] Besides this, another study reported a significant relation in the allele and genotype frequencies of rs4680 between BD patients and controls in the Han population. In the same study, a meta-analysis has also been performed and it has been reported that the lower COMT activity Met allele in rs4680 was associated with BD in a sample comprising different ethnic groups and concluded that the Met allele confers risk for BD in the Han population while it needs further investigation for Caucasian population.[17] Contrary to these, other studies concluded that the low-activity allele of *COMT* was not related to EOBD.[18,19] In addition, another study reported no association in *COMT* Val158Met polymorphism between Turkish adult BD patients and controls. They also reported that among Met/Met cases BD patients had higher activity than controls in the left and right lateral edges of the prefrontal cortex.[20] A meta-analysis performed with adult-onset BD has reported that there may be differences based on ethnicity.[21] A review table for the association studies of *COMT* rs4680 and *DRD2* rs6275 is shown in Supplementary Table S1 (Supp S1).[22] However, as far as we know, *COMT* Val/Met polymorphism has not been studied in children with BD in the Turkish population.

Dopamine receptors affect learning, motivation, and memory in humans. D2 subtype of the dopamine receptor, DRD2, is critical in regulating the dopaminergic pathway in the brain and functions as the primary domain for antipsychotic drug therapy.[23] Data were obtained on DRD2 contribution to the regulation of prefrontal cortex activity and maintenance of executive functions.[24] The functional polymorphism, *DRD2* rs6275, also known as 939C/T was associated with heroin usage[25] and attention deficit in schizophrenia.[26] *DRD2* rs6275 polymorphism affects the stability of *DRD2* transcript.[27] There was no significant relationship between dopamine receptor genes and the disease in a genome-wide association study conducted in BD.[28] As far as we know, *DRD2* rs6275 polymorphism has not been investigated in EOBD.

Although many studies have been conducted so far regarding genes that may cause genetic susceptibility at EOBD, the data is not sufficient yet. Therefore, more data is needed in the area. In this research, we hypothesized that the catecholaminergic gene *COMT* (Val158Met), and the dopaminergic gene *DRD2* (rs6275) variants can be associated with EOBD development and disease-related phenotypes. Therefore, we explored whether these genetic variants were associated with EOBD in a sample of Turkish EOBD patients.

Material and methods

Study design

This study was comprised of 102 patients with EOBD (<18 years) and 168 disease-free controls. Patients with EOBD were recruited from the inpatient units of a tertiary care psychiatry-teaching mental health hospital. This study was led according to the principles of the Helsinki Declaration. The study was accepted by the Local Ethics Committee of Cerrahpasa Medical Faculty, Istanbul, Turkey (Ethics Committee issue #12349). Written informed consent was taken from the participants before they took part in the investigation.

Each subject underwent a psychiatric examination. The diagnosis of BD was conducted by two clinicians according to the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR) through a psychiatric interview (American Psychiatric Association (APA), 2013). The severity of BD was measured by the Young Mania Rating Scale (YMRS)[29] and it was administered to patients with mania, hypomania, or mixed episodes according to DSM-IV diagnostic criteria. Patients thought to have bipolar depression were excluded from the study to avoid heterogeneity in the case group. According to the history and evaluation results of two different clinicians, patients with any psychiatric diagnosis other than BD, such as mental retardation, autism spectrum disorder, or substance use disorder, were excluded from the study in order not to disturb the homogeneity of the case group. Patients and healthy controls with neurological diseases were excluded from the study as well. The mean age of the EOBD group was 16.25 $\pm$ 1.34 years (range 12-18

years), and 66 (64.7%) of the 102 patients were male. Family history information, smoking habits, alcohol consumption, and drug usage were obtained through the interviews with the patient.

The control group was preferred from age and sex-matched healthy people who visited Cerrahpasa Medical Faculty Hospital for routine health screenings. The inclusion criteria of the adolescents who came to the routine examination were that they did not have any previous mental or neurological disease and they did not have any past or present mental complaints. The mean age of the control group was 15.70 $\pm$ 3.39 years (range 11-25 years), and 94 (56.0%) of 168 control subjects were male.

Young mania rating scale (YMRS)

Young Mania Rating Scale (YMRS) is the most commonly benefited rating scale assessing manic symptoms. This scale has 11 items and reflects the patient's clinical condition over the previous 48 hours based on his/her subjective report. Clinical observations during the interview also supply additional information. The items display the published characterization of mania symptoms. The YMRS resembles the design of the Hamilton Rating Scale for Depression (HRSD) used for depression scoring in which each item has a severity rating. Four components (irritability, speech, thought content, disruptive/aggressive behavior) are scored on a scale of 0 to 8. The other seven components are scored on a scale of 0 to 4. The four items have twice the weight of the other seven items for the compensation for the poor cooperation from severe patients. For each severity grade, there are finely described points. YMRS is a rating scale used to assess manic symptoms at baseline and over time in patients suffering from mania. The scale is accomplished with a clinician or a trained person having experience with manic patients and it takes 15-30 minutes to perform.[29]

Blood samples and DNA isolation

Venous blood samples were attained from the EOBD group and healthy people and taken into EDTA tubes. Genomic DNA was purified from peripheral blood using a commercial kit (Roche Diagnostics, Mannheim, Germany).

Analysis of *COMT* Val158Met and *DRD2* rs6275 variations

The missense variance *COMT* Val158Met (rs4680) and the synonymous variance *DRD2* rs6275 single nucleotide polymorphisms (SNPs) have been performed by the real-time polymerase chain reaction (RT-PCR) method. Hybridization probes were used for SNP genotyping (TIB MOLBIOL, GmbH, Berlin, Germany). Light-Cycler 1.5® system was used to detect the variants. Genotyping was achieved in a total of 20 mL volume having 2.0 mL of Master Mix, 1.0 mL reagent mix, 3.0 mM $MgCl_2$ (Roche Diagnostics, Mannheim, Germany), and 50 ng of genomic DNA. The genotyping quality was validated by amplifying the randomly selected samples.

Statistical analyses

The student's *t*-test was performed for the statistical analysis for the comparison of two continuous variables. The analysis of variance (ANOVA) test was used for the comparison of more than two groups. Data are expressed as mean $\pm$ standard deviation of the mean (SD). The Chi-square (χ^2) or Fisher's exact test were used for categorical variables. Genotype and allelic relations between patients and controls and the deviation of genotype distribution from Hardy-Weinberg equilibrium (HWE) were performed with the χ^2 test as well. The power of the study was calculated as 0.95 using G power version 3.1.9.4 software.[30] $p \leq 0.05$ was considered statistically significant. Statistical analyses were accomplished by SPSS for Windows software (Version 21.0) (IBM Corp, Armonk, NY, USA).

Results

Demographic data and Hamilton and Beck scores of MDD patients

One hundred and two patients with EOBD and 168 healthy controls were involved in this study. The two groups were not statistically significant according to age (p = 0.064) or gender (p = 0.156). EOBD patients were also examined according to their medication status. 30 (29.4%) patients were not having any medication during admission. 24 (23.5%) patients used to receive antipsychotic treatment. 4 (3.92%) patients were having mood stabilizers and 43 (42.1%) patients were receiving combination drug therapy in the treatment of EOBD (Table 1).

We also investigated the relationship between family history and EOBD development. 35 (34.3%) patients did not have any relatives suffering from EOBD/BP disorder. The first-degree relatives of 35 (34.3%) patients suffered from the same disease. 29 (28.4%) patients had second-degree relatives of BD (Table 1).

The outpatient treatment was as follows; 13 (12.7%) patients were treated with antipsychotic therapy, 2 (1.96%) patients underwent mood stabilizers and 47 (46.0%) patients underwent combined therapy. 38 (37.2%) patients were treated with clozapine or a combination of mood stabilizers and antipsychotics since they displayed resistant states (Table 1).

Genotype frequencies of *DRD2* rs6275 and *COMT* Val158Met (rs4680)

Genotype and allele frequencies of *DRD2* rs6275 and *COMT* Val158Met (rs4680) are shown in Table 2. The genotype distributions were consistent with Hardy-Weinberg equilibrium (HWE) expectations for *DRD2* rs6275 polymorphism among both patients and controls (χ^2=0.003, p = 0.95; χ^2=1.07, p = 0.30, respectively). The genotype distributions were consistent with HWE expectations for *COMT* Val158Met variation among controls (χ^2=0.048, p = 0.82), however, were not consistent with HWE expectations among patients (χ^2=4.33, p = 0.03). This result may be because of our limited sample size.

Table 1 General characteristics of EOBD disorder patients and controls.

Parameter	EOBD patients (n = 102)	Controls (n = 168)	p value
Age (mean ± SD)	16.25 ± 1.34	15.70 ± 3.39	0.064
Gender (M/F), %	66/36 (64.7/35.3)	94/74 (56.0/44.0)	0.156
Previous treatment (n, %)			
None	30 (29.4)	0	
Outpatient	40 (39.2)	0	
Inpatient	31 (30.4)	0	
Psychotropic medication during hospitalization (n, %)			
None	30 (29.4)	0	
Antipsychotic	24 (23.5)	0	
Mood stabilizer	4 (3.92)	0	
Combined	43 (42.1)	0	
Family history (n, %)			
None	35 (34.3)	0	
1st-degree relatives	35 (34.3)	0	
2nd-degree relatives	29 (28.4)	0	
Outpatient treatment (n, %)			
Antipsychotic	13 (12.7)	0	
Mood stabilizer	2 (1.96)	0	
Combined	47 (46.0)	0	
Resistant states (clozapine or combination of mood stabilizer and antipsychotic)	38 (37.2)	0	

Some data of the patients could not be reached. The available data are given in the table.

The genotype frequencies of *DRD2* rs6275 polymorphism was 49.0% CC, 42.2% CT, 8.8% TT in patients and 50.6% CC, 38.7% CT, 10.7% TT in controls. There was no statistically significant difference in *DRD2* rs6275 variants between subjects and controls in the co-dominant genetic model (p = 0.79) (Table 2).

The genotype frequencies of *COMT* Val158Met (rs4680) were 28.4% GG, 58.8% GA, 12.7% AA in patients and 29.8% GG, 48.8% GA, 21.4% AA in controls. The genotype frequencies of SNP *COMT* Val158Met were not statistically significant between EOBP patients and controls in the co-dominant genetic model (p = 0.143). Besides, no significant difference was observed in the allele frequencies of *DRD2* rs6275 and *COMT* Val158Met (rs4680) variations between EOBP patients and controls (p = 0.96; p = 0.404, respectively).

The genotype frequencies were also observed between the EOBD patients and controls in terms of dominant, recessive, and over-dominant models. There was no significant difference in the *DRD2* rs6275 genotype frequencies between EOBD patients and controls when compared with dominant (χ^2=0.01, p = 0.9), recessive (χ^2=0.08, p = 0.76), and over-dominant models (χ^2=0.18, p = 0.66) (including Yates correction) (data not shown in Table 2). Also, no significant difference was observed in the *COMT* Val158Met (rs4680) genotype frequencies between EOBD patients and controls when compared with dominant (χ^2=0.009, p = 0.92), recessive (χ^2=2.66, p = 0.10), and over-dominant models (χ^2=2.16, p = 0.14) (data not shown in Table 2).

EOBD symptom severity, age onset, and *DRD2* rs6275, *COMT* Val158Met (rs4680) variations

We also analyzed YMRS scores of EOBD patients and compared the scores with genotype frequencies of *COMT*

Table 2 The genotype comparison of *DRD2* rs6275 and *COMT* Val158Met (rs4680) genotype of EOBD and healthy controls.

Genotype/allele	EOBD patients n (%) (n = 102)	Controls n (%) (n = 168)	p value
***DRD2* rs6275**			
CC	50 (49.0)	85 (50.6)	
CT	43 (42.2)	65 (38.7)	
TT	9 (8.8)	18 (10.7)	0.79
C allele frequency	0.70	0.70	
T allele frequency	0.30	0.30	χ^2=0.0015, p = 0.96
***COMT* Val158Met (rs4680)**			
GG	29 (28.4)	50 (29.8)	
GA	60 (58.8)	82 (48.8)	
AA	13 (12.7)	36 (21.4)	0.143
G allele frequency	0.58	0.54	
A allele frequency	0.42	0.46	χ^2=0.69, p = 0.404

Table 3 The comparison of *DRD2* rs6275 and *COMT* Val158Met (rs4680) genotypes with YMRS scores and age onset of EOBD patients.

DRD2 rs6275	CC; (*n* = 42)	CT; (*n* = 40)	TT; (*n* = 8)	*p* value
YMRS score (mean ± SD)	28.31 ± 7.64	27.75± 7.68	35.38 ± 8.01	**0.039**
Age onset (years)	15.14 ± 1.9	15.40 ± 1.72	14.11 ± 1.9	0.169
***COMT* Val158Met (rs4680)**	**GG (*n* = 24)**	**GA (*n* = 55)**	**AA (*n* = 11)**	***p*-value**
YMRS score (mean ± SD)	30.33 ± 8.86	28.40 ± 7.62	26.55 ± 6.99	0.386
Age onset (years)	14.10 ± 2.440	15.64 ± 1.349	15.31 ± 1.494	**0.001**

YMRS, Young Mania Rating Scale. Some data of the patients could not be reached. The available data are given in the table.

Val158Met and *DRD2* rs6275. A significant relationship was observed between YMRS scores and *DRD2* rs6275 variants. TT genotype carriers demonstrated a significantly higher YMRS score than CC and CT genotype carriers in EOBD patients ($p = 0.039$). However, there was no relation between YMRS scores and *COMT* Val158Met variants ($p = 0.386$) (Table 3). In addition, a significant relation was observed between *COMT* Val158Met variants and age of onset. *COMT* Val158Met GG wild-type carriers displayed a lower age of onset than heterozygous GA and mutant AA genotype carriers ($p = 0.001$). However, age of onset did not significantly differ between *DRD2* rs6275 genotypes ($p = 0.169$) (Table 3).

SNPs regarding EOBD risk

We also investigated the possible effects of *DRD2* rs6275 and *COMT* Val158Met variants with a multivariate logistic regression model with adjustments for age and gender. Enter method was used in this analysis. Increasing age was observed as a significant risk factor for the disease ($p < 0.001$, OR=1.516, 95% CI: 1.205-1.907). However, *DRD2* rs6275 and *COMT* Val158Met gene variants did not have a significant effect on EOBD risk ($p > 0.05$) (Table 4).

Discussion

Bipolar disorder (BD) is a clinical condition that manifests itself with at least one manic, hypomanic or mixed attacks. The genetic effects were found to be important in EOBD.[19] The risk of this disorder in first-degree relatives increases the prevalence up to 8-10 fold.[31]

COMT is a methylation enzyme and plays an important role in the pathophysiology of mood disorders.[19,32] It affects the catecholamine inactivation and cortical and subcortical dopaminergic interactions. Val158Met polymorphism of *COMT* plays an important role in gene association studies (GWAS) which has been implicated in anxiety disorders, manic depressive disorders, and schizophrenia.[5,16,33] Our work did not show any significant association between *COMT* Val158Met, *DRD2* rs6275 variants, and EOBD development.

Several studies are evaluating the relation between *COMT* variation and EOBD.[4,19,33] Several groups analyzed Val158Met polymorphism of *COMT* in EOBD subjects and controls and reported both negative and positive results.[19,33] For instance, Mick et al. studied *COMT* Val158Met polymorphism in affected children but they did not find any relationship between Val158Met variants and the disease.[19] Massat et al. performed a European multicenter study and examined early-onset major depressive disorder (MDD) and EOBD-diagnosed children. They found an important relationship in *COMT* Val158Met variants between MDD and controls but no relationship was observed between the *COMT* Val158Met variants and EOBD development.[33] In another study by Massat et al., an important relationship was reported between rs4680 of *COMT* and EOBD patients. They also reported significant results in *COMT* rs4818 and rs2075507 polymorphisms but this significance did not remain after Bonferroni

Table 4 *COMT* Val158Met and *DRD2* rs6275 variants and their association with EOBD risk.

Parameter	*p* value	Exp (B)	95.0 % CI for Exp (B) Lower-Upper
Age	<0.001	1.516	1.205-1.907
Gender			
Female	Ref.		
Male	0.138	1.722	0.840-3.529
***COMT* Val158Met**			
GG (Val/Val)	0.388		
GA (Val/Met)	0.828	1.096	0.478-2.512
AA (Met/Met)	0.291	0.553	0.185-1.659
DRD2 rs6275			
CC	0.963		
CT	0.783	1.115	0.515-2.414
TT	0.953	1.039	0.295-3.656
Constant	0.001	0.002	

Adjustments for age and gender were performed.
Exp (B) exponentiation of the B coefficient, 95.0% CI difference of means at 95% confidence interval.

corrections.[16] Besides, Goghari et al. found that the high activity methionine allele was related to EOBD.[34] In a meta-analysis, it was reported that the Met allele was associated with Asian adult BD patients.[21] The findings of these two authors do not support our results. In another work performed in an Asian population, the low activity Met allele of *COMT* was related to BD, but this relationship could not be shown in adult Caucasian subjects.[17] We also worked with the Caucasian samples in our study and the results of this previous study have supported our results.

The inconsistency between several studies may be because of the differences in socioeconomic conditions, sample size, and environmental factors of the populations. Although we could not detect a reliable relationship between the *COMT* and EOBD, we found that GG genotype carriers had lower age of onset than GA and AA variants. The *COMT* GG genotype synthesizes COMT which has higher enzyme activity and may result in excess dopamine catabolism. The dopamine levels may be low in GG genotype carriers since the patients may develop the disease earlier than the GA and AA genotype carriers. Moreover, increasing age was observed as a significant risk factor for EOBD in our study. However, since our results were negative in the multivariate analysis, these results need to be confirmed with larger samples of patients and control groups.

DRD2 receptor has significant roles in mood disorders and addiction.[25,35] *DRD2* rs6275 polymorphism can generate a conformational change in the receptor and affect neurotransmission. Squassina et al. have found an important relationship between EOBP and *DRD2* Taq IA polymorphism. Their study has been performed on 110 males and 190 females, and they showed an over-representation of the C allele in an early-onset group compared to the later-onset group.[36] A European multicenter study demonstrated an important relationship between *DRD2* and BD, and then they also examined this significant relationship in EOBD either.[37] However, the results of this study do not support our research.

Bocchetta et al. performed a study about the relationship between *DRD2* polymorphism and EOBD but they did not find any relationship between the disease and the gene variant. Besides, they did not report any information about the disease scores.[38] In another study, hypomanic personality scale (HPS) scores were compared with several candidate genes previously linked to BD in an undergraduate student group. It has been reported that the hypomanic personality scale was associated with some dopamine-relevant variants and with early adversity. *COMT* Met allele was related to higher HPS scores than the Val allele.[39] In our work, although we could not find any relationship between EOBD and *DRD2* polymorphism, we noted an association between YMRS scores and TT genotype of *DRD2* polymorphism. YMRS scores were higher in TT genotype carriers. The TT genotype may have a role in the conformation alterations of the receptor and deregulation of neurotransmission. However, this result should be confirmed with higher sample size.

The inconsistencies between the studies may be because of the ethnic differences or sample size. Our work did not show any significant association between *COMT* Val158Met, *DRD2* rs6275 variants, and EOBD development. *DRD2* rs6275 polymorphism may hold promise in the severity of the EOBD, however, this should be confirmed with higher sample size. This is the first report to show a relationship between YMRS scores and *DRD2* rs6275 variants in EOBD patients. Limitations in this investigation include relatively small sample size, lack of gene expression, and methylation status data. Another limitation is the lack of comparison between early and non-early onset bipolar patients. Larger sample studies along with gene expression and methylation analysis are needed for confirming the roles of *COMT* and *DRD2* in early-onset bipolar disorders.

Ethical considerations

This study was led according to the principles of the Helsinki Declaration. The study was accepted by the Local Ethics Committee of Cerrahpasa Medical Faculty, Istanbul, Turkey (Ethics Committee issue #12349). Written informed consent was taken from the participants before they took part in the investigation.

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Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ejpsy.2022.07.003.

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