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Original Article

Association of the brain-derived neurotrophic factor gene G196A rs6265 polymorphisms and the cognitive function and clinical symptoms of schizophrenia

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Abstract: This study aimed to explore the association between BDNF G196A gene rs6265 polymorphisms and the cognitive function and clinical symptoms of schizophrenia. Methods: BDNF G196A rs6265 genotype and allele frequency were measured using Polymerase Chain Reaction (PCR) methods in 224 drug-free patients with schizophrenia and 220 controls. Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), and cognitive functioning was assessed using the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT). In the patient group, differences in severity of symptoms across the three genotypes (i.e., G/G, G/A and A/A) of G196A were assessed using one-way analysis of variance. Results G/A genotype had higher frequencies than GG or AA genotype in both patients and controls. There was no significant difference in G/G, G/A, A/A genotype frequency between patients and controls ($P > 0.05$). The allele G had higher frequencies than allele A in both patients and controls. There was no significant difference in G or A allele frequency between patients and controls ($P > 0.05$). There was significant difference in A/A genotype frequency between positive group patients and negative group patients. There was no significant difference in cognitive performance between patients with G/G, G/A and A/A genotype (all $P > 0.05$). Conclusion BDNF G196A gene rs6265 polymorphism is not associated with the cognitive function but with the clinical symptoms of schizophrenia.

Keywords: Brain-derived neurotrophic factor, G196A gene, cognitive function, molecular psychiatry, schizophrenia

Introduction

Schizophrenia is a complex genetic disorder characterized by a heterogeneous syndrome comprising delusions, hallucinations, and cognitive impairment. Unlike neurodegeneration diseases which have irreversible neuronal degeneration and death, schizophrenia lacks agreeable pathological hallmarks and makes it one of the least understood psychiatric disorders. Some studies have begun to shed light on underlying pathological mechanisms with the identification of susceptibility putative genes [1]. More psychiatrists think that the signs and symptoms arise from complex gene-environment interactions [2].

Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the central nervous system (CNS), and plays important biological roles in neural survival, maintenance and growth, differentiation and plasticity of neurons [3, 4]. Recent studies suggested that a BDNF prodomain single nucleotide polymorphism resulting in a valine (Val)–to–methionine (Met) substitution is associated with impaired declarative memory in patients with schizophrenia [5-7]. Many BDNF genes polymorphisms have been studied for a role in schizophrenia, including the rs6265 (also known as Val66Met or G196A) variant of BDNF and some studies have been performed to explore whether BDNF rs6265 could serve as a useful clinical diagnostic biomarker for schizophrenia [8-12].

Zintzaras [4] conducted a meta-analysis to confirm the association between BDNF gene

rs6265 polymorphisms and schizophrenia. The meta-analysis included genotype data on 1404 schizophrenics and 1597 controls. The overall analysis for investigating the association of rs6265 allele G and the risk of developing schizophrenia relative to the allele A, showed significant evidence of heterogeneity ($P = 0.05$) between the studies and non-significant association.

Kanazawa [8] conducted a similar meta-analysis to see if BDNF rs6265 polymorphisms influence risk for schizophrenia. The results showed that the pooled results from the schizophrenia sample (2955 patients; 4035 controls) indicated lack of significance with schizophrenia.

Relatively little is known about genetic determinants of cognitive dysfunction in schizophrenia. In fact, there are many evidences that the cognitive function is a reasonable endophenotype of schizophrenia [13-16] although contradictory negative findings have also been reported. These studies indicate that the BDNF variant may mediate hippocampal cognitive functions by modulating intracellular trafficking and activity-dependent BDNF release including rs6265 [17-21]. We want to know the relationship between the cognitive function impairment and rs6265 in schizophrenia.

In Russia, Mandelman [22] conducted a meta-analysis of the genetic association about BDNF Val66Met and cognition. But the meta-analysis did not establish significant genetic associations between the Val66Met polymorphism and any of the phenotypes that were included. In Taiwan, Huang's study [23] investigated the relationships between BDNF G196A gene polymorphism and clinical phenotypes in schizophrenia patients in the Taiwanese population. They had not found positive results in the study.

In China mainland, several studies [24-27] have been conducted to confirm the relationship between BDNF gene such as C270T, G712A polymorphism and schizophrenia. However we have not found study about the relationship between BDNF G196A gene rs6265 polymorphism and the cognitive function of schizophrenic patients.

Therefore, we designed this study to test whether BDNF G196A gene rs6265 polymorphisms may affect the cognitive function of schizophrenic patients.

Materials and methods

Participants

This study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Jining Medical University in Shandong China, and written informed consent was obtained from each of the participants. The sample included 224 unrelated schizophrenia patients (118 males and 102 females, mean age 31.4 ± 12.5 years, mean education 12.4 ± 2.1 years) and 220 healthy volunteers (115 males and 105 females, mean age 30.5 ± 11.8 years, mean education 13.5 ± 2.8 years). All subjects were Han Chinese population. The patients had been fulfilled the ICD-10 criteria for schizophrenia based on the diagnostic consensus of two experienced psychiatrists. The patients were recruited from the Second Affiliated Hospital of Jining Medical University, a division of the Jining Medical University, from January 2008 to December 2011. The positive and negative syndrome scale (PANSS) [28] was used to assess each patient's positive (SAPS) and negative (SANS) symptoms at the time of the administration of the cognitive tests. The mean score of the patients' SAPS was 19.1 ± 6.5) and the mean score on the SANS was 16.8 ± 6.6. The mean duration of illness was 3.5 ± 4.5), and the mean number of previous hospitalizations was 1.5 ± 3.4. All patients were undergoing mono-therapy with atypical antipsychotics.

Exclusion criteria for the patients included a history of other psychiatric disorders, a history of severe head injury, currently having acute psychotic episodes, current substance abuse, low IQ, and failure to cooperate during the cognitive tests.

Healthy volunteers were recruited from the community through newspaper advertisements or poster. They were from the same geographical region as the patients. They were initially screened by telephone and further evaluated using an abbreviated version of the Comprehensive Assessment of Symptoms and History to exclude subjects with current or past medical, neurological, or psychiatric illnesses. All the healthy controls were interviewed by two experienced psychiatrists to exclude any with a family history of psychiatric disorders, history of current or past medical, neurological, or psychiatric illnesses.

Table 1. Genotype and allele distributions of BDNF rs6265 polymorphism in schizophrenia patients and healthy controls

	Genotypes			Alleles	
	G/G (%)	G/A (%)	A/A (%)	G (%)	A (%)
Patients (n = 220)	55 (25.0)	133 (60.5)	32 (14.6)	246 (55.9)	194 (44.1)
Controls (n = 224)	60 (26.8)	134 (59.8)	30 (13.4)	245 (54.7)	203 (45.3)
2	0.424	0.224	0.553	0.527	0.429
P value	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Cognitive assessment

All the patients and healthy volunteers finished the Wisconsin card sorting test (WCST-64) and the Trail Making Test (TMT), TMT include A and B. TMT A: there are twenty-five arabic numbers 1-25 in a piece of 16 K white paper, subject was asked to connect every arabic number in order. TMT B: there are thirteen arabic numbers 1-13 and twelve English letter in a piece of 16 K white paper, subject was asked to connect one arabic number then a English letter in order.

SNPs genotyping

Genomic DNA was extracted from l0 ml venous blood sample from each subject using the QuickGene-Mini80 equipment and QuickGene DNA whole blood kit S (Fujifilm, Tokyo, Japan).

Genotypic data for the BDNF gene rs6265 and its 2 kb upstream and downstream regions in both Chinese and Japanese populations were downloaded from HapMap. Only SNPs with a minor allele frequency (MAF) > 10% were considered. Data in HapMap showed that the SNPs in this gene were highly linked with one another. We selected tags from this subset of SNPs using the Tagger program [29] implemented in the Haploview program (version 4.2). To increase throughput, the SNPs were genotyped by ligase detection reaction. All the SNPs were genotyped using Taqman allele-specific assays on the 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Genotypes were read automatically. Ambiguous genotypes were excluded if repeat assays could not be read automatically. The sample success rate was 100% and the reproducibility of the genotyping was 100% according to a duplicate analysis of 2% of the genotypes.

The rs6265 polymorphism was achieved using the following pair of primers: Forward primer: 5′-CTG GAG AGC GTG AAT GGG CC-3′. Reverse primer: 5′-TCC AGC AGA AAG AGA AGA GGA GGC-3′. Polymerase chain reaction (PCR) amplifications were done. The PCR conditions included denaturing at 94°C 5 min, followed by 35 cycles with profiling at 94°C for 30 sec, 60°C for 30 sec, and 72°C for 30 sec, with a final extension at 72°C for 5 min. Enzymatic digestion was done by restriction enzyme PmaCI 5U (Roche).

Statistical analysis

The genotype frequencies were investigated with a chi-square test for the Hardy-Weinberg equilibrium. Pearson chi-square tests or Fisher's exact test was used to evaluate the differences in genotype and allele frequencies in the schizophrenia patients and healthy controls and the differences in genotype frequencies of clinical phenotypes (e.g., positive symptoms or negative symptoms) in patients with schizophrenia. One-way ANOVA (F test) was used to evaluate the differences in cognitive performance among three groups with genotype G/G, G/A and AA. An alpha value of $P < 0.05$ was used for statistical significance.

Results

There were no significant deviations from the Hardy-Weinberg equilibrium in either schizophrenia patients or healthy controls for the investigated BDNF rs6265 polymorphism.

The G/A genotype had higher frequencies than the GG genotype or AA genotype in both patients and controls. However, there was no significant difference between patients and controls in genotype frequency ($P > 0.05$). Similarly, the G allele had higher frequencies than the A allele in both patients and controls. However, there was no significant difference between patients and controls in G or A allele frequency ($P > 0.05$) (**Table 1**).

Similarly, The G/A genotype had higher frequencies than the G/G genotype or A/A genotype, the G allele had higher frequencies than the A allele in both positive group patients and negative group patients. There was no significant

Table 2. Genotype and allele distributions of BDNF rs6265 polymorphism in positive schizophrenia patients and negative schizophrenia patients

	Genotypes			Alleles	
	G/G (%)	G/A (%)	A/A (%)	G	A
Positive (n = 114)	28 (24.6)	65 (57. 0)	23 (20.2)	121 (53.1)	107 (46.9)
Negative (n = 106)	30 (28.3)	66 (62.3)	10 (9.4)	117 (55.2)	95 (44.8)
2	3.326	2.124	4.558	2.227	3.029
P value	> 0.05	> 0.05	< 0.05	> 0.05	> 0.05

Table 3. Cognitive performance of patients with G/G, G/A and A/A genotype (mean ± SD)

Genotypes	Completed classification number	Last wrong number	TMTa†	TMTb‡
G/G (n = 55)	1.38 ± 2.78	15.87 ± 6.88	46.54 ± 17.47	114.38 ± 45.65
G/A (n = 133)	1.37 ± 2.69	15.96 ± 7.75	46.65 ± 19.06	115.45 ± 46.75
A/A (n = 32)	1.36 ± 2.88	16.34 ± 7.73	45.78 ± 17.67	116.79 ± 48.95
F	1.468	2.052	2.224	2.868
P value	> 0.05	> 0.05	> 0.05	> 0.05

†TMTa = Trail Making Test A. ‡TMTb = Trail Making Test B.

difference between patients and controls in G/G and G/A genotype frequency and allele frequency between two groups. However, there was significant difference in A/A genotype frequency between positive group patients and negative group patients (**Table 2**).

There was no significant difference in cognitive performance between patients with G/G, G/A and A/A genotype (**Table 3**).

Discussion

The development of modern molecular biology has promoted the pathomechanism study of schizophrenia enormously in decades. Simple dopamine theory of schizophrenia has received a strong challenge. Scientists have paid close attention to some new theories of schizophrenia pathomechanism, such as neural development hypothesis, apoptosis hypothesis and brain-derived neurotrophic factor (BDNF) [4]. Impairment of neural plasticity and cytothesis may be one of the theories of pathophysiological basis in schizophrenia [1, 30-32].

BDNF plays an important role in promoting and modifying growth, development, and survival of neuronal populations and, in the mature nervous system, is involved in activity-dependent neuronal plasticity. It provides nutritional support for many kinds of neurons and key encephalic regions in CNS. Lines of evidence have suggested that BDNF gene may be involved in the pathogenesis and phenotype such as psychopathology and cognitive function of schizophrenia, but negative results have been found also [3-7].

Rs 6265 is one member of BDNF family. It is at amino acid position 66 in exon 1 of the BDNF gene on chromosome 11p13. Many case-control association studies have been performed to see if BDNF Rs 6265 polymorphisms could serve as a useful clinical diagnostic biomarker for schizophrenia, but results have been equivocal [22-24, 27].

Studies indicated that rs6265 producing a valine (Val)–to–methionine (Met) substitution in the proBDNF protein at codon 66 (Val66Met) is related to hippocampus-mediated memory performance in humans. Hippocampal neurons transfected with the BDNF Met variant show less depolarization-induced BDNF secretion. In addition, these studies also indicated that Met allele carriers have poorer episodic memory than their respective Val-homozygous counterparts, regardless of healthy volunteers, probands with schizophrenia, or their unaffected siblings. Heterozygotes also have significantly lower left hippocampal N-acetyl aspartate levels. Healthy volunteers who are Met allele carriers have lower hippocampal functional MRI blood oxygenation level while performing a declarative memory task and have smaller hippocampal and prefrontal GM volumes [33-36].

Our results showed that there were no significant differences between patients and controls in BDNF rs 6265 G/G, G/A and A/A genotype and G or A allele frequencies. This means that BDNF rs 6265 polymorphism is unlikely to cause more genetic susceptibility to schizophrenia in Chinese.

Neurocognitive impairment, a hallmark of schizophrenia, is not restricted to a small subset of patients. Measurable deficits are present in 40% to 60% of patients with schizophrenia [2].

A meta-analysis found that compared with healthy volunteers, the mean effect sizes for impairment in the Benton Judgment of Line Orientation test and the WAIS-R block design subtest were 0.60 and 0.46, respectively [37]. Such deficits in visuospatial performance have often been attributed to failures of attention or short-term visual memory [2]. We have not assessed every aspect of cognitive function of schizophrenia; this is a shortage of our study.

How about the associations between BDNF rs6265 Gene polymorphism and clinical phenotypes in schizophrenia patients? Huang and his team conducted a study. Their study showed that the BDNF rs6265 genotypes and their allele distributions did not differ between patients with schizophrenia and healthy controls. No significant differences were noted in the BDNF rs6265 genotypes and allele distribution between schizophrenia patients with and without a family tendency for schizophrenia or between those with an age of onset before or after 25 years old. However, there was a significant difference in BDNF rs6265 genotype distribution between schizophrenia patients with and without a suicide history. They made a conclusion that BDNF rs6265 gene polymorphism is associated with a susceptibility to a suicide history in schizophrenia patients in the Taiwanese population [23].

Several studies have connected BDNF with treatment response to neuroleptics. In recent studies, the BDNF expression was reduced by typical neuroleptics. Anttila conducted a retrospective study on 94 patients with schizophrenia and 98 controls. The BDNF G196A and C270T polymorphisms are not associated with treatment response to typical neuroleptics or with age at first hospitalization. Moreover, these polymorphisms of the BDNF gene are not associated with the risk of schizophrenia [38].

Our study found that there was a significant difference in BDNF rs6265 genotype A/A distribution between positive schizophrenia patients and negative schizophrenia patients. The patients with extrusive positive symptoms had a high frequency of the A/A genotype. We thought that BDNF G196A gene rs6265 polymorphism is associated with clinical psychopathology in schizophrenia. These results were helpful for predicting the effect and prognosis of the disorder.

In conclusion, our results show that BDNF G196A gene rs6265 polymorphism is not associated with susceptibility, is not associated with the cognitive function of schizophrenia in the Chinese population, but is associated with clinical psychopathology in this disorder. However, research with a larger number of samples is needed to prove this finding.

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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