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Research Progress of Brain-Derived Neurotrophic Factor Val66Met Gene Polymorphism in Schizophrenia

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Abstract: *Schizophrenia is now considered to be a severe mental disorder caused by complex gene-environment interactions. Brain-derived neurotrophic factor (BDNF) is involved in the development, differentiation, and plasticity of neurons. The Val66Met polymorphism has been associated with impaired neurocognitive function in healthy adults and has been identified as a risk site for a range of neuropsychiatric disorders, including schizophrenia. In this paper, the relationship between BDNFVal66Met polymorphism and schizophrenia is reviewed.*

Keywords: *Schizophrenia; BDNF; Val66Met gene polymorphism*

1. Introduction

Schizophrenia is an inherited severe mental illness caused by complex gene-environment interactions, affecting almost 1% of the world's total population [1]. Brain-derived neurotrophic factor (BDNF) Val66Met (rs6265) is one of the most widely studied gene variants in the psychiatric neuroscience literature. A functional single nucleotide polymorphism leads to the substitution of valine (Val) to methionine (Met) at codon 66(Val66Met), resulting in abnormal sequencing and release of mature BDNF via an activity-dependent secretion pathway [2]. The Val66Met polymorphism has been associated with impaired neurocognitive function in healthy adults and has been identified as a risk site for a range of neuropsychiatric disorders, including schizophrenia. Here, we synthesize evidence from clinical psychiatry, behavioral neuroscience, and neuroimaging to provide a comprehensive review of the association between BDNFVal66Met polymorphism and schizophrenia. We believe that while the Val66Met polymorphism itself may not be a major risk factor for the development of schizophrenia, there is increasing evidence that the polymorphism modulates a range of clinical features of the disease, including age of onset, symptoms, treatment responsiveness, neurocognitive function, and brain morphology. Schizophrenia is an inherited severe mental illness caused by complex gene-environment interactions, affecting almost 1% of the world's total population [1]. Brain-derived neurotrophic factor (BDNF) Val66Met (rs6265) is one of the most widely studied gene variants in the psychiatric neuroscience literature. A functional single nucleotide polymorphism leads to the substitution of valine (Val) to methionine (Met) at codon 66(Val66Met), resulting in abnormal sequencing and release of mature BDNF via an activity-dependent secretion pathway [2]. The Val66Met polymorphism has been associated with impaired neurocognitive function in healthy adults and has been identified as a risk site for a range of neuropsychiatric disorders, including schizophrenia. Here, we synthesize evidence from clinical psychiatry, behavioral neuroscience, and neuroimaging to provide a comprehensive review of the association between BDNFVal66Met polymorphism and schizophrenia. We believe that while the Val66Met polymorphism itself may not be a major risk factor for the development of schizophrenia, there is increasing evidence that the polymorphism modulates a range of clinical features of the disease, including age of onset, symptoms, treatment responsiveness, neurocognitive function, and brain morphology.

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2. Relationship between BDNFVal66Met polymorphism and schizophrenia

2.1 Age of onset

Age of onset has been described as "the first clue in the etiology of schizophrenia", and earlier onset is associated with poorer clinical outcomes [3]. Numata et al. [4] found that BDNF Val66Met polymorphism was significantly correlated with age of onset (P=0.023). The mean age of onset of BDNF Val/Val was 27.5±9.5 years, the mean age of onset of BDNF Val/Met was 25.5±7.4 years, and the mean age of onset of BDNF Met/Met was 22.9±6.0 years. However, this finding has not been confirmed by independent studies [5]. Nor has it been observed in Caucasian populations [6]. The association between the BDNF Val66Met genotype and age of onset of schizophrenia may be race-specific but will need to be confirmed by further investigation in a larger study population. Suchanek et al. [7] genotyped the val66met (rs6265) polymorphism of BDNF gene in 208 patients with paranoid schizophrenia and 254 control patients in Poland. An association was found between age of onset and psychopathology in paranoid schizophrenia and earlier onset in men with the val/ met genotype, which predisposed to more severe symptoms. Changes in brain-derived neurotrophic factor (BDNF) expression and Val66Met (rs6562) polymorphism are involved in the pathogenesis of schizophrenia, but few studies have investigated their effects on the relationship between age of onset, cognitive function, and clinical symptoms of schizophrenia. However, a recent study found different relationships among age of onset, cognitive function and clinical symptoms of schizophrenia under different serum BDNF levels and BDNF Val66met polymorphisms [8].

2.2 Symptoms

Sun et al. [9] used fluorescence resonance energy transfer to genotype BDNF Val66Met polymorphisms in 456 schizophrenia patients and 483 control patients. The BDNF Val66Met polymorphism explained 16% of the variation in anxiety/depression symptoms in patients with schizophrenia after the assessment of psychiatric symptoms using the positive and negative syndrome scales. Sun Mengmeng et al. [10] used TaqM an fluorescence probe technology to genotype 135 patients with first-episode schizophrenia and 483 normal controls. positive and negative syndrome scale (positive and negative syndrome scale, After assessing the clinical characteristics of patients with schizophrenia, it was found that the total score of PANSS, anxiety (depression) factor scores and cognitive impairment factor scores of Met/Met genotype patients were higher than those of Val/Val and Val/Met genotype patients, indicating that the Val66Met polymorphism of BDNF gene may be related to the incidence of schizophrenia. The Met/Met genotype may be more clinically severe in patients with first-episode schizophrenia. Suicide is a major cause of premature death in schizophrenia, and the BDNFVal66Met polymorphism is a promising genetic marker for increased suicide risk, as a history of suicide has been reported to be associated with Met/Met genotypes in schizophrenia, but not Val/Val or Val/Met genotypes [11]. Kaya et al. [12] studied 102 patients with schizophrenia and 98 healthy control patients with BDNF Val66Met gene polymorphism and found that patients with Met alleles (Val/Met and Met/Met) had significantly higher rates of suicide attempts. The Met allele is associated with inattention and response suppression in schizophrenia. The presence of the Met allele may be associated with the risk of suicide attempts in patients with schizophrenia. Impairments in executive function areas, such as attention and response suppression, appear to be associated with the Met allele. Xia et al. [13] genotyped 825 chronic schizophrenia patients with (n=123) and no (n=702) suicide attempts and 445 healthy controls with no suicide attempts and found that the Val allele (p=0.023) and the Val/Val genotype (p=0.058) were associated with suicide attempts. In addition, several clinical characteristics, including age and daily smoking, interact with BDNF gene variants and appear to play an important role in suicide attempts in people with schizophrenia. The BDNF Val66Met polymorphism itself and its interaction with some clinical variables may influence suicide attempts in patients with schizophrenia. Another recent study noted that patients carrying the Val/Met genotype scored higher on the hallucinatory behavior quantification item on the Positive and Negative Symptom Scale (PANSS), providing further (albeit weak) support for the idea that the 66Met allele may be associated with positive symptom classes of schizophrenia [7]. Gene-environment (G × E) interaction is associated with severe mental disorders. Bi et al. [14] studied the interaction between BDNF Val66Met and childhood trauma (ChT) on psychotic symptoms in Chinese Han population and found that in all patients, Emotional abuse (11.9 percent), physical abuse (19.4 percent), sexual abuse (SA), emotional neglect (EN) and physical neglect (PN) accounted for 11.9 percent, 19.4 percent, 23.4 percent, 26.4 percent and 73.6 percent, respectively. Anxiety/depression factors were negatively correlated with ChT scores.

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2.3 Therapeutic response

BDNF regulates major neurotransmitter systems, including the dopaminergic, glutaminergic, and serotonergic systems, and dopamine D2 receptor antagonists are a unifying feature of all antipsychotics. Therefore, BDNF is considered to be significantly involved in the effect of antipsychotic therapy. However, Huang et al. [15] analyzed the relationship between functional BDNFVal66Met variant and antipsychotic response in patients with schizophrenia (SCZ), and the results showed that BDNFVal66Met variant was not associated with the response to antipsychotic drugs in patients with SCZ. However, given the current sample size, a small effect cannot be ruled out. A pharmacogenetic study evaluating BDNF Val66Met polymorphisms found no difference in clozapine reaction between the three Val66Met genotypes, but reported that when compared to the frequency of occurrence of Val/Val genotypes between controls. The frequency of clozapine reaction in patients with Val/Val genotype was significantly higher than that of the Val/Val genotype [16]. One recent report found that patients with the Val/Val genotype and carriers of the Val allele were overrepresented in patients who responded to antipsychotic therapy [17], while two other reports found no association between Val66Met polymorphisms and typical antipsychotic reactivity [18] or risperidone [19]. Perkovic et al. [20] evaluated the correlation between BDNF Val66Met polymorphism and the response of schizophrenia patients to atypical antipsychotic olanzapine therapy, and the possible predictive value of BDNF Val66Met genotype status in antipsychotic therapy response. The results showed that BDNFVal66Met polymorphism was significantly correlated with patients' response to treatment with zapine. The Val/Val genotype was observed more frequently in olanzapine treatment responders and was associated with improved clinical symptoms. A growing number of studies have shown that brain-derived neurotrophic factor (BDNF) is associated with weight gain in patients with schizophrenia during antipsychotic treatment [17]. Liu et al. [21] found that in patients with Val/Val genotype, the increase of serum BDNF level was negatively correlated with risperidone-induced weight gain ($r = -0.44$, $p = 0.008$), indicating that the BDNF signaling pathway may be related to risperidone-induced weight gain. In addition, the negative association between weight gain and increased BDNF levels in ANFE (antipsychotic-naive and first-episode (ANFE) schizophrenics during risperidone treatment depended on the BDNF Val66Met polymorphism.

2.4 Neurocognitive function

The effect of Val66Met polymorphism on cognition is particularly relevant in schizophrenia, because cognitive dysfunction is a core component of schizophrenia, and the severity of cognitive symptoms predicts long-term disability in patients with schizophrenia [22]. Zhang Chengcheng et al. [23] used TaqMan fluorescent probe technology to detect the Val66Met(rs6265) polymorphism of BDNF gene in 87 patients with first-episode schizophrenia and 76 controls, and used Wechsler intelligence adult test to assess cognitive function, analyze the interaction between diagnosis and gene polymorphism on IQ, and analyze the abnormal IQ of patients After the correlation analysis with the severity of clinical symptoms, it was found that the verbal IQ of patients with Val/Val genotype was lower than that of patients with Val/Met and Met/Met genotype, the verbal IQ of Met/Met genotype control was lower than that of Val/Met genotype, and the total IQ of Met/Met genotype control was lower than that of Val/Met and Val/V al genotype control. The total IQ of the Val/Val genotype of schizophrenia was negatively correlated with positive symptom score ($r=-0.65$,$P=0.03$) and thinking disorder score ($r=-0.61$,$P=0.02$). These findings suggest that cognitive impairment in first-episode schizophrenia is associated with clinical features and Val66Met polymorphism of BDNF gene, which is a susceptibility gene for schizophrenia. In addition, the cognitive symptom area of schizophrenia has proven resistant to pharmacological interventions, leading to limited treatment options. Therefore, it is important to determine the effect of the Val66Met polymorphism on neurocognitive function in schizophrenic progenies, as the mutation may provide insight into the molecular mechanisms behind variable cognitive performance and lead to the identification of novel pharmacological targets for cognitive enhancement. Impaired episodic memory is reported to be a class of cognitive impairment associated with carriers of the 66Met allele. In a groundbreaking study, Egan et al. [24] reported that while they found no significant differences in semantic or working memory between the three Val66Met genotypes, compared to the other genotype groups, Episodic memory was significantly impaired in healthy Met/Met genotypic controls, schizophrenic progenitors, and siblings. When their sample was stratified for individual group analysis, the effect of the Val66Met genotype on episodic memory was found to be more pronounced in controls and relatives than in schizophrenia proband. In a follow-up study, similar results were reported where the 66Met allele affected episodic memory in healthy relatives, but not in patients [25]. These results suggest that while Val66Met polymorphisms may have an effect on episodic memory in healthy

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controls, episodic memory deficits are not consistent in patients with schizophrenia and may require further study. Another neurocognitive area disrupted by the Val66Met polymorphism is visuospatial ability. In a sample of 293 patients with a schizophrenia spectrum diagnosis, visuospatial cognition, as measured by four neuropsychological tests, was reported to be impaired in patients with the 66Met allele but not in healthy controls [26]. This defect was accompanied by a reduction in the volume of gray matter in the temporal and occipital regions, the authors report. Further analysis using voxel-based morphometry showed that patients with the 66Met allele had reduced left marginal superior gyri volume compared to those with the 66Val homozygote. Given the absence of parietal gray matter differences among the three Val66Met genotypes in healthy carriers, the authors conclude that Val66Met polymorphisms may selectively cause visual spatial dysfunction in precursors of schizophrenia. The finding that Val66Met polymorphisms are associated (though not selectively) with visuospatial cognitive function in schizophrenia has been replicated [27], and Val66Met-mediated visuospatial dysfunction is considered to be a phenotype that may be exacerbated by schizophrenia-related dysfunction.

2.5 Brain Morphology

The BDNFVal66Met polymorphism has previously been shown to alter brain morphology in healthy adult carriers [28]. A meta-analysis found a significant correlation between serum BDNF levels and left and right hippocampal volume, with lower BDNF corresponding to lower volume [29]. Guo Fang et al. [30] found that patients with BDNF gene (Val66Met) A/A genotype in children with schizophrenia had significant ventricular enlargement and increased width of right temporal horn. Paula et al. [31] found that we did not detect a significant association between brain changes and BDNF Val66Met polymorphisms in patients and controls (all $p>0.060$). At baseline, there was no significant association between brain abnormalities and BDNF genotypes. After 3 years of follow-up, functional deficits were similar between met - carriers and Val homozygous patients ($X2=0.66$; $P = 0.564$); Significant volume changes over time were not associated with functional outcomes. In addition, alcohol consumption rates were significantly higher in the met vector control group compared to the Val homozygous control group ($p=0.019$). The results of this study do not support the idea that BDNF genotype variation may mediate changes in brain macromorphology over time. Yukako Kawasaki et al. [32] conducted BDNF-rs6265 genotyping on 66 newborns and conducted brain MRI scanning, and found that compared with MET-infants, the hippocampus ($p = 0.013$) and amygdala ($p = 0.041$) of Met + infants were smaller. There was also less dramatic age-related decline in total brain volume and % of white matter volume. The relatively small hippocampal and amygdala volumes of Met + infants suggest that Met + genotypes influence prenatal development. In addition, the age-dependent decline in relative total brain and white matter volume was slower in the Met + group in this cross-sectional data set, suggesting that the BDNF-Val66Met variant may have persistent negative effects on postnatal developmental processes.

3. Discussion

In summary, the BDNF Val66Met polymorphism plays an important role in the pathogenesis of schizophrenia. It has been suggested that, although the Val66Met polymorphism is not a pathogenic factor of schizophrenia, it shows pleiotropy by modulating a range of clinical features, including age of onset, symptomology, therapeutic responsiveness, cognition, and brain morphology. The importance of synthesizing the status of Val66Met polymorphisms in schizophrenia is twofold, helping to (1) guide further research and (2) highlight new ways to improve clinical management of individual cases. Given that Val66Met polymorphisms have consistently been shown to alter age of onset, there is great potential to tailor early interventions to high-risk patients with schizophrenia who carry Val66Met. Knowledge of how the BDNF genotype affects the presence and severity of symptoms and treatment responsiveness also provides opportunities for new therapeutic approaches in clinical Settings.

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