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ORIGINAL ARTICLE

Association between brain-derived neurotropic factor gene variant (rs6265; C > T) and schizophrenia, its psychopathology and intelligence

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Abstract
Background and objectives: The etiology of schizophrenia (SCZ) is not yet known, but the genetic factor has an essential role. Its heritability is estimated up to 85 percent. This study aimed to determine whether the selected brain-derived neurotropic factor (*BDNF*) gene variant (rs6265) is associated with SCZ, its psychopathology and intelligence quotient (IQ).
Methods: Rs6265 was genotyped in 159 participants, including 71 unrelated patients with SCZ (males = 40 [56%]) and 88 healthy controls (males = 35 [40%]). Psychopathology assessment was done by using positive and negative symptoms scale (PANSS), and IQ was measured by Wechsler adult intelligence scale (WAIS). COCAPHASE and CLUMP22 softwares were used to compare allele and genotype frequencies respectively. Two-way multivariate ANOVA was done using SPSS22 to evaluate the effects of the group (patients and healthy control) and the genotype on the test scores, including PANSS and WAIS scores, considering sex and smoking status as covariates.
Results: The study showed that the *BDNF* rs6265 C allele and CC genotypes, psychopathology, including PANSS scores, and also IQ were significantly different in all, male and female patients compared to healthy participants. For rs6265, we found significantly higher frequencies of the C allele ($P = 0.04$) in all participants with SCZ.

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The findings also revealed that BDNF polymorphism (rs6265) increased significantly the risk of SCZ in different genetic models.
Conclusion: The results showed that the *BDNF* rs6265 may be associated with the risk of SCZ development in an Iranian group of patients with SCZ. These results may be helpful in better understanding the role of the *BDNF* gene in the pathogenesis of the disorder.

Introduction

Schizophrenia (SCZ)[OMIM: 181500] is a serious mental disorder and has a heterogeneous nature. Although its etiology is not yet known, but the genetic factor has an essential role.[1–5] Also, the neurodevelopmental hypothesis is one of the most important explanations for its pathogenesis in which it is claimed that any impairments occurring in neuronal migration, connections, plasticity, and their related brain structural abnormalities play a significant role in the development of SCZ.[6] Brain-derived neurotropic factor (located on the short arm of chromosome 11 [11p14.1; GRCh38/hg38])[7] causes neurons to be produced and survive.[8] It is activated according to the type of brain region.[9] The *BDNF* plays an important role in the development of the central nervous system (CNS). It has an impact on the serotonergic signaling, glial cells,[10] hippocampus neurons, and the brain cortex.[11] It plays a critical role in the process of neurogenesis, neuronal survival, synaptogenesis, synaptic plasticity, cognitive functions, and influence on the functioning of dopaminergic neurons.[12,13] The *BDNF* interacts with the membrane receptor tropomyosin-related kinase B (TrkB), followed by a cascade of protein phosphorylation inside the cell. This leads to diverse effects, such as changes in gene expression.[14] Evidence shows alterations in *BDNF* signaling in SCZ.[13]

The most commonly studied single nucleotide polymorphism (SNP) of the *BDNF* is rs6265 (C > T) the results of which indicate the presence of amino acids valine or methionine in the 66th position of the polypeptide.[15,16] It was observed, however, that Val66Met affects the release of neurotrophin depending on the excitation of the cell.[12] Studies showed that the Val allele is related to a higher risk of SCZ.[17,18] The genotype Val/Val correlates with a lower volume of the hippocampus and impaired memory.[19] However, the results of studies are controversial.[20,21] The *BDNF* variants also affect the age of onset, symptoms, therapeutic responsiveness, neurocognitive function, and brain morphology of SCZ.[15,22]

It should be noted that the data coming from studies on different ethnicities may lead to different interpretations and results.[8] However, the involvement of *BDNF* in the development of the CNS, the activity of dopaminergic neurons, synapses, and the neurogenesis process suggest its role in the etiology of SCZ. The purpose of this study was to develop the insight into the role of *BDNF* SNP rs6265 and SCZ, its psychopathology, and IQ in a sample of the Iranian population.

Materials and methods

Participants

One hundred and fifty-nine men and women participated in this study. The participants consisted of 71 unrelated participants with SCZ, with a mean age of 37.74 ± 10.14, including 40 male [56%], with a mean age of 38.00 ± 10.44, and 31 female with a mean age of 37.37 ± 9.95, and also 88 healthy controls with a mean age of 34.46 ± 7.46, including 35 male [40%], with a mean age of 38.79 ± 8.91, and 31 female with a mean age of 33.02 ± 7.63. Schizophrenia patients were recruited from the Roozbeh psychiatry hospital, Tehran University of Medical Sciences (TUMS), Tehran, Iran. In the case group, the inclusion criteria were the SCZ diagnostic criteria based on the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-V), and no other mental disorder. Healthy controls were recruited from the same geographical area with the inclusion criteria of not suffering from any mental disorders based on DSM-V criteria and not having first-degree relatives with any mental disorder. The exclusion criteria for both groups of participants were IQ score below 70, history of any other medical disorders, substance addiction or use in the past year, and severe head trauma. Written informed consent was obtained from all participants. This study was carried out following the approved guidelines of the Ethical Committee of TUMS. Demographic features are shown in Supplementary Table 1.

Clinical assessments

The clinical diagnosis of SCZ was made independently by two psychiatrists according to the DSM-V criteria. The psychopathology, including positive and negative symptoms, general psychopathology, and total scores of the patients were assessed according to the PANSS.

Cognitive assessments

Intelligence quotient assessment was done in both case and control groups using the WAIS.

DNA preparation, SNP selection, and genotyping

Blood samples were taken by vacuum tubes pre-filed with the anticoagulant EDTA. Genomic DNA was prepared from venous blood using the salting out procedure.[23] Rs6265 was

genotyped by using the tetra-primer amplification refractory mutation system polymerase chain reaction (T-ARMS-PCR),[24] and DNA sequencing. Genotyping was performed blind to status. Primers were designed using the Primer3. Primer sequences and PCR product sizes are shown in Supplementary Table 2.

The annealing temperature was 60 °C. All of the genotypes were callable, and minor allele frequency was greater than 2%. The T-ARMS-PCR fragments were fractionated on 1% agarose gel. Also, to eliminate the genotyping errors, all raw genotyping data were independently read by two experts and the suspect genotypes were retyped. Furthermore, a random group of samples was re-genotyped by direct sequencing to confirm the genotyping results.

Statistical analysis

The Hardy–Weinberg equilibrium for genotypic distribution was tested using the χ^2 goodness-of-fit test. The odds ratio and 95% confidence interval (CI) were calculated to evaluate the effect of different genotypes. The allelic association was estimated using the COCAPHASED (UNPHASED) program. The genotype frequencies were compared using the CLUMP22 software by running 1000 Monte Carlo permutation.[25] The genotypic association was tested by the chi-square test to assess the significance of the results. The independent-samples *t*-test was used to compare the means of the age and quantitative test scores. We used two-way multivariate ANOVA (MANOVA) to evaluate the effects of the group (patients and healthy control) and the genotype as independent factors on the test scores as dependent factors, considering sex and smoking status as covariates. The significance level for all statistical tests was $P < 0.05$. The power analysis was %80.

Results

Clinical assessments

The scores of PANSS were increased significantly in all male and female SCZ patients vs. healthy controls (Table 1).

Regarding the cognitive impairments between patients with schizophrenia and healthy controls

The scores of WAIS were decreased significantly in all male and female patients with SCZ vs. healthy controls (Table 2).

Association of a genetic variant with SCZ

The rs6265 was polymorphic and included in the analysis. We found a significant increase in C allele frequency in patients with SCZ rather than healthy controls in all subjects ($P = 0.04$). We also found a trend towards the significant increase of C allele frequency in patients rather than healthy controls in male subjects ($P = 0.05$) (Table 3).

Additionally, the findings also revealed that BDNF polymorphism (rs6265) increased significantly the risk of SCZ in different genetic models in total subjects (co-dominant [CC vs. CT or TT; P < 0.0001, OR = 3.530, 95% CI = 1.79–6.96], dominant [CC vs. CT + TT; P = 0.0007, OR = 3.120, 95% CI = 1.60–6.10], and recessive [CC + CT vs. TT; P = 0.01, OR = 0.00, 95% CI = 0.00-NA]), in male subjects (co-dominant [CC vs. CT or TT; P = 0.002, OR = 4.630, 95% CI = 1.71–12.52], and dominant [CC vs. CT + TT; P = 0.003, OR = 4.080, 95% CI = 1.53–10.88]), and in female subjects (co-dominant [CC vs. CT or TT; P = 0.03, OR = 2.310, 95% CI = 0.87–6.12], and recessive [CC + CT vs. TT; P = 0.04, OR = 0.00, 95% CI = 0.00–NA]) (Table 4), (Fig. 1).

Association of genetic variants with PANSS and WAIS scores

We used two-way MANOVA to evaluate the effects of the group (patients and healthy control) and the genotype as independent factors on the PANSS and WAIS scores, considering sex and smoking status as covariates. The results showed that only the group factor has significant effects on PANSS positive, negative, general psychopathology, and total, and also performance, and total IQ scores. The results also showed that the genotype factor has a trend towards the significant effect on PANSS negative symptoms score (Table 5).

Discussion

We investigated the association between *BDNF* SNP rs6265 and SCZ, its psychopathology, and IQ. We found that rs6265 has a significant effect on the risk of SCZ development. This effect was detected in all male and female participants. The results showed that the C allele may be the risk allele with an increased risk of SCZ development throughout the sample. In the male sample, the C allele showed just a trend towards a significant effect. We also found that the CC genotype increases significantly in SCZ patients in all, male and female samples.

The neurodevelopmental hypothesis is well established in SCZ, and *BDNF* may be involved in the pathogenesis of this disorder.[26] Rs6265 is identified as a promising SCZ risk variant.[27] Although the results of some studies could not confirm its role in SCZ development,[28] other studies confirm this role.[16,17] The *BDNF* gene is essential for brain development and plasticity and is sensitive to environmental stressors and harbors the functional SNP rs6265 which creates or abolishes a CpG dinucleotide for DNA methylation. It has been concluded that rs6265 methylation interacts with genotype to bridge early environmental exposures to adult phenotypes, relevant for SCZ.[16] Zakharyan and Boyajyan[29] report that carriers of the rs6265 minor allele (T/C + T/T) which is significantly more frequent in SCZ patients than in controls, had decreased BDNF levels. Although Suchanek et al.[30] could not found any association between rs6265 and the development of paranoid SCZ, they could find an association between rs6265 and age at onset of SCZ. Men with the Val/Met genotype had an earlier age at onset.[30,31] Li et al. could not find any significant association between rs6265 and SCZ in the Chinese Han population, but they found a significant difference in haplotype frequencies, with more frequent haplotype ATC of rs6265-rs12273539-rs10835210 in the patients with SCZ than in controls. Besides, these authors reported that

Table 1 PANSS analysis of patients with schizophrenia compared to healthy controls.

Clinical assessments (PANSS scores)	Case N = 71	Control N = 88	Statistics	
			F	*P* value
All				
[•]PS	21.41 ± 7.44	7.13 ± 0.33	131.683	**<0.001***
[•]NS	23.70 ± 11.39	7.21 ± 1.22	138.626	**<0.001***
[•]GPS	39.02 ± 11.59	15.91 ± 12.63	8.011	**<0.001***
[•]TS	84.12 ± 26.07	31.76 ± 1.86	83.969	**<0.001***
Male				
[•]PS	21.03 ± 3.95	7.08 ± 0.28	47.933	**<0.001***
[•]NS	21.21 ± 10.92	7.44 ± 1.80	43.595	**<0.001***
[•]GPS	37.14 ± 11.16	13.72 ± 18.78	0.019	**<0.001***
[•]TS	79.38 ± 24.54	31.62 ± 1.88	33.053	**<0.001***
Female				
[•]PS	21.90 ± 8.18	7.16 ± 0.37	100.131	**<0.001***
[•]NS	26.96 ± 11.41	7.03 ± 0.18	199.521	**<0.001***
[•]GPS	41.50 ± 11.93	17.68 ± 1.8	40.439	**<0.001***
[•]TS	90.36 ± 27.26	31.87 ± 1.86	60.271	**<0.001***

* Significant, PS = Positive score, NS = Negative score, GPS = General psychopathology score, TS = Total score.

Table 2 WAIS analysis patients with schizophrenia compared to healthy controls.

Intelligence assessments (WAIS scores)	Case N = 71	Control N = 88	Statistics	
			F	*P* value
All				
[•]VIQ	86.63 ± 14.65	94.86 ± 14.83	0.322	**0.019***
[•]PIQ	84.90 ± 15.51	99.92 ± 29.16	1.282	**0.012***
[•]TIQ	85.48 ± 13.60	98.30 ± 15.12	0.452	**<0.001***
Male				
[•]VIQ	89.50 ± 14.70	98.42 ± 12.89	0.423	0.052**
[•]PIQ	89.63 ± 14.56	101.21 ± 20.80	1.362	0.054**
[•]TIQ	88.63 ± 12.61	98.70 ± 17.20	1.625	**0.045***
Female				
[•]VIQ	80.90 ± 13.44	92.60 ± 15.73	0.020	**0.04***
[•]PIQ	75.90 ± 13.67	104.55 ± 15.94	0.533	**<0.001***
[•]TIQ	80.50 ± 14.15	98.30 ± 15.12	0.452	**<0.001***

VIQ = verbal intelligence quotient, PIQ = performance intelligence quotient, TIQ = total intelligence quotient.
* Significant.
** Trend awards the significant effect.

Table 3 Allele frequency analysis between patients with schizophrenia and healthy controls.

Groups	Alleles	Allele number (frequency)		Statistics (COCAPHASE)	
		Case (N = 71)	Control (N = 88)	F	*P* value
All	C	104 (73)	110 (63)		
	T	38 (27)	66 (37)	4.159	**0.04***
Male	C	65 (77)	43 (63)		
	T	19 (23)	25 (37)	3.646	0.05**
Female	C	39 (67)	67 (62)		
	T	19 (33)	41 (38)	0.446	0.50

* Significant effect.
** Towards the significant effect.

Table 4 Genotype frequency analysis of BDNF polymorphism (rs6265) in patients with schizophrenia and healthy controls.

Groups	Genotypes	Genotype number (frequency)		Statistics	
		Case (N = 71)	Control (N = 88)	OR (95% CI)	*P* value
Total					
Co-dominant	CC	37 (52)	22 (25)	3.530 (1.79–6.96)	<**0.0001***
	CT	30 (42)	66 (75)		
	TT	4 (6)	0 (0)		
Dominant	CC	37 (52)	22 (25)	3.120 (1.60–6.10)	**0.0007***
	CT + TT	34 (48)	66 (75)		
Recessive	CC + CT	67 (94)	88 (25)	0.00 (0.00–NA)	**0.01***
	TT	4 (6)	0 (0)		
Male					
Co-dominant	CC	25 (59)	9 (26)	4.630 (1.71–12.52)	**0.002***
	CT	15 (36)	25 (74)		
	TT	2 (5)	0 (0)		
Dominant	CC	25 (59)	9 (26)	4.080 (1.53–10.88)	**0.003***
	CT + TT	17 (41)	25 (74)		
Recessive	CC + CT	40 (95)	34 (100)	0.00 (0.00–NA)	0.12
	TT	2 (5)	0 (0)		
Female					
Co-dominant	CC	12 (39)	13 (25)	2.310 (0.87–6.12)	**0.03***
	CT	17 (55)	40 (75)		
	TT	2 (1)	0 (0)		
Dominant	CC	12 (39)	13 (25)	2.050 (0.78–5.37)	0.14
	CT + TT	19 (61)	40 (75)		
Recessive	CC + CT	29 (94)	53 (100)	0.00 (0.00–NA)	25 (74)
	TT	2 (6)	0 (0)		

* Significant effect.

the interaction of *BDNF* and neurotrophic tyrosine kinase receptor 2 (*NTRK2;* the high-affinity receptor of BDNF), genes polymorphisms (BDNF-rs6265, NTRK2-rs1387923, and NTRK2-rs2769605) may be involved in the susceptibility to paranoid SCZ.[32]

We could not find significant associations between the rs6265 and PANSS scores. Suchanek et al.[30] could found a significant association between Val66Met polymorphism and the psychopathology of paranoid SCZ. Men with the Val/Val genotype predisposed to more severe symptoms. The analysis of PANSS single items has shown that patients with the *BDNF* Val66Met had higher scores on positive symptoms,[33] especially on a hallucinatory behavior item.[30] It has been postulated that the correlation between rs6265 and positive symptoms of SCZ might be associated with the increased dopamine function caused by *BDNF* signaling.[34,35] Zhang et al.[36] found the association of the two haplotypes including the rs6265 Val allele with positive symptoms, but they did not find a direct association between Val66Met and clinical symptoms. Chang et al.[37] found that Val/Val patients displayed the highest negative symptom scores among the Han Chinese population. Li et al.[26] showed a significant association between the *BDNF* polymorphisms, including rs6265 (A)-rs12273539 (C)-rs10835210 (A) haplotype and just negative symptom scores. The discrepancies among the studies may be attributable to several reasons. The *BDNF* genotypes can be regarded as trait-dependent features, while the assessment of SCZ severity is state-dependent. So, it can be postulated that a comparison of genotypes with the severity of disorder could be different at any given time. Also, inconsistency can arise from differences in clinical subtypes of SCZ, and in stages of disorder progression (e.g., acute, chronic, active phase, or in remission), in disorder courses, and exposure to different types, dosages, and durations of antipsychotic medications.[36]

We could not find any significant associations between the rs6265 and WAIS scores. In their two separate meta-analyses to investigate the association between the Val66Met polymorphism and neurocognition in patient with SCZ, Ahmed et al.[38] also found a non-significant differences between the genotype groups on most neurocognitive domains. However, in a few studies, different domains of IQ have been reported to be associated with rs6265.[39] Moreover, it has been reported that the IQ in patients with the first-episode of SCZ is associated with the Val66Met polymorphism of the *BDNF* gene.[39] In their study in a group of paranoid SCZ patients, Mak et al.[40] reported that the patients with rs6265 G/G genotype started the rehabilitation program from a higher level of difficulty than patients with the A/G genotype. They explained it as a possible negative influence of Val66Met on cognitive functioning.

A possible explanation for all of the inconsistencies in genetic studies of SCZ may be in the diversity of ethnic background. For example, whereas in our study the Met allele frequency of rs6265 was 37%, was around 50%[41] in the Chinese population, and, around 20% in Caucasian subjects.[42]

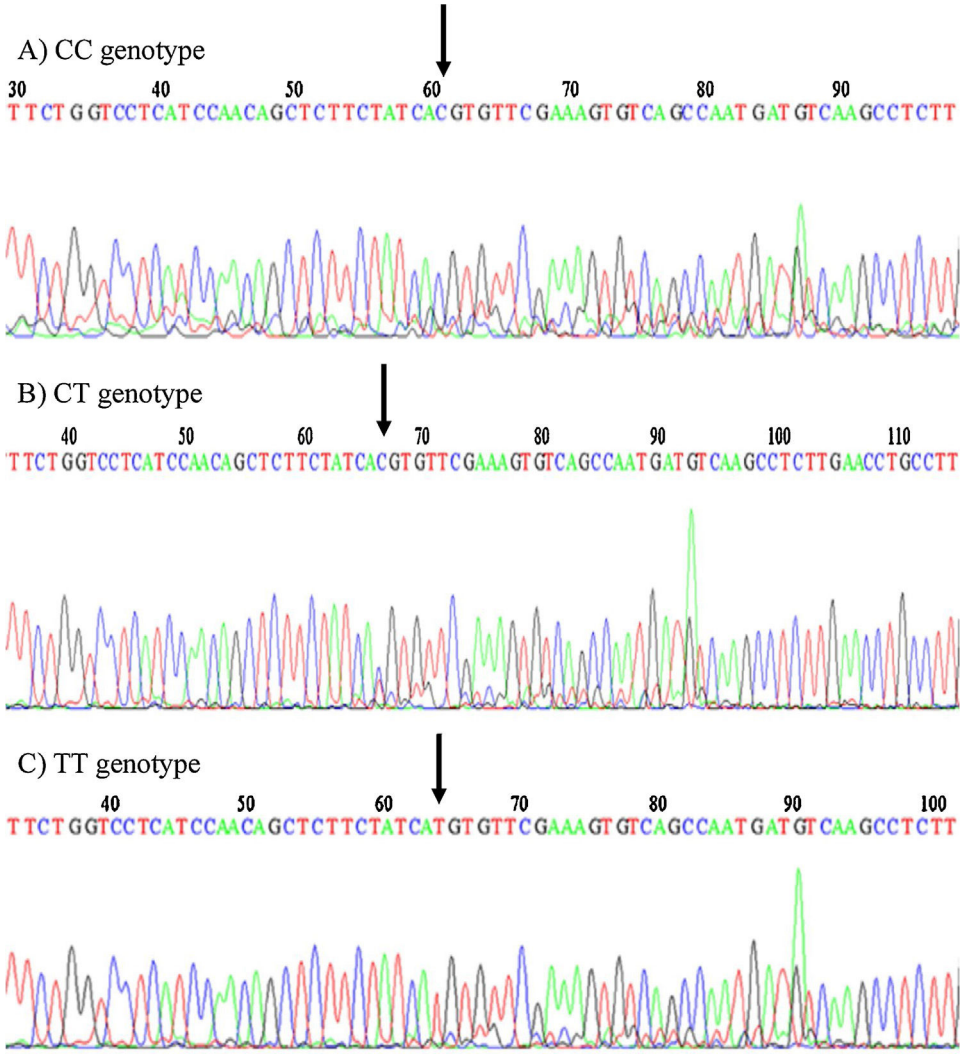

Fig. 1 Sequencing of rs6265 genotypes PCR amplification.

Additionally, it should be noted that the SCZ is a heterogeneous disorder, and leading to inconsistent results. So, haplotypes may be more specific risk markers than single SNPs, and their use reduces false-positive associations.[43] Also, the interaction among multi-genes is probably playing the main role in the pathogenesis of SCZ. So, due to study differences and contrasting findings, further research will be required to understand in better detail the association between *BDNF* SNPs and SCZ.

There were limitations to the current study. The first was the small sample size which may impact the statistical power of our study. The second was that all participants with SCZ were recruited from hospitals. So there was an inherent selecting bias that was an unavoidable problem. The other limitation was that we matched the patients and healthy groups just based on age and handedness, but could not match them on sex and ethnicity. The last limitation was that although it may be convenient to obtain a large sample, but studying a sample of SCZ patients at any time of their treatment is not as strong as studying first-episode patients.

Conclusion

According to our knowledge, this is for the first time that the association of *BDNF* SNP rs6265 is reported with the risk of SCZ, its psychopathology, and IQ in an Iranian sample. Our findings were consistent with the theory stating that the *BDNF* gene variants may mediate the risk of SCZ. However, further studies in different ethnic groups are needed.

Ethical considerations

This study was carried out fallowing the approved guidelines of the Ethical Committees of Tehran University of Medical Sciences, Tehran, Iran. All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants.

Table 5 The groups (SCZ vs. healthy Controls) and genotype factors effects on PANSS and WAIS scores.

Source	Dependent variable	df	F	*P* value	Partial eta squared
Sex	PANSS Positive	1	0.659	0.420	0.010
	PANSS Negative	1	0.663	0.418	0.010
	PANSS General	1	0.074	0.787	0.001
	PANSS Total	1	0.045	0.832	0.001
	Verbal IQ	1	2.781	0.100**	0.042
	Performance IQ	1	0.000	0.990	0.000
	Total IQ	1	0.816	0.370	0.013
Smoking	PANSS Positive	1	0.067	0.797	0.001
	PANSS Negative	1	3.719	0.058**	0.055
	PANSS General	1	3.135	0.081	0.047
	PANSS Total	1	2.228	0.140	0.034
	Verbal IQ	1	0.002	0.961	0.000
	Performance IQ	1	0.000	0.997	0.000
	Total IQ	1	0.005	0.947	0.000
Group	PANSS Positive	1	144.048	0.000*	0.692
	PANSS Negative	1	101.357	0.000*	0.613
	PANSS General	1	131.903	0.000*	0.673
	PANSS Total	1	161.004	0.000*	0.716
	Verbal IQ	1	3.043	0.086	0.045
	Performance IQ	1	11.408	0.001*	0.151
	Total IQ	1	7.456	0.008*	0.104
Genotype	PANSS Positive	2	0.290	0.749	0.009
	PANSS Negative	2	2.197	0.119**	0.064
	PANSS General	2	0.213	0.809	0.007
	PANSS Total	2	0.340	0.713	0.011
	Verbal IQ	2	0.561	0.573	0.017
	Performance IQ	2	0.230	0.795	0.007
	Total IQ	2	0.318	0.728	0.010
Group X Genotype	PANSS Positive	1	0.390	0.534	0.006
	PANSS Negative	1	2.470	0.121	0.037
	PANSS General	1	0.182	0.671	0.003
	PANSS Total	1	0.068	0.795	0.001
	Verbal IQ	1	0.043	0.837	0.001
	Performance IQ	1	0.313	0.578	0.005
	Total IQ	1	0.091	0.764	0.001

* Significant effect.
** Towards the significant effect.

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Conflict of interest

The authors declare there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejpsy.2021.04.004.

References

1. Hatami M, Karamghadiri N, Mohaghegh H, Yoosefee S, Karimipoor M, Hadjighasem M, et al. Neuregulin-1 gene and schizophrenia, and its negative symptoms in an Iranian population. Iran J Psychiatry Behav Sci. 2016;11(4).
2. Ananloo E, Yoosefee S, Karimipour M. Neuregulin1 gene variants as a biomarker for cognitive impairments in patients with schizophrenia. Eur J Psychiatry. 2020;34(1):11–9.
3. Lam M, Chen C-Y, Li Z, Martin AR, Bryois J, Ma X, et al. Comparative genetic architectures of schizophrenia in East Asian and European populations. Nat Genet. 2019;51(12):1670–8.

4. Consortium SWGotPG. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421–7.
5. Yoosefee S, Ananloo ES, Joghataei M-T, Karimipour M, Hadjighassem M, Mohaghghegh H, et al. Association between neuregulin-1 gene variant(rs2439272) and schizophrenia and its negative symptoms in an Iranian population. Iran J Psychiatry. 2016;11(3):147.
6. Wang J, Wang B, Yang SC, Zhang CX, Zheng YL, Li YL, et al. Decreased levels of serum brain-derived neurotrophic factor in drug-naïve first-episode schizophrenia: relationship to clinical phenotypes. Psychopharmacology. 2009;207(3):375–80.
7. Hanson IM, Seawright A, van Heyningen V. The human BDNF gene maps between FSHB and HVBS1 at the boundary of 11p13–p14. Genomics. 1992;13(4):1331–3.
8. Libman-Sokołowska M, Drozdowicz E, Nasierowski T. BDNF as a biomarker in the course and treatment of schizophrenia. Psychiatr Pol. 2015;49(6):1149–58.
9. Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. Genomics. 2007;90(3):397–406.
10. Djalali S, Höltje M, Grosse G, Rothe T, Stroh T, Grosse J, et al. Effects of brain-derived neurotrophic factor (BDNF) on glial cells and serotonergic neurones during development. J Neurochemistry. 2005;92(3):616–27.
11. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci. 2001;24(1):677–736.
12. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003;112(2):257–69.
13. Pandya CD, Kutiyanawalla A, Pillai A. BDNF–TrkB signaling and neuroprotection in schizophrenia. Asian J Psychiatry. 2013;6(1):22–8.
14. Patapoutian A, Reichardt LF. Trk receptors: mediators of neurotrophin action. Curr Opin Neurobiol. 2001;11(3):272–80.
15. Notaras M, Hill R, Van den Buuse M. A role for the BDNF gene Val66Met polymorphism in schizophrenia? A comprehensive review. Neurosci Biobehav Rev. 2015;51:15–30.
16. Ursini G, Cavalleri T, Fazio L, Angrisano T, Iacovelli L, Porcelli A, et al. BDNF rs6265 methylation and genotype interact on risk for schizophrenia. Epigenetics. 2016;11(1):11–23.
17. Neves-Pereira M, Cheung J, Pasdar A, Zhang F, Breen G, Yates P, et al. BDNF gene is a risk factor for schizophrenia in a Scottish population. Mol Psychiatry. 2005;10(2):208–12.
18. Rosa A, Cuesta MJ, Fatjó-Vilas M, Peralta V, Zarzuela A, Fañanás L. The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with risk for psychosis: evidence from a family-based association study. Am J Med Genet B Neuropsychiatr Genet. 2006;141(2):135–8.
19. Smith GN, Thornton AE, Lang DJ, MacEwan GW, Ehmann TS, Kopala LC, et al. Hippocampal volume and the brain-derived neurotrophic factor Val66Met polymorphism in first episode psychosis. Schizophr Res. 2012;134(2-3):253–9.
20. Gratacòs M, González JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. Biol Psychiatry. 2007;61(7):911–22.
21. Kayahan B, Kaymaz BT, Altıntoprak AE, Aktan Ç, Veznedaroğlu B, Kosova B. The lack of association between catechol-O-methyltransferase (COMT) Val108/158Met and brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms and schizophrenia in a group of Turkish population. Neurol Psychiatry Brain Res. 2013;19(3):102–8.
22. Baig BJ, Whalley HC, Hall J, McIntosh AM, Job DE, Cunningham-Owens DG, et al. Functional magnetic resonance imaging of BDNF val66met polymorphism in unmedicated subjects at high genetic risk of schizophrenia performing a verbal memory task. Psychiatry Res Neuroimaging. 2010;183(3):195–201.
23. Miller S, Dykes D, Polesky H. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988;16(3):1215.
24. Ye S, Dhillon S, Ke X, Collins AR, Day IN. An efficient procedure for genotyping single nucleotide polymorphisms. Nucleic Acids Res. 2001;29(17), e88–e.
25. Sham P, Curtis D. Monte Carlo tests for associations between disease and alleles at highly polymorphic loci. Ann Hum Genet. 1995;59(1):97–105.
26. Li W, Zhou N, Yu Q, Li X, Yu Y, Sun S, et al. Association of BDNF gene polymorphisms with schizophrenia and clinical symptoms in a Chinese population. Am J Med Genet B Neuropsychiatr Genet. 2013;162(6):538–45.
27. Saravani R, Galavi HR, Sargazi ML. Catechol-O-methyltransferase (COMT) gene (Val158Met) and brain-derived neurotropic factor (BDNF)(Val66Met) genes polymorphism in schizophrenia: a case-control study. Iran J Psychiatry. 2017;12(4):265.
28. Kawashima K, Ikeda M, Kishi T, Kitajima T, Yamanouchi Y, Kinoshita Y, et al. BDNF is not associated with schizophrenia: data from a Japanese population study and meta-analysis. Schizophr Res. 2009;112(1–3):72–9.
29. Zakharyan R, Boyajyan A. Brain-derived neurotrophic factor blood levels are decreased in schizophrenia patients and associate with rs6265 genotypes. Clin Biochem. 2014;47(12):1052–5.
30. Suchanek R, Owczarek A, Paul-Samojedny M, Kowalczyk M, Kucia K, Kowalski J. BDNF val66met polymorphism is associated with age at onset and intensity of symptoms of paranoid schizophrenia in a Polish population. J Neuropsychiatry Clin Neurosci. 2013;25(1):88–94.
31. Chao HM, Kao HT, Porton B. BDNF Val66Met variant and age of onset in schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2008;147(4):505–6.
32. Lin Z, Su Y, Zhang C, Xing M, Ding W, Liao L, et al. The interaction of BDNF and NTRK2 gene increases the susceptibility of paranoid schizophrenia. PLoS One. 2013;8(9):e74264.
33. Numata S, Ueno S-i, Iga J-i, Yamauchi K, Hongwei S, Ohta K, et al. Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism in schizophrenia is associated with age at onset and symptoms. Neurosci Lett. 2006;401(1–2):1–5.
34. Narita M, Aoki K, Takagi M, Yajima Y, Suzuki T. Implication of brain-derived neurotrophic factor in the release of dopamine and dopamine-related behaviors induced by methamphetamine. Neuroscience. 2003;119(3):767–75.
35. Nikulina EM, Johnston CE, Wang J, Hammer RP Jr. Neurotrophins in the ventral tegmental area: role in social stress, mood disorders and drug abuse. Neuroscience. 2014;282:122–38.
36. Zhang XY, da Chen C, Tan YL, Tan S, Luo X, Zuo L, et al. BDNF polymorphisms are associated with cognitive performance in schizophrenia patients versus healthy controls. J Clin Psychiatry. 2016;77(8):e1011–8.
37. Chang H-A, Lu R-B, Shy M-J, Chang C-C, Lee DPHM-S, Huang S-Y. Brain-derived neurotrophic factor Val66Met polymorphism: association with psychopathological symptoms of schizophrenia? J Neuropsychiatry Clin Neurosci. 2009;21(1):30–7.
38. Ahmed AO, Mantini AM, Fridberg DJ, Buckley PF. Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: a meta-analysis. Psychiatry Res. 2015;226(1):1–13.
39. Zhang C, Gu X, Wang Q, Li M, Deng W, Guo W, et al. Association of Val66Met polymorphism of brain-derived neurotrophic factor gene with cognitive impairment and clinical symptoms in first episode schizophrenia. Chin J Med Genet. 2017;34(4):592–6.

40. Mak M, Samochowiec J, Tybura P, Bienkowski P, Karakiewicz B, Zaremba-Pechmann L, et al. The efficacy of cognitive rehabilitation with RehaCom programme in schizophrenia patients. The role of selected genetic polymorphisms in successful cognitive rehabilitation. Ann Agric Environ Med. 2013;20(1).
41. Yi Z, Zhang C, Wu Z, Hong W, Li Z, Fang Y, et al. Lack of effect of brain derived neurotrophic factor (BDNF) Val66Met polymorphism on early onset schizophrenia in Chinese Han population. Brain Res. 2011;1417:146–50.
42. Varnäs K, Lawyer G, Jönsson EG, Kulle B, Nesvåg R, Hall H, et al. Brain-derived neurotrophic factor polymorphisms and frontal cortex morphology in schizophrenia. Psychiatric Genet. 2008;18(4):177–83.
43. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat Genet. 2003;33(2):177–82.