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Association between Brain-derived Neurotrophic Factor (BDNF) Val66Met polymorphism and Clinical Outcomes as Measured with PANSS Scale in Patients With Schizophrenia in Two Psychiatric Centres in East Java – Indonesia

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Key-words

Polymorphism, genetic; brain-derived neurotrophic factor; Indonesia; schizophrenia

Abstract

Aim: The etiology of schizophrenia has been linked to complex interactions of genetic and environmental factors, and among them are genes that regulate BDNF (Brain-derived Neurotrophic Factor) expression. The BDNF has been linked to the pathophysiology of schizophrenia, particularly the Val66Met polymorphism. This study aims to assess BDNF Val66Met polymorphism and its role in positive and negative symptoms in patients with schizophrenia in East Java. **Subjects and Methods:** A total of 52 subjects with schizophrenia living in East Java were assessed for BDNF Val66Met polymorphism. The analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 22. Clinical assessment was conducted using the positive and negative syndrome scale (PANSS). Data were analyzed using linear regression multivariate analysis. **Results:** Our study found that Val/Met polymorphism is associated negatively with the total PANSS scores (beta coefficient = -12.299, p = 0.017). The Val/Val polymorphism is associated with negative symptoms (beta coefficient = 22.607, p = 0.043). The present study's findings considered age, gender, education level, number of antipsychotics consumed, medication adherence, and duration of untreated psychosis. **Conclusion:** Val/Val polymorphism is associated with a higher PANSS total score.Val/Met genotype is associated with more severe positive symptoms, while the Val/Val genotype is associated with more negative symptoms. Further study with a larger and multicenter sample is needed to clarify further the relationship of BDNF polymorphism to clinical outcomes of schizophrenia.

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Introduction

Schizophrenia is a psychiatric disorder clinically characterized by delusion, hallucinations, irregular speech, catatonic behavior, or negative symptoms for at least one month [1]. According to the 2019 data in Indonesia, the number of people with schizophrenia reaches 400,000 individuals (1,7 per 1000 population), and many live in the urban settings [2]. Based on the Basic Health Research conducted by the Ministry of Health of the Republic of Indonesia in 2018, it was found that in the province of East Java, the prevalence of individuals with psychotic disorders, including schizophrenia, was 0.64 % among the population [3]. Schizophrenia is a multigenic and debilitating psychiatric disorder with a chronic course that starts in early brain development. The etiology of schizophrenia has been linked to complex interactions of genetic and environmental factors. There have been no central pathophysiology mechanisms, diagnostic neuropathology, or biological markers, yet among these biomarkers, neurotrophins seem to have an important role in the disease mechanism [4]. Given their role in the pathophysiology of schizophrenia, the development of neurotrophin as a biomarker in the clinical use of schizophrenia management is promising.

Brain-derived neurotrophic factor (BDNF) is the brain's most abundant and widely distributed neurotrophin, the growth factor that plays vital in the brain tissue. BDNF is a protein that promotes the survival of specific neuronal populations. All brain regions contain significant amounts of BDNF mRNA, with the hippocampus having the highest levels, followed by the cerebral cortex [5]. BDNF has potent and diverse effects on neuronal and non-neuronal cell proliferation, differentiation, survival, and death, making it critical to the nervous system's health and well-being. In various neurological and psychiatric disorders studies, BDNF aberration has been implicated as a predisposing and perpetuating factor with predictive utility in treatment outcomes [6]. It is thought that the BDNF protein contribute to the etiology of schizophrenia through several mechanisms, including altering the development and function of neurons and synapses, regulating the level of neurotransmitters (such as dopamine and serotonin which are involved in mood and cognition), as well as influencing the stress response and the ability to cope with stress [7].

BDNF is essential for developing the nervous system because it binds to a high-affinity tyrosine kinase receptor B and the p75 neurotrophin receptor. Val66Met polymorphism (refSNP Cluster Report: rs6265) is a common and functional single nucleotide polymorphism (SNP) that affects the activity-dependent release of BDNF [8]. Other SNPs that might contribute to the BDNF in the context of schizophrenia are less studied, such as the rs 11030104 and rs [9]. Other BDNF-related SNPs also have been found to contribute to aspects of other mental disorders and metabolism, such as rs925946 in cognition in depression and also other obesity-related studies. BDNF deficiency has long been proposed as a marker for neuroplastic and cognitive deficits in schizophrenia [10]. Low BDNF levels in the brain and blood are associated with schizophrenia; however, little is known about the role of BDNF Val66Met polymorphism in various schizophrenia symptoms [11]. A study conducted in 2010 suggested that Val66Met genotype affects the NMDA receptor-mediated transmission and plasticity within the hippocampus and infralimbic-mPFC. In the glutamatergic hypothesis of schizophrenia, glutamate hypofunction is considered as one of the causes of this disease. The NMDA receptor activity mediates glutamate hypofunction, which is considered a major pathway involved in the production of positive or negative symptoms [11].

Subjects and Methods

Subjects

Blood samples were collected from 52 subjects between October 2018 and July 2019 based on inclusion and exclusion criteria. The present study included patients with schizophrenia who were inpatients and outpatients at Dr. Saiful Anwar General and Dr. Radjiman Wediodiningrat Mental Hospital, Malang, East Java, Indonesia. These two centres are the only healthcare facilities that provide inpatient treatment in the East Java province, which had an estimated population of 39.74 million in 2019. The following inclusion criteria were used to include subjects: (1) diagnosed with schizophrenia according to the International Classification of Disease, Tenth Revision or Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, diagnosis is made by attending psychiatrists and based on the history in the medical record; (2) aged 18–60 years old; and (3) signed an informed consent form for the study. The following exclusion criteria were used to exclude subjects: (1) a history of or comorbidity with organic mental disorders and metabolic syndrome and (2) a history of or comorbidity with schizoaffective and bipolar disorder. This study was approved by Dr. Saiful Anwar General Hospital Ethical Committee (Ethical Clearance No: 400/93/K.3/302/2018)

Clinical Assessment

The clinical assessment in the current study was performed using The Positive and Negative Syndrome Scale (PANSS). The PANSS instrument was used to examine the positive symptoms, negative symptoms, and severity of schizophrenia.

BDNF Genotyping

According to the catalog, DNA was isolated from peripheral blood using the Blood DNA Preparation-Column Kit (Jena Bioscience). BDNF Val66Met gene polymorphism was confirmed using the polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP) method. The nested PCR method was used to amplify the area containing the examined single nucleotide polymorphism (SNP). The first amplification of PCR was performed using a 25 µl mixture of 10 µM upstream primer, ten µM downstream primer, 12.5 µl PCR Master mix 2× (containing 50 U/ml DNA Taq Polymerase, 400 M dNTPs, and three mM $MgCl_2$) (Promega), and 1 – 5 µl DNA Template. The primer sequences used were as follows: external sense 5'-CCCCATGAAAGAAGCAAACA-3' and antisense 5'-TTTGTCTGCTGCCGTTACC-3' with an amplicon length of 403 bp and internal sense 5'-GCACTCTGGAGAGCGTGAATG-3' and antisense 5'-GAGAAGAGGAGGCTCCAAAGG-3' with an amplicon length of 200 bp that was designed using sequences AC087446 and AC087446.13 (NCBI). In the first PCR step, 300 ng of DNA and external primers were used. The cycling parameters used were: initial step at 95°C for 3 min; 40 cycles at 95°C for 45 s, 53°C for 35 s, and 72°C for 45 s, and final elongation at 72°C for 10 min. Two µl aliquots containing PCR amplification products were transferred to another mixture containing internal primers. The second amplification was diluted as much as 1:100 with a cycling parameter of 95°C for 2 min; 35 cycles at 95°C for 35 s, 51°C for 30 s, and 72°C for 25 s, and final elongation at 72°C for 10 min. The PCR products were analyzed by agarose electrophoresis in 2% gel stained with ethidium bromide.

RFLP Analysis

The BDNF Val66Met genotype was determined based on RFLP analysis. The PCR product was restricted with NIaIII (NEB) enzyme with 0.1 µg DNA, 10× NEBuffer, with 1 U restriction enzyme in 10 µl solution. The product of the restriction was divided and analyzed on a 3 % agarose gel with ethidium bromide. Then, 123 and 77 bp for the Met allele and 200 bp for the Val allele were compared.

Statistical Analysis

Data were analyzed using linear regression multivariate analysis with independent variables of polymorphism, age, sex, education, age of onset, the sum of antipsychotics, adherence, and duration of untreated psychotic with the dependent variables of PANSS scores with Enter Step. The analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 26.0. Mann-U Whitney Tests were used to analyze the difference between the demographic data, linear and logistic regression were used to analyze the multivariate of PANSS score, PANSS positive domain and PANSS negative domain as the dependent variable.

Results

The research subjects included 34 (65.38 %) men and 18 (34.62 %) women. According to the data on the subjects' characteristics presented in Table 1, the average age of the subjects was 36.04 (SD = 9.418). Among 52 subjects, the average age of onset of schizophrenia symptoms was 25.02 ± 9.132 years. The average duration of schizophrenia was 9.99 ± 8.65 years. The study subjects had received antipsychotic treatment for an average of 8.75 ± 7.61 years, with most patients complying with the treatment (n = 47/52, 90.38 %). Most of the subjects (n = 44/nn, 84.62 %) received therapy within one year after the appearance of symptoms. The treatment given varied between subjects. A total of 34.62 % of subjects received atypical antipsychotic medication, 26.92 % received typical antipsychotic, 9.62 % received a combination of atypical and atypical antipsychotic, 13.46 % received a combination of typical and typical antipsychotic medications, and 15.38 % received a combination of typical antipsychotic and atypical antipsychotic medications.

Table 2 summarizes the subject's demographic characteristics as well as the variables being measured. Some of the variables listed, such as a,b,c, etc. were presumed to be correlated to the clinical parameters due to the BDNF polymorphism. Thus, multivariate analysis was performed to examine the canonical correlation (between those factors to PANSS).

The Val66Met BDNF polymorphism significantly correlated negatively to the PANSS score (Table 3). In the analysis, if some other factors (age, sex, education level, number of antipsychotics consumed, medication adherence, and duration of untreated psychosis) were included, Val/Met polymorphism has more negative correlation value to the PANSS score than Val/Val polymorphism (Table 2). These variables were found to have a 3.8 % effect on the PANSS score. According to the analysis, subjects with the Val/Val polymorphism are associated with higher disease severity than those with the Val/Met polymorphism.

The Val/Met BDNF polymorphism was found to be positively correlated with the PANSS Positive Domain score using this data (Table 4). When the effects of age, gender, education level, number of antipsychotics consumed, medication adherence, and duration of untreated psychosis were considered, we found that Val/Met genotype increased the PANSS Positive Domain score more than the Val/Val genotype. These variables were found to have a 51.9 % effect on the positive domain score. According to the analysis, subjects with the Val/Met type polymorphism had more

Table 1. Subject characteristics

Characteristic	n	Mean	%	SD
Age		36.04		9.418
Sex				
Male	34		65.38	
Female	18		34.62	
Education level				
Primary school	10		19.23	
Junior high school	16		30.77	
Senior high school	19		36.54	
Diploma	1		1.92	
Bachelor	5		9.62	
Master	1		1.92	
Marital status				
Unmarried	28		53.85	
Married	23		44.23	
Divorced	1		1.92	
Age of onset (years)		25.02		9.132
Duration of illness (years)		9.99		8.65
Duration of medication (years)		8.75		7.61
Adherence to medication				
Adherence	47		90.38	
Non-adherence	5		9.62	
Duration of untreated psychosis				
<1 year	44		84.62	
≥1 year	8		15.38	
Type of antipsychotics medication				
Atypical antipsychotic	18		34.62	
Typical antipsychotic	14		26.92	
Combination of atypical and atypical antipsychotics	5		9.62	
Combination of typical and typical antipsychotics	7		13.46	
Combination of typical and atypical antipsychotics	8		15.38	

severe positive symptoms than those with the Val/Val type polymorphism.

Table 5 shows the Val/Met BDNF polymorphism was negatively associated with the PANSS Negative Domain score. According to this research, individuals with the Val/Met codon were shown to have lower negative symptoms, including lack of social interaction, communication, and motivation, than those with the Val/Val genotype due to age, gender, education level, number of antipsychotics consumed, medication adherence, and length of untreated psychosis. It was found that these variables had a significant effect on the PANSS negative symptoms score, with a relationship of 36.3 %. This study suggests that Val/Met polymorphism is associated with more severe schizophrenia's symptom than that of Val/Val polymorphism.

Table 2. Demographic characteristics and duration of untreated psychosis in its correlation with BDNF polymorphism

Characteristic		Genotype	N	Median	(min–max)	Sig.
Age (years)		Val/Val	13	35	18 – 60	0.31
		Val/Met	39	37	16 – 57	
Sex	Male	Val/Val	8			0.027
		Val/Met	26			
	Female	Val/Val	5			
		Val/Met	13			
Age of onset (years)		Val/Val	13	20	5 – 56	0.075
		Val/Met	39	25	12 – 42	
Duration of untreated psychotic (years)	< 1 year	Val/Val	13	1	1 – 2	0.244
	≥ 1 year	Val/Met	39	1	1 – 2	

Table 3. Multivariate analysis with Total PANSS score as the dependent variable

Parameter	Parameter estimate	Standard error	95 % CI	P-value
Intercept	−19.012	31.576	−82.904 – 44.839	0.551
Val66Met polymorphism	−12.299	8.338	−21.123 – 14.525	0.017
Age	−0.199	0.487	−1.182 – 0.783	0.684
Sex	17.526	8.059	1.374 – 33.779	0.015
Education	6.728	4.091	−1.522 – 14.979	0.107
Age of onset	0.460	0.494	−0.536 – 1.455	0.357
Sum of antipsychotic	5.019	6.400	−7.888 – 17.927	0.437
Adherence	16.746	13.400	−10.278 – 43.770	0.218
Duration of untreated psychotic	11.612	10.141	−8.839 – 32.064	0.259
Adjusted R value: 3.8 %				

Table 4. Multivariate analysis with PANSS Positive Domain score as the dependent variable

Parameter	Parameter estimate	Standard error	95 % CI	P-value
Intercept	−13.171	8.648	−30.611 – 4.270	0.135
Val66Met polymorphism	8.215	2.413	−4.552 – 5.180	0.397
Age	0.026	0.133	−0.242 – 0.294	0.844
Sex	4.273	2.200	−0.165 – 8.710	0.059
Education	3.221	1.117	0.968 – 5.473	0.006
Age of onset	0.125	0.135	−0.147 – 0.396	0.360
Sum of antipsychotic	−2.149	1.747	−5.673 – 1.375	0.225
Adherence	6.185	3.658	−1.193 – 13.563	0.098
Duration of untreated psychotic	1.463	2.769	−4.120 – 7.047	0.876
Adjusted R value: 52.9 %				

Table 5. Multivariate analysis with PANSS Negative Domain score as the dependent variable

Parameter	Parameter estimate	Standard error	95 % CI	P-value
Intercept	22.607	10.837	0.751 – 44.463	0.043
Val66Met polymorphism	−12.377	3.024	−8.372 – 3.721	0.235
Age	−0.176	0.167	−0.512 – 0.160	0.297
Sex	−1.830	2.757	−7.390 – 3.731	0.511
Education	−0.240	1.400	−3.063 – 2.583	0.865
Age of onset	−0.029	0.169	−0.370 – 0.311	0.864
Sum of antipsychotic	2.712	2.190	−1.705 – 7.128	0.222
Adherence	1.952	4.585	−7.293 – 11.198	0.672
Duration of untreated psychotic	1.832	3.470	−5.166 – 8.829	0.600
Adjusted R value: 38.3%				

Discussion

According to the present study, the population of subjects with the Val/Met polymorphism tended to have worsened positive symptoms compared with those with the Val/Val genotype. The PANSS revealed that subjects with the Val/Val genotype had more negative symptoms and higher degree of severity than those with the Val/Met genotype. The findings of the present study considered age, sex, education level, number of antipsychotics consumed, medication adherence, and duration of untreated psychosis.

A study on the Polish by Suchanek and associates population discovered a link between this polymorphism and the age at onset and psychopathology of paranoid schizophrenia. Men with the Val/Met genotype had symptoms at a younger age [12]. The connection between age of onset, cognitive function, and clinical symptoms of schizophrenia varies according to blood BDNF levels and BDNF Val66Met polymorphisms. Patients diagnosed at an earlier age had greater negative symptoms and cognitive impairment, as well as lower serum BDNF levels [13]. In a study conducted in Beijing with 387 patients with schizophrenia with a disease duration of >5 years, it was discovered that the BDNF Val66Met polymorphism has a greater effect on age of onset than on the clinical symptoms encountered [14].

In another previous study of the BDNF – COMT gene interaction, individuals with the genotype BDNF Met/Met had a higher level of positive symptoms in schizophrenia such as hallucination or delusion [15]. This finding is supported by another previous study that yielded similar results [16]. PANSS single-item analysis revealed that patients with the Val/Met genotype scored higher on a hallucinatory behavior item than those with other genotypes [12]. In a study that connected childhood violence to BDNF gene polymorphisms, Met carriers reported more positive psychotic-like episodes when exposed to childhood trauma than Val/Val carriers [17]. In contrast to the findings of the present study, another previous study found that the Val/Val genotype was associated with more positive symptoms than the Val/Met genotype, whereas negative symptoms were not significantly different across genotypes [18]. The present study found that patients with the Val/Val genotype had a higher PANSS score than those with the Val/Met genotype. When compared with other studies, the conclusions of the current study appear to be inconsistent. Individuals with the Met/Met genotype had a 19 % higher chance of developing schizophrenia and other psychotic illnesses than those with the Val/Met genotype [19]. However, similar to our findings, the Val/Val genotype was associated with more severe symptoms, especially on the PANSS, General Psychopathology Scale [12].

The Val66Met polymorphism in the BDNF gene has some significant impact on positive symptoms of schizophrenia due to various factors, one of which is significant in this study is sex. These findings were consistent with research by Wei and associates where there were significant sex X genotype interactions in which Val homozygotes showed higher rCBF in females than males, but Met carriers showed the opposite relationship [20,21]. Other than sex, education also has a significant result with the PANNS positive domain score. Education correlates with cognitive function, that is also affected by schizophrenia. This significant result is thought to be caused by a smaller hippocampal volume of Met allele carriers compared to Val allele [22]. According to studies, Val66 Mett also affects the NMDA receptor-mediated transmission that mediates glutamate hypofunction,

which is involved in producing positive symptoms [9]. This condition might further worsen the positive symptoms of schizophrenia. In addition, studies have also shown a decreased volume in the dorsolateral prefrontal cortex and subcortical regions in the Met allele [22]. Up to this point, there was no direct association between the educational level and the incidence of schizophrenia, nor the polymorphism found among schizophrenia patients. These findings further imply that genetically dictated changes in neuroimmune modulators may be among the risk factors for schizophrenia, contributing to disease-specific pathological abnormalities in neuronal synaptic plasticity and the immune system [23]. The Val66met polymorphism in the BDNF gene may account for some of the diversity in hippocampus formation size [24]. Variations in the BDNF gene's rs6265 SNP have a major impact on memory function as well as the structure and physiology of the hippocampus, with met allele carriers suffering the most [25]. The effect of BDNF Val66met on hippocampus volume appears to be independent of childhood abuse and psychiatric condition. Individual differences in hippocampus volume and memory-related activity have been linked to the BDNF gene polymorphism Val66met. However, these findings have not been replicated consistently, and no research to date has adjusted for the potentially confounding influence of early life stressors such as childhood maltreatment and mental status [26].

The inhibitory intracortical interneuron network, cortical plasticity, and the BDNF - Val66Met polymorphism all interact in a complex way [27]. Interactions between BDNF genotype expression and five human brain areas are noteworthy (cerebellum, cortex, nucleus accumbens, caudate, and cerebellar hemisphere). Despite the fact that the amount of these alterations differed throughout the studied regions, 30 distinct SNPs in two haplotype blocks were associated with expression alterations in these five places [28]. The dysregulation of BDNF signaling is not exclusive to schizophrenia. However, BDNF polymorphism might be seen as one of the genetic variables that contribute to the onset of schizophrenia, combining with other genetic and environmental variables [29]. Age, gender, environmental factors, ethnicity, the genetic model used for analysis, and gene–gene interaction can all be blamed for inconsistencies in BDNF Val66Met genetic studies [8].

Several limitations should be noted in the current study. First of all, the number of participants in this study is relatively small compared to other studies. However, it is noteworthy that the Val66Met BDNF polymorphism significantly correlated negatively to PANSS score. In addition to this, this study only assesses the Val66Met polymorphism. The Val66Met polymorphism, as well as any common genetic variation, may be a pleiotropic modulator of disease-associated phenotypes, where multiple genetic variants simultaneously inherited might modify the BDNF - TrkB signaling balance in a probabilistic way [30]. To this regard, recent evidence showing that chromatin loop formation may mediate the mechanism of risk of schizophrenia-associated variants makes intriguing to explore the potential link between a schizophrenia locus on other genetic codon including chromosome 9 and NTRK2, the gene codifying for the TrkB receptor, ~ 2.5 Mb far from the index SNP of this locus [31]. It remains unclear whether the decline is accelerated by disease progression in patients or is a reflection of lower basal levels that occurred earlier during the development and lagged behind for the rest of life. Stratifying the general population for genetic risk for schizophrenia before disease onset (e.g., decile of the polygenic risk score) and following longitudinally groups with different genetic load may help to answer whether the dynamic of BDNFgene expression is related to disease pathogenesis. It should also be noted that the ancestry information, whether by using single nucleotide polymorphism or mitochondrial haplotypes, was not assessed in the current study. As Indonesia has a diverse ethnic group across the archipelago, it might influence the results due to single nucleotide polymorphism. Future studies considering genetic ancestry information would be necessary to investigate the network-based brain endophenotypes of the BDNF Val66Met polymorphism.

Val/Met polymorphism is associated with more severe schizophrenia symptoms, while Val/Val polymorphism correlates with more negative symptoms in the population of people with schizophrenia in East Java, Indonesia. Further study is needed on the relationship of BDNF polymorphism in a larger and wider population of various races and regions in Indonesia.

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Conflict of Interest

None to declare.

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