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ORIGINAL ARTICLE

BDNF Val66Met polymorphism is associated with negative symptoms in early-onset schizophrenia spectrum and other psychotic disorders



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KEYWORDS
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Abstract
Background and Objectives: To investigate the clinical characteristics of adolescents with early-onset full psychotic disorders either with Brain-derived neurotrophic factor (BDNF) Val66Met (rs6265) or DRD2/ANKK1 Taq1A (rs1800497) polymorphisms.
Method: 101 cases with early-onset schizophrenia (EOS) or other psychotic spectrum disorders (SSD) and 150 healthy controls were included in the current study. Using the Positive and Negative Symptom Scale (PANSS), patient subgroups were compared for their psychotic symptoms, age-onset, duration of untreated illness, and family history of psychiatric disorders. The real-time polymerase chain reaction (RT-PCR) was implemented for genotyping procedures.

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Results: Study groups and patient subgroups were similar regarding their sociodemographic characteristics (16.4 ± 2.6 years, 62.2% male for all participants). Results did not reveal any difference between patients and healthy controls for DRD2/ANKK1 Taq1A and BDNF Val66Met genotypes. Patients with A1A2 (Gly/Lys) allele reported higher rates of substance use compared to A2A2 (Glu/Glu) counterparts. Other clinical variables were found similar. EOS/SSD group with Val66Met heterozygote allele revealed lower levels of negative symptoms than Val/Val homozygotes. Conversely, the age onset of full psychotic disorder, total positive symptom score, and total general psychopathology score of PANSS were found comparable between Val/Met and Val/Val groups. In the logistic regression model, Glu/Lys genotypes remained significant for the presence of substance use.

Conclusion: The interaction between substance use and the DRD2 gene should be investigated for the development of early-onset psychotic disorders. BDNF Val66Met polymorphism also could be a disease-modifying factor for the presence of negative symptoms.

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Introduction

Schizophrenia spectrum and other psychotic disorders (SSD) have been considered as multifactorial neurodevelopmental disorders arisen from the complex interactions of many genes and environmental conditions.[1] Studies reported the heritability estimates of schizophrenia could be approximately between 80–85%.[2,3] Family, twin, and adoption studies across all age groups have revealed the polygenic model based on the interplay of multiple genes could be more likely to fit schizophrenia, rather than the effect of a single gene.[1–3] Early-onset schizophrenia (EOS) had several genetic components demonstrated in the previous literature.[4] Investigating schizophrenia susceptibility genes composing the genetic components of EOS is also crucial for clarifying the underlying etiology of the disease. Studies to date have shown EOS might be associated with a wide variety of copy number variations and single nucleotide variations.[4]

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that plays an important role in the development, differentiation, neuroplasticity, and synaptogenesis of neurons.[5–7] According to the neurodevelopmental hypothesis of schizophrenia, impairments in synaptogenesis and neuroplasticity could give rise to structural abnormalities in certain areas of the brain associated with the etiology of illness.[8] Therefore, many studies evaluating the symptomatology of schizophrenia focused on serum BDNF levels.[9–14] The substitution of valine to methionine in the codon 66 of the precursor BDNF (proBDNF) protein, called Val66Met polymorphism, results in the disruption of activity-dependent BDNF release.[8,15] Current evidence revealed no clear relationship between the Val66Met polymorphism of the BDNF gene and the development of schizophrenia. However, Val66Met was found to be associated with various clinical features of schizophrenia including the age of onset, treatment response, and cognitive dysfunction.[8,16–25] Some evidence indicated Val66Met was also associated with earlier age-onset and paranoid symptoms among adult patients.[26–29] Although many studies have been performed in adult patients, relatively few studies have been implemented to investigate Val66Met polymorphism among subjects with SSD or EOS, revealing inconclusive findings for clinical characteristics.[4,28,30]

A significant body of research has been conducted to investigate the relationship between the dopamine D2 receptor gene (DRD2) and treatment response.[31,32] DRD2 located in the 11q22-q23 region exhibits clinically relevant polymorphisms.[31–33] Of these, The Taq1A polymorphism (known as rs1800497, C/T, Glu713Lys) was previously thought to be located in DRD2, then it was identified within exon 8 of the ankyrin repeat and kinase domain-containing 1 (ANKK1).[34] In the previous studies, compared to the A2 allele, the presence of the A1 allele could affect DRD2 gene expression, which could be associated with lower D2 receptor density in the striatum.[35,36] Taq1A has become a research interest for both psychosis and alcohol/substance use disorders.[37–42] Several studies also have shown that the Taq1A polymorphism of DRD2/ANKK1 increases susceptibility to schizophrenia.[43,44] Nevertheless, meta-analyses did not find any clear effect of Taq1A polymorphism on the risk of schizophrenia and treatment outcomes.[31,41,45,46] However, in the existing literature, early-onset psychosis was not extensively investigated for the clinical implications of DRD2/ANNK1 variants. In one study, neurocognitive features of the patients aged between 7–17 years with the first episode psychosis were not found to be associated with DRD2 TaqA1 variants.[47] Yet, this study endorsed both non-affective and affective psychosis, and its results were mainly limited to neuropsychological assessments.[47] Therefore, compared to adult-onset schizophrenia, more studies are still needed to fill the gap in the field of EOS and SSD.

Given the underlying genetic etiology of SSD in the child and adolescent population was not clearly understood, there is still a paucity of knowledge about the clinical characteristics of EOS and SSD in terms of the above-mentioned genetic alterations. The importance of Val66Met and/or DRD2 Taq1A polymorphisms was previously shown for the age-onset, clinical characteristics, treatment response, and clinical symptoms of schizophrenia. In this study, we focused on the Val66Met and DRD2 Taq1A polymorphisms in adoles-

cents with early-onset full psychotic disorders. To this end, we aimed to demonstrate the clinical features of cases with an early-onset SSD regarding Val66Met or Taq1A polymorphisms. Also, we compared the prevalence of BDNF Val66Met and DRD2/ANKK1 Taq1A gene polymorphisms among patients with SSD and healthy controls.

Materials and methods

Participants and clinical procedures

251 subjects involving 101 cases with SSD and 150 healthy controls participated in the study. Patients with SSD were recruited from the inpatient units of a tertiary care psychiatry-teaching mental health hospital. A disease-free control group was taken from the outpatient clinics of the child health and disease department. Healthy controls were only allowed when they did not have any chronic medical illness. Healthy controls also matched with the SSD group regarding their demographic characteristics. All the participants, both patients, and caregivers gave written informed consent before the inclusion. The Local Ethics Committee of Cerrahpasa University Medical Faculty approved the study.

All psychiatric interviews were conducted by experienced clinicians specialized in child and adolescent psychiatry. Research diagnoses of psychotic disorders were determined as per the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR). According to the definition, a non-affective early-onset psychotic disorder was endorsed when patients were fully syndromal under the age of 18. Our exclusion criteria were i) caregivers who were not able to give reliable information during the diagnostic interview due to intellectual disability and ii) chronic medical illnesses that might affect mental health.

The positive and Negative Symptom Scale (PANSS) was implemented to assess the severity of the psychotic symptoms. PANSS was developed for the categorical and dimensional evaluation of schizophrenia.[48] Kostakoglu et al. demonstrated the reliability and validity of the scale in the Turkish population.[49] Likert-type 7-point severity scale was used for positive symptoms (7 items), negative symptoms (7 items), and general psychopathology symptoms (16 items). All items of these three subscales were rated by an experienced clinician in the child and adolescent psychiatry field.

Genotyping procedures

Venous blood samples were drawn from both study groups using EDTA tubes. Genomic DNA was purified from peripheral blood using a commercial kit (Roche Diagnostics, Mannheim, Germany). The DRD2 Taq1A (rs1800497) and BDNF Val66Met (rs6265) single nucleotide polymorphisms (SNPs) genotyping have been performed in 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 MgCl2 (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 or Mann-Whitney *U* test was used as per the normality of distribution to compare continuous variables. The chi-square test or Fisher's exact test was preferred for the categorical variables. Genotype/allelic relations among study participants were tested using Hardy-Weinberg equilibrium (HWE) and the chi-square test. Since very few patients with Met/Met genotype of BDNF and Lys/Lys genotype of DRD2/ANNK1 variants were available, we opted to exclude these allelic variants from subgroup comparisons to reduce heterogeneity. The effect size of the significant results was also calculated (Cohen's d).[50] Logistic regression analysis was performed to determine the odds ratio of categorical variables that differed between study subgroups. Alpha value was set at 0.05 two-sided for the lowest threshold of statistical significance. False discovery rate correction was not implemented regarding the explorative and hypothesis-generating features of the study in the early-onset cases. Statistical Package for Social Sciences (SPSS) Version 24.0 was used for data analysis (IBM Corp, Armonk, NY).

Results

Table 1 demonstrated demographic information and allelic variants of the study participants. The average age of the SSD group was comparable to that of healthy controls (16.3 ± 1.3 years vs. 16.5 ± 3.2 years, $p = 0.578$). There was no statistically significant difference between study groups for the frequencies of male and female patients ($p = 0.392$). The genotype distributions were consistent with HWE expectations for DRD2 Taq1A and BDNF Val66Met polymorphism among patients and controls (all p values >0.05).

The genotype distribution of DRD2 Taq1A polymorphism in patient group were similar to control group (For patients, CC = 65,3%, CT = 31,7%, TT = 3.0%; for controls CC = 74,7%, CT = 22,7%, TT = 2,7%, $p = 0.269$). The genotype frequencies of BDNF Val66Met polymorphism also did not differ between study groups (In patient group, GG = 73,3%, GA = 24,8%, AA = 2.0%; in control group GG = 70.0%, GA = 28.0% and AA = 2.0%, $p = 0.848$). There was no significant difference regarding the frequencies of DRD2 Taq1A and BDNF Val66Met alleles in study groups ($p > 0.05$ for both) (Table 1).

Table 2 demonstrates patient subgroups either with homozygote (Glu/Glu) or heterozygote (Glu/Lys) DRD2/ANKK1 Taq1A allelic variants. SSD patients having Glu/Glu allele had similar age and sex characteristics with Glu/Lys group (16.2 ± 1.2 years vs. 16.4 ± 1.4 years, $p = 0.445$; %36.4 female vs. %28.1 female, $p = 0.418$, consecutively). On the other hand, SSD patients who carried Lys/Glu polymorphism had higher levels of substance use than Glu/Glu carriers (40.6% vs. 15.2%, $p = 0.005$). Total PANSS scores of positive symptoms, negative symptoms, and general psychopathology items did not differ for both study groups.

SSD patients were also divided into Val/Val and Val/Met groups for BDNF Val66Met polymorphism. Both study groups

Table 1 Demographic information and allelic variants of study participants.

Characteristics	SSD group, n = 101	Control group, n = 150	χ^2 / t	p
Demographic information				
Age, years, mean ± SD	16.3 ± 1.3	16.5 ± 3.2	−0.6	0.578
Sex, n (%)			0.733	0.392
Male	66 (65.3)	90 (60.0)		
Female	35 (34.7)	60 (40.0)		
DRD2 Taq1A polymorphism, n (%)			2.6	0.269
Glu/Glu	66 (65.3)	112 (74.7)		
Glu/Lys	32 (31.7)	34 (22.7)		
Lys/Lys	3 (3.0)	4 (2.7)		
Allele frequency			2.1	0.149
Glu	164 (0.81)	258 (0.86)		
Lys	38 (0.19)	42 (0.14)		
BDNF Val66Met polymorphism, n (%)			0.3	0.848
Val/Val	74 (73.3)	105 (70.0)		
Val/Met	25 (24.8)	42 (28.0)		
Met/Met	2 (2.0)	3 (2.0)		
Allele frequency			0.3	0.616
Val	173 (0.86)	252 (0.84)		
Met	29 (0.14)	48 (0.16)		

Glu: glutamate, Lys: lysine, Met: methionine, SD: standard deviation, SSD: schizophrenia spectrum, and other psychotic disorders, Val: valine.

Table 2 The subgroup analysis of SSD patients regarding the presence of DRD2 Taq1A polymorphism.

Characteristics	Glu/Glu Group, n = 66	Glu/Lys, n = 32	t /z / χ^2	p
Age, years, mean ± SD [a]	16.2 ± 1.2	16.4 ± 1.4	−0.8	0.445
The age-onset of SSD, years, mean ± SD	15.0 ± 1.9	15.3 ± 1.6	-0.1 [b]	0.897
Duration of untreated illness, weeks, mean ± SD	31.0 ± 42.1	37.7 ± 63.0	−0.2[b]	0.808
Age at the time of diagnosis, mean ± SD	15.6 ± 1.4	16.0 ± 1.3	−1.4 [b]	0.168
Sex, n (%)			0.7	0.418
Female	24 (36.4)	9 (28.1)		
Male	42 (63.6)	23 (71.9)		
Family history of psychosis, n (%) [c]	19 (31.1)	9 (31.0)	0.0	0.991
Family history of bipolar disorder [c]	4 (6.8)	1 (3.3)	0.4	0.659
Any substance use n (%)	10 (15.2)	13 (40.6)	7.8	**0.005**
PANSS Scores, mean ± SD				
Total PANSS score	102.6 ± 19.0	100.3 ± 20.0	−0.7[b]	0.494
Total positive subscale score	27.4 ± 7.3	27.4 ± 8.1	−0.2[b]	0.867
Total negative subscale score	28.1 ± 8.7	27.0 ± 7.3	−0.6[b]	0.552
Total general psychopathology subscale score	47.4 ± 10.1	45.9 ± 11.2	−0.7[b]	0.494

Glu: glutamate, Lys: lysine, SD: standard deviation, SSD: schizophrenia spectrum, and other psychotic disorders.
Bold values are significant at < 0.05 level.
[a] At the time of the clinical interview.
[b] Mann-Whitney *U* test.
[c] Data is not available for 8 cases.

had similar sociodemographic characteristics regarding age, sex, the duration of untreated illness, and family history of psychiatric disorders (Table 3). Besides, the age-onset of psychotic disorders did not reveal any statistical difference Val66Met variants (Val/Val group = 15.1 ± 1.8 years vs. Val/Met group = 15.5 ± 1.2 years, p = 0.573). Additionally, after excluding female patients with SSD, the age-onset of male patients was not also statistically different between both genotypes (Val/Val group = 15.3 ± 1.9 vs. Val/Met group = 15.6 ± 0.9, p = 0.976). Val/Val group had a higher score of negative symptoms in PANSS compared to Val/Met group (28.6 ± 8.5 vs. 24.6 ± 5.8, p = 0.018, Cohen's d = 0.55). We divided SSD patients into two equal subgroups from the median value of negative symptoms. This analysis also indicated the prevalence of Val/Val and Val/Met genotypes in both negative symptom groups were significantly different (χ^2 = 4.2, p = 0.040). The positive symptom subscale of PANSS did not differ between Val/Val and Val/Met groups

Table 3 The subgroup analysis of SSD patients regarding the presence of Val66Met polymorphism.

Characteristics	Val/Val Group, n = 74	Val/Met Group, n = 25	t / z / χ^2	p
Age, years, mean ± SD [a]	16.2 ± 1.3	16.4 ± 1.2	−0.7	0.504
The age-onset of SSD, years, mean ± SD	15.1 ± 1.8	15.5 ± 1.2	−0.6 [b]	0.573
Duration of untreated illness, weeks, mean ± SD	31.5 ± 51.1	32.4 ± 42.9	−0.2 [b]	0.829
Age at the time of diagnosis, mean ± SD	15.7 ± 1.4	16.1 ± 1.1	−0.9 [b]	0.358
Sex, n (%)			0.2	0.685
Female	27 (36.5)	8 (32.0)		
Male	47 (63.5)	17 (68.0)		
Family history of psychotic disorder, n (%) [c]	22 (32.8)	6 (25.0)	0.5	0.475
Family history of bipolar disorder, n (%) [c]	4 (6.0)	2 (8.3)	0.2	0.652
Any substance use, n (%)	17 (23.0)	7 (28.0)	0.3	0.612
PANSS Scores, mean ± SD				
Total PANSS score	101.9 ± 18.7	99.8 ± 18.9	−0.7 [b]	0.491
Total positive subscale score	27.0 ± 7.5	27.9 ± 8.0	−0.1 [b]	0.882
Total negative subscale score	28.6 ± 8.5	24.6 ± 5.8	−2.4 [b]	**0.018**
Total general psychopathology subscale score	46.4 ± 10.1	47.8 ± 10.7	−0.4 [b]	0.710

Met: methionine, SD: standard deviation, SSD: schizophrenia spectrum, and other psychotic disorders, Val: valine.
Bold values are significant at < 0.05 level.
[a] At the time of the clinical interview.
[b] Mann-Whitney *U* test.
[c] Data is not available for 8 cases.

(27.0 ± 7.5 vs. 27.9 ± 8.0, p = 0.882). Finally, general psychopathology and total PANSS score were similar between BDNF Val66Met variants.

We implemented a logistic regression analysis for the presence of substance use to calculate odd ratios of Val/Met and Glu/Lys variants (see Table 4). DRD2/ANNK1 Taq1A polymorphism remained significant in the model (Wald = 7.2, p = 0.007). Exp(B) value of the Glu/Lys allele was 4.9 (95%CI = 1.5−15.6) comparing to Glu/Glu allele. BDNF Val66Met polymorphism and BDNF*DRD2/ANKK1 interaction was not statistically significant in the logistic regression model.

Discussion

Our study contributed to the extant knowledge by demonstrating the link between clinical features and genotype within an EOS/SSD sample. Considering multiple genes and environment play a key role in the development of psychosis, genotype-related illness characteristics have become more important to understand the etiology of psychotic disorders in youth. Specifically, higher negative symptom levels and the presence of substance use were crucial clinical aspects of the illness that were associated with the genotype of patients. Accordingly, the results of this study suggested a higher prevalence of substance use in the DRD2/ANKK1 A1A2 (Glu/Lys) allele compared to the A2A2 (Glu/Glu) counterparts. Val/Met heterozygotes had decreased levels of negative symptoms in comparison to Val/Val homozygotes. Other clinical characteristics between patient subgroups did not differ regarding age-onset, clinical symptomatology, family history, and substance use. Both healthy controls and patients with EOS/SSD did not have any deviation from HWE. Genotype frequencies of study groups were not distinctive, indicating a lack of association for both genes in psychotic spectrum disorders. Finally, logistic regression analysis did not show any additive effect of Val66Met polymorphism on substance use.

In line with the previous literature, DRD2 Taq1A polymorphism was found to be associated with substance use in our study population. As previously stated, current evidence did not support the notion that DRD2 Taq1A modifies the risk of schizophrenia and the clinical aspects of the illness.[31,41,45,46] A study by Aslan et al. also did not find any association between DRD2 rs1800497 polymorphism and schizophrenia, providing further evidence for the Turkish population.[51] Also, there was no significant effect of DRD2 Taq1A polymorphism on the neurocognitive features of EOS patients.[47] In other respects, current knowledge indicated a relationship between the DRD2/ANKK1 Taq1A polymorphism and alcohol use disorder.[52] Previous research also suggested DRD2 Taq1A A1/A1 genotype carriers were more prone to cannabis use.[37,53] Cannabis use was known to play a putative role in psychosis development in vulnerable populations.[54] More specifically, Kraan et al. (2016) demonstrated that current cannabis use had a significant impact on psychosis development in ultra-high risk populations rather than lifetime cannabis use.[55] A recent meta-analysis suggested that nearly a quarter of patients with SSD reported cannabis use.[56] The presence of any substance use disorder was also estimated as 41.7% within the SSD population.[56] In a study conducted in the first-episode psychosis population, Colizzi et al. (2015) showed patients carrying T allele of rs1076560 polymorphism in DRD2 gene more commonly reported cannabis use than controls.[57] Another study including cannabis users suggested higher levels of hypermethylation at exon 8 of DRD2.[58] When taken together, DRD2/ANKK1 Taq1A polymorphism was associated with substance use but not with the risk of psychosis, this polymorphism could alter the course of illness. In parallel with these results, our findings suggested DRD2/ANKK1 Taq1A polymorphism was not associated with the risk of EOS/SSD. Yet, it could be a risk factor for substance use

Table 4 The results of the logistic regression analysis for the presence of substance abuse.

Characteristics	B	SE	Wald	*p*	*Exp (B)*	95%CI
Val/Met genotype [a]	0.6	0.7	0.8	0.368	1.9	0.5 - 7.8
Glu/Lys genotype [b]	1.6	0.6	7.2	**0.007**	4.9	1.5 – 15.6
Val/Met * Glu/Lys genotype [a,b]	−1.0	1.2	0.7	0.389	0.4	0.0 – 3.7

Bold values are significant at < 0.05 level.
[a] Val/Val genotype is the reference category for the BDNF gene.
[b] Glu/Glu genotype was the reference category for DRD2/ANKK1 Taq1A polymorphism.

among patients with early-onset psychosis, which indirectly affects the prognosis of the illness. Increased prevalence of substance use in DRD2 Taq1A Glu/Lys genotype might point to an interaction between DRD2 gene alterations and substance use. Some patients might be inherently more susceptible to substance use that might complicate the course of illness. Nevertheless, our cross-sectional study similar to the previous research was not able to clarify this hypothesis for the longitudinal course. Considering the increasing body of literature emphasizing the impact of cannabis use on psychosis development, clinical and community-based cohorts should explicate this finding.

Consistent with the previous literature, our results proposed the lack of association between BDNF Val66Met polymorphism and EOS/SSD. In a study with adult subjects, Chang et al. (2009) categorized patients with schizophrenia regarding the presence of positive family history or an early-onset illness.[59] Their findings did not support an association between BDNF Val66Met polymorphism and EOS.[59] Similarly, they found higher levels of negative symptoms among Val/Val genotype compared to Met carriers.[59] Conversely, Sun et al. found a higher level of negative symptoms in Met carriers.[60] Nevertheless, some investigators found similar levels of negative symptoms among the three genotypes.[29] Another study with adult patients with schizophrenia suggested serum BDNF levels were positively correlated with emotional and social withdrawal symptoms.[61] Akyol et al. (2015) also compared patients having deficit syndrome (DS) with the non-deficit (ND) group and healthy controls in terms of serum BDNF levels.[62] Their results proposed lower serum BDNF levels in DS than the ND counterparts.[62] ND group also had similar serum BDNF levels to those of healthy controls in this study.[62] In contrast, Valiente-Gomez et al. (2014) found comparable BDNF levels between DS and ND subgroups.[12] Although previous results were not consistent for the difference in negative symptoms levels, our results indicated higher negative symptom severity for Val/Val genotype. This is especially important when considering negative symptoms were clinically predominant in early-onset cases.[63] Furthermore, severe negative symptoms pose a further risk for treatment failure on the long-term course of EOS.[64] Therefore, genotype-based differences in negative symptoms could be associated with the etiologic difference for the development of psychosis. On the other hand, it might be argued that different DSM diagnoses, illness duration, medication status, and assessment tools for negative symptoms could account for the previous inconclusive results regarding the effects of BDNF polymorphisms. Since our sample included various SSD diagnoses, the effect of the Val66Met genotype on EOS still requires further exploration by using more comprehensive assessment tools for negative symptoms. Considering that current evidence provided discrepant findings for both serum BDNF levels and BDNF gene polymorphisms, reliable neural correlates of BDNF activity also could be helpful to establish its role in negative symptoms.

Somewhat surprisingly, we could not find any difference in the age-onset of illness between Val/Val and Val/Met groups. Previous literature yielded an earlier illness onset among Val/Met carriers,[27,29] which was more prominent in male patients.[27] Yi et al. (2011) also replicated this finding in the EOS population.[28] They found an earlier-age onset of male patients with Met allele in Kaplan-Meier survival analysis.[28] Our sample size, smaller than both former studies, might not provide the required power to reach statistical significance. Besides, SSD diagnoses have heterogeneous onset patterns including insidious and abrupt illness-onset. Accordingly, it could be hypothesized that the effects of Val66Met might be more prominent in schizophrenia that generally show a gradual onset pattern, rather than other psychotic disorders. One meta-analysis suggested BDNF Val66Met polymorphism could also be a risk factor for substance use disorders.[23] However, in our study, we could not confirm the effect of Val66Met polymorphism on substance use in early-onset illness. According to our results, DRD2/ANKK1 Taq1A polymorphism had a prominent role in substance use rather than BDNF Val66Met. Considering the alterations in the dopamine system are involved in the pathogenesis of psychosis, BDNF polymorphisms could be associated with negative symptoms linked to the prefrontal cortex and DRD2 might have a role in the striatal reward system.[65] Therefore, it could be argued that BDNF and DRD2 have different etiologic roles in early-onset psychosis. Besides, in our sample, Val/Val and Val/Met groups yielded similar levels of positive and general symptoms. This finding was not parallel with the previous literature asserting higher levels of symptomatology in Met carriers including positive symptoms, depression, and anxiety.[8,27,29,60] However, we only included acutely admitted psychotic patients, which also should be considered to interpret the levels of positive and general symptoms. Of note, the severity of positive symptoms, depression, and anxiety might fluctuate in the course of SSD, depending on the illness severity and medications. Therefore, it would be more beneficial to analyze symptom levels of SSD subgroups at the remission state or in the course of chronic illness.

Our results should be taken into account with their limitations. First, we investigated only two different poly-

morphisms (rs1800497 and rs6265) in the early-onset SSD. Yet, a wide range of polymorphisms has been defined for both genes in the current knowledge. Therefore, the findings of this study were limited to rs1800497 and rs6265 polymorphisms rather than other possible variants of both genes. These polymorphisms are generally prominent in the extant literature regarding the studies involving adult cases with schizophrenia. Second, the sample size of our study was modest given the newly emerging studies generally involve quite a few participants from large consortiums. Third, early-onset psychotic disorders are composed of heterogenous psychiatric diagnoses that might show different levels of positive, negative, and neurocognitive symptoms. Thus, affective symptoms and returning to the premorbid level of functioning after remission might depend on the DSM diagnosis. Similarly, the cross-sectional design of our study might impede predicting the clinical outcome for the long-term follow-up. Despite all these limitations, studies investigating early-onset SSD were outnumbered by those conducted in adult patients. Our study contributed to the relatively limited literature on SSD.

In clinical practice, most patients suffer from negative symptoms causing significant illness-related burdens. Higher rates of negative symptoms in the Val/Val genotype of the BDNF gene could shed light on various outcomes of illness. Accordingly, it could be helpful for future efforts to characterize individuals with severe negative symptoms based on different allelic variants. Likewise, DRD2 polymorphisms could change dopamine sensitivity and facilitate substance use in youth. This variation comes to the fore to prevent a poor prognosis of patients with persistent substance use.

Conclusion

Val66Met polymorphism could be a disease-modifying marker for SSD. Increased frequency of substance use in A1 allele carriers might indicate a possible interaction between genes and the environment. Longitudinal studies involving the high-risk group could investigate this interaction to improve our understanding. These efforts will lead to genotype-based approaches to improve the outcomes of individuals with early-onset psychosis.

Ethical considerations

All the participants, both patients, and caregivers gave written informed consent before the inclusion and all the ethical procedures were performed. The Local Ethics Committee of Cerrahpasa University Medical Faculty approved the study.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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