



BDNF Val66Met Polymorphism and Incidence of Childhood Trauma in Bataknese Schizophrenia Patient

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Abstract

Background: Schizophrenia is a severe brain disease with severe and persistent psychotic manifestations accompanied by dysfunction of cognitive and psychosocial variables. Numerous studies indicate that a mix of genetic and environmental variables may be responsible for the aetiology of schizophrenia. BDNF Val66Met, functional polymorphism is a candidate genetics, and childhood trauma is an environmental factor thought to be associated with the incidence of schizophrenia. This study aimed to analyze the relationship between BDNF Val66Met polymorphism and childhood trauma between Bataknese people with schizophrenia (SP) and Bataknese healthy people.

Method: This is a multivariate comparative analytical study with a case-control design. Blood samples were taken from a total of 200 subjects (n = 100) for each Schizophrenia patient (SP) and control group (CO), then BDNF Val66Met allele and genotype identification was carried out using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique. The WHO-ACE IQ is used as an instrument for childhood trauma.

Results: There was no significant difference between the BDNF Val66Met polymorphism allele in SP and healthy controls with a value of $p = 0.107$, OR 1.413 IK95% (0.951-2.099). There was no significant difference between the BDNF Val66Met polymorphism genotype in SP and healthy controls of Met/Met vs Val/Val genotypes with p values of 0.063, OR 0.486 (0.227-1.039)CI95%, Val/Met vs Val/Val with $p = 0.291$, OR 1.414 (0.744-3.689)CI95%. There is a significant difference between the incidence of childhood in the CM and FD domains with $p < 0.001$, in the CM domain with an OR 5.096 (2.473-10.5)CI95% and in the FD domain with OR 10.778 (3.135-37.054)CI95%, in the VIO domain, there is no significant difference of $p = 0.056$ with OR 4.846 (1.020-23.028) CI95%. There was no significant difference between Val66Met's BDNF polymorphism and the incidence of childhood trauma, domains CM, FD and VIO, with a $p > 0.05$ value.

Conclusions: There was no difference between allele and genotype polymorphism BDNF Val66Met between SP and healthy controls. A significant difference between CM and FD, domain childhood trauma, exists between SP and healthy controls. There was no association between BDNF Val66Met polymorphism and childhood trauma in SP and control.

Keywords: BDNF Val66Met, polymorphism, schizophrenia, childhood trauma, Bataknese

Introduction

Schizophrenia is a severe brain disease with severe and persistent psychotic manifestations accompanied by cognitive and psychosocial variables dysfunction. The onset of the disease, at least from psychotic manifestations, occurs in late adolescence/adulthood, and early symptoms often go undetected early in life. People with psychotic illnesses generally suffer greatly throughout life and need medical help, with its prevalence worldwide continuing to be very high [1].

The advancement of knowledge in understanding and treating schizophrenia depends on the discovery of neural mechanisms of influential elements, one of which is the mechanism of psychosis. Numerous studies have revealed that a hereditary and environmental component may play a role in the development of the central nervous system (CNS) and neurotransmission problems that underlie schizophrenia. A fundamental paradigm for comprehending the pathophysiology of schizophrenia is the role of neurotrophic factors (NFs) on neurodevelopmental abnormalities [1], [2].

A range of environmental influences, including exposure to substances such as alcohol and trauma such as abuse and neglect, strongly impact brain development. Another aspect influencing brain growth is hereditary influences [1].

Brain-derived neurotrophic (BDNF) component, which has previously been connected with variations in brain volume, is a compelling candidate for a genetic component that regulates brain growth. An intriguing point is the functional polymorphism BDNF Val 66 Met, defined by the replacement of Valin with Metionin at codon 66 in the protein pro-domain. Individuals with the Met allele (heterozygous p. Val66Met and homozygous p. Met66) had lower serum BDNF levels and a smaller hippocampus and prefrontal cortex than those with the Val allele [1].

Childhood trauma has an ongoing effect on brain development, including alterations in the structure and function of numerous stress-sensitive areas such as the hippocampus, prefrontal cortex (PFC), and amygdala. Under standard neurobiological settings, the hippocampus receives perceptual and contextual information [4].

Genetics and environmental exposure have an essential influence on the development of mental illness. Some researchers have identified specific interactions between genes and the environment contributing to psychosis. In accordance with the neurodevelopmental hypothesis, schizophrenia can be caused by both genetic and environmental factors and manifest with cognitive and emotional impairment along with the appearance of positive and negative symptoms [5].

Brain-derived neurotrophic factor is a neurotrophic factor that promotes the formation and maintenance of synapses and cortical neurons. BDNF is widely distributed in the CNS and plays an important role in neonatal neuron survival, differentiation and growth, as well as synaptic plasticity and behaviour in adults. Evidence suggests that BDNF has a role in the pathophysiology of schizophrenia [1], [3].

Research by Weickert et al. USA has shown a decrease in BDNF production and the amount of BDNF in the dorsolateral prefrontal cortex in post-mortem studies of schizophrenia patients. This study also found that due to decreased BDNF, there was a decrease in support for cortical, afferent and target neurons. Takahashi et al. the Molecular Neurobiology, Brain Research Institute, Niigata University, Japan, a post-mortem study also assessed neurotrophic levels, where there was an increase in the amount of BDNF in the anterior cingulate cortex and hippocampus in schizophrenic patients; on the contrary, there was a significant decrease in the expression of TrkB and calbindin-D receptors, BDNF influences both receptors in the hippocampal region and prefrontal cortex [5] – [7].

Gratacos et al.'s study in Barcelona, Spain, on Met/Met homozygous carrier polymorphisms, found a 19% increased risk of schizophrenia compared to heterozygotes. In the study, the proportion of Val/Val genotypes was 40.9%, Val/Met 42.8%, and Met/Met 16.3% in schizophrenia patients in outpatient polyclinics at nine hospitals in Tokushima Prefecture. In a study by Zhou et al. in China that compared the frequency of occurrence of both the genotypes and alleles, Val and Met obtained an OR 1.03 (95% CI) [8] – [10].

In the study of Fu et al. in China, a positive association of BDNF Val66Met

(G196A) with schizophrenia was found, where the minor allele (A) had a protective effect against schizophrenia (OR=0.89). Kim SW et al.'s research in Korea states a gender-specific relationship exists between the Val allele and neurocognitive function. In women, total PANSS scores were associated with higher career Val. In addition, SOFAS and SWN-K scores were significantly lower in Val's career [11], [12].

Functional polymorphisms in the BDNF gene (Val66Met) are reported to interact with childhood trauma in the formation of psychotic symptoms, and patients with schizophrenia, bipolar disorder, and Met carrier in BDNF Val 66 Met who experience severe childhood trauma will form more severe cognitive symptoms and brain abnormalities [13].

An observational study by Xiao-jiao Bi et al. in China in 2018 examined the interaction of childhood trauma with BDNF Val66Met, which affects schizophrenia symptoms. In this study, there was a significant negative correlation between anxiety/depression factors and the total score of the childhood trauma questionnaire. Two-way interaction is also found in Val 66 Met with physical neglect, as three-way interaction with Val 66 Met, physical neglect and physical abuse, and in four-way interaction found in Val 66 Met, physical neglect, physical abuse, and emotional neglect. This study suggests the influence of BDNF Val66Met polymorphism after childhood trauma, which is considered a risk factor for schizophrenia symptoms [13].

In 2014, Monica Aas et al. conducted a study in Norway on the relationship between childhood trauma and Val 66Met BDNF polymorphism on BDNF mRNA levels and hippocampal volume in patients with schizophrenia and bipolar disorder. Val's BDNF 66 Met carrier has lower BDNF mRNA levels compared to Val's carrier. When divided into childhood trauma subtypes, associations between subtypes with unidirectional BDNF mRNA levels, except for high trauma levels, were found to be lower [14].

Silvia Alemany's study et al. entitled Childhood abuse, the BDNF-Val 66Met polymorphism, and adult psychotic-like experiences in 2011 in Spain suggested that childhood abuse has significant positive effects with positive dimensions of psychotic-like experiences. There is also a moderate association with BDNF Val66Met polymorphism [15].

Researchers saw an association between BDNF Val 66 Met polymorphism and childhood trauma in people with schizophrenia; therefore, based on the above background, researchers want to find out the demographic characteristics of research subjects, allele frequency, and genotype of BDNF Val 66 Met in research subjects, frequency of childhood trauma in research subjects and the difference of BDNF Val 66 Met polymorphism and childhood trauma in SP and healthy controls.

Material and Method

Subject

We recruited 100 healthy subjects (CO) and 100 schizophrenia patients (SP) who met inclusion and exclusion criteria and provided written informed consent following the Medical Research Ethics Committee of Universitas Sumatera Utara.

The inclusion criteria are schizophrenia patient in RSUD H. Amri Tambunan with Batak tribe and diagnosed based on the PPDGJ III, two generations/degrees and above are Batak tribes, minimum age of 18 years, cooperative and willing to follow the research, in the stabilization phase and stable conditions. In this study, we exclude patients with neurological diseases, endocrine disorders, autoimmune diseases, and a history of alcohol and addictive substance use, except nicotine and caffeine.

Questionnaire distribution

The present study used the World Health Organization Adverse Childhood Experiences International Questionnaire (WHO-ACE IQ) to assess the incidence of childhood trauma/adverse events. This questionnaire is a self-report and has been validated in Indonesian by Trihapsari et al. It contains 29 questions divided into three domains: childhood maltreatment, family/household dysfunction, and violence outside the home [16,17].

Blood sample collection and whole blood DNA extraction

Each individual had 3 mL of EDTA blood drawn. All blood samples were kept at -80 °C until further examination. DNA was extracted from blood using the DNA extraction kit according to the manufacturer's instructions, carried out in accordance with the procedures in previous research conducted by Mardhiyah S., Effendy E. and Nasution NM. We then performed Restriction fragment length polymorphism (RFLP), PCR amplification, Restriction analysis, Gel electrophoresis, and visualization [18],[19].

Results

A total of 200 bands of agarose gel electrophoresis were analyzed, with details of 200 bands resulting from the BDNF Val66Met variant. Agarose gel electrophoresis was used to analyze the BDNF Val66Met variant after PCR products were digested with the restriction enzyme. The 300 bp amplified product was digested with ten units (1 ml) of Eco72I (PmlI) restriction enzyme (recognition site;50-CACYGTG-30) (Thermo Scientific, USA). The reading of the results was carried out according to the study conducted by Al-Hatamleh et al. [18].

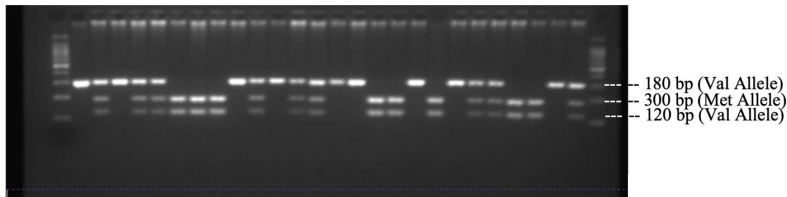


Figure 1. Agarose gel electrophoresis polymorphism BDNF Val66Met

Table 1 shows the demographic characteristics of median age values in the SP was 32 years. The median age value of healthy controls was 30 years old, with the youngest age of 20 and the oldest age of 40. For gender, it was found that the male sex from the SP group was 71% and healthy controls 65%. The onset of disease in the SP group had a median age of 27 years old, with the youngest age of 18 and the oldest at 37 years old. Duration of the disease in the SP group, a median of 5 years, was found.

Table 1.
Demographic Characteristics

Variable	Group	
	Schizophrenia Patients (n=100)	Healthy Control (n=100)
Age	32 (19-51)*	30 (20-40)*
Gender		
Man	71 (71%)	65 (65%)
Woman	29 (29%)	35 (35%)
Onset of disease	27 (18-37)*	
Duration of disease	5 (0-14)*	

* In Year

2. Comparison Allele Polymorphism BDNF Val66Met between SP and CO

BDNF Val 66 Met variant consists of two alleles, the Val and the Met alleles. Allele variables are categorical (nominal) variables, so data is presented with a frequency distribution.

There was no significant difference between the frequency of allele occurrence in the SP group and the control group ($p = 0.107$), OR 1.413 (0.951- 2.099) CI 95%.

Table 2. Comparison between Val 66Met BDNF polymorphism allele in SP and healthy controls

Variable	Group		P value	OR (CI 95%)
	Case (n=100)	Control (n=100)		
All BDNF Val66Met				
Val	189 (47,3%)	208 (52%)	0,107	1,413 (0,951-2,099)
WithMet	211 (52,8%)	192 (48%)		

3. Comparison between Genotype Polymorphism BDNF Val66Met in SP and Healthy Control

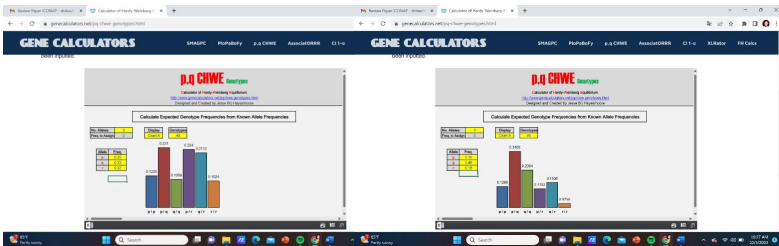
The BDNF Val 66 Met genotype variant is a combination of Val and Met alleles, consisting of the Val/Val, Val/Met, and Met /Met genotypes.

The results of this study showed no significant difference between genotype (Met / Met vs Val / Val) and genotype (Val / Met vs Val / Val) with a p-value of > 0.05 .

Table 3. Comparison between BDNF Val66Met polymorphism genotype in SP and healthy control

Variable	Group		P value	OR (95% CI)
	Case (n=100)	Control (n=100)		
Genotip BDNF Val66Met				
Met/Met	35 (35%)	36 (36%)	0,063	0,486 (0,227-1,039)
Val/Met	33 (33%)	48 (48%)	0,291	1,414 (0,744-3,689)
Val/Val	32 (32%)	16 (16%)		

Hardy-Weinberg Equilibrium for this study used Gene Calc (genecalculators.net/pq-chwe-genotypes.html)



These SP number is not the expectation of HWE because the area of this study is surrounded by many regencies, and the people may have migrated and been married to people of different tribes.

4. The results of this study showed a significant difference between SP and CO on the CM domain with a value of $p = <0.001$, OR value (CI 95%) = 5.096 (2.473-10.5). There is a significant difference between SP and CO on the FD domain with $p\text{-value} = <0.001$, OR

value (CI 95%) = 10.778 (3,135-37,054). There was no significant association between schizophrenia and domain VIO with a value of $p = 0.056$.

Table 4 Comparison between childhood trauma in SP and healthy controls

CM				
	Group		P value	OR (95% CI)
	With	Without		
Control	12 (12%)	88 (88%)	<0,001	5,096 (2,473-10,5)
Case	41 (41%)	59 (59%)		
FD				
	Group		P value	OR (95% CI)
	With	Without		
Control	3 (3%)	97 (97%)	<0,001	10,778 (3,135-37,054)
Case	25 (25%)	75 (75%)		
VIO				
	Group		P value	OR (95% CI)
	With	Without		
Control	2 (2%)	98 (98%)	0,056	4,846 (1,020-23,028)
Case	9 (9%)	91 (91%)		

4.8 this study showed no significant difference between genotype (Met/Met vs Val/Val) and genotype (Val /Met vs Val /Val) in the CM domain. There was no significant difference between genotype (Met/Met vs Val/Val) and genotype (Val/Met vs Val /Val) in the FD domain. There was no significant difference between genotype (Met/Met vs Val/Val) and genotype (Val/Met vs Val /Val) in domain VIO. Table 4.8. Comparison between BDNF Val66Met polymorphism genotype and incidence of childhood trauma in SP and healthy controls.

CM				
Variable	With	Without	P value	OR (95% CI)
Genotype Val66Met	BDNF			
Met/Met	16 (33,3%)	32 (66,7%)	0,346	1,472 (0,659-3,289)
Val/Met	19 (23,5%)	62 (76,5%)	0,786	0,679 (0,430-1,894)
Val/Val	18 (25,4%)	53 (74,6,4%)		
FD				

Variable Genotip	With	Without	P value	OR (95% CI)
Val66Met	BDNF			
Met/Met	8 (16,7%)	40 (83,3%)	0,973	0,983 (0.369-2,521)
Val/Met	9 (11,1%)	72 (88,9%)	0,615	0,613 (0,242-1,558)
Val/Val	12 (16,9%)	59 (83,1%)		
VIO	BDNF			
Variable Genotip	With	Without	P value	OR (95% CI)
Val66Met	BDNF			
Met/Met	4 (8,3%)	44 (91,7%)	0,566	1,523 (0.362-6,409)
Val/Met	3 (3,7%)	78 (96,3%)	0,274	0,644 (0,139-2,982)
Val/Val	4 (5,6%)	67 (94,4%)		

Discussion

The median age in the SP group was 32 years. This finding aligns with the results of Charlson et al.'s 2018 study titled "Global Epidemiology and Burden of Schizophrenia", which reported the prevalence of schizophrenia globally. The median age value of healthy controls was 30 years, with the youngest age of 20 years and the oldest age of 40 years. The finding in the gender group was found that the male sex from the SP group was 71% and healthy controls 65%. The onset of disease in the SP group had a median age of 27 years, with the youngest age of 18 and the oldest at 37 years. Duration of the disease in the SP group, a median of 5 years, was found [19] – [22], [20] – [23].

This study is reinforced by another study stating that the morbidity risk of schizophrenia is 1%, and there is no difference in prevalence between the sexes. However, the probability of incidence of schizophrenia is indeed higher in males. The research conducted by Sanchez et al. found that the prevalence of schizophrenia in men reached 64.3%, almost twice as high as in women at 35.7%. The prevalence of schizophrenia in men was also higher in all age groups studied. This difference may be due to differences in sampling, particularly in terms of sex, where there were more male than female participants in the study, as well as differences in samples that may affect results. Besides that, there was an association between age and BDNF level, in which BDNF level decreases with age [19] – [22].

There were no variations in the alleles and genotypes of BDNF Val66Met between the SP and CO groups. These findings are consistent with previous research in China, which demonstrated no significant connection between the BDNF Val66Met polymorphism allele in the ODS and the control groups. Yi Z et al. found no link between the Val 66 Met BDNF polymorphism allele with ODS or control groups. Furthermore, the study found that the polymorphism was substantially linked with age and onset in male patients but not in female patients [22], [23].

The study differs from studies conducted in Scottish populations, which found an association between the BDNF Val66Met allele in the ODS and healthy control groups. This study found that the Val allele had a significant association with the ODS group and healthy controls. The method used to measure BDNF expression or activity or identify the Val 66Met BDNF allele may vary between studies. This can affect the accuracy of the results and the interpretation of the study [23], [24].

This study supports the findings of Tan YL et al., who discovered no link between the genotype of the BDNF Val66Met polymorphism in ODS and healthy controls. 36.38 This study is further confirmed by analytical investigations of Met, which show no connection between the BDNF Val66Met polymorphism in ODS and healthy controls in Asian populations [24] – [27].

This study contradicts prior findings that the Met/Met genotype was associated with a 19% greater risk of schizophrenia when compared to Val/Met. Environmental factors, other genetic factors, or factors that alter BDNF expression or activity, for example, may be confounding factors that influence the link between Val 66 Met's BDNF genotype and schizophrenia [27], [28].

This study found a significant association between childhood trauma and schizophrenia in the CM and FD domains. In contrast, in the VIO domain, no relationship was found between the two groups of study samples. The findings align with Popovic D's research that found a link between childhood trauma and schizophrenia and is supported by research conducted in Canada. Working memory, executive function, language learning, and attention are all impaired in schizophrenic individuals with a history of childhood trauma. Furthermore, more intense positive symptoms, generalized symptoms, and depressed symptoms, as well as poorer cognitive performance on executive function and the visual end of episodic memory, were associated with greater rates of childhood trauma [28] – [30].

Differences in research results on the relationship between the incidence of childhood trauma and schizophrenia can be caused by factors such as differences in criteria and methods used to diagnose schizophrenia, differences in inclusion and exclusion criteria in sample selection, differences in sample size, differences in definition and measurement of childhood trauma, differences in other uncontrolled risk factors in statistical analysis, and genetic and environmental differences among populations researched. In addition, the use of different measuring instruments to measure schizophrenia symptoms and severity can also affect the results of the study. Therefore, broader research is needed to reveal a more transparent relationship between the incidence of childhood trauma and the risk of schizophrenia.

The findings of this investigation revealed that there was no link between the genotype of the BDNF Val66Met polymorphism and the occurrence of childhood trauma. This outcome is consistent with the findings of a comparable study conducted in Germany, which found no link between the BDNF Val66Met polymorphism genotype and the occurrence of childhood trauma [13], [30] – [32]. Genetic variants, environmental factors and cultural factors at each study site significantly impact these disparities.

Conclusions

There was no difference between allele and genotype polymorphism BDNF Val66Met between SP and healthy controls. A significant difference between CM and FD, domain childhood trauma, exists between SP and healthy controls. There was no association between BDNF Val66Met polymorphism and childhood trauma in SP and control.

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