Original Article

Association of *BDNF* Val66Met polymorphism with clinical severity, cognitive function, and treatment response in schizophrenia

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Abstract

The brain-derived neurotrophic factor gene (*BDNF*) Val66Met polymorphism has been implicated in neuroplasticity, cognitive performance, and variability in antipsychotic treatment response. However, evidence from Indonesian populations, particularly among individuals with schizophrenia from Aceh, remains limited. The aim of this study was to assess the association of *BDNF* Val66Met polymorphism with clinical symptom severity and cognitive function and to determine its association with clinical and cognitive outcomes after antipsychotic treatment. A prospective cohort study was conducted among Acehnese individuals with schizophrenia. Genotyping was performed using polymerase chain reaction–restriction fragment length polymorphism. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), and cognitive function was assessed using the Montreal Cognitive Assessment–Indonesian version (MoCA-INA) at Day 0, Day 14, and Day 42 post-therapy. Genotype–outcome associations were examined using genotype comparisons and genetic models. A total of 207 individuals with schizophrenia were analyzed. The Val/Met genotype was the most frequent genotype (52.2%), followed by Val/Val (28.0%) and Met/Met (19.8%). Baseline PANSS total score was significantly different across all genetic models, with the lowest symptom severity observed in the Val/Val group. In the dominant model, Met-allele carriers had higher PANSS total scores than Val/Val individuals ($p<0.001$). Baseline cognitive function also differed significantly, with Met-allele carriers showing lower MoCA-INA scores than Val/Val individuals ($p<0.001$). Clinical symptom improvement was consistently greater in Val/Val individuals, whereas Met-allele carriage was associated with smaller PANSS reductions at Day 14 and Day 42. For cognitive outcomes, Val/Val participants showed the greatest early improvement, while Met-allele carriers demonstrated slower initial recovery followed by later gains, resulting in more comparable cognitive improvement by Day 42 in some models. In conclusion, *BDNF* Val66Met polymorphism was significantly associated with clinical symptom severity, cognitive function, and treatment-related improvement among Acehnese individuals with schizophrenia. The Val/Val genotype was associated with a more favorable clinical and cognitive profile and stronger early clinical and cognitive response. These findings support the potential relevance of *BDNF* Val66Met as a population-specific biomarker for clinical stratification in schizophrenia, although further studies with longer follow-up and biological validation are warranted.

Keywords: Schizophrenia, *BDNF* Val66Met, cognitive impairment, PANSS, MoCA-INA

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Introduction

Schizophrenia is a chronic and disabling psychiatric disorder characterized by disturbances in thought, perception, affect, cognition, and behavior. It affects approximately 0.3–0.7% of the global population and remains a major contributor to disability worldwide [1,2]. According to the 2019 Global Burden of Disease study, schizophrenia is among the leading causes of disability-adjusted life years (DALYs) related to mental disorders, with a substantial burden in low- and middle-income countries where access to specialized psychiatric care is often limited [1]. In Indonesia, the prevalence of schizophrenia has been estimated at 6.7 per 1,000 households, with Aceh Province reporting a higher prevalence of 8.7 per 1,000 households [3,4]. This regional burden, together with the increasing recognition of schizophrenia as a long-term public health problem, highlights the need to better understand biological factors that may influence clinical severity, cognitive impairment, and treatment response among patients with schizophrenia.

Schizophrenia is widely considered a multifactorial disorder involving complex interactions between genetic vulnerability, neurodevelopmental alterations, and environmental exposures. Among the candidate biological pathways implicated in schizophrenia, brain-derived neurotrophic factor (BDNF) has received considerable attention because of its critical role in neuronal survival, differentiation, synaptic plasticity, learning, memory, and higher cognitive function [5]. Altered BDNF expression has been associated with impaired neuroplasticity, cognitive dysfunction, and variation in clinical symptom severity in schizophrenia [6,7]. One of the most extensively studied functional variants in the *BDNF* gene is the Val66Met polymorphism, also known as rs6265. This single-nucleotide polymorphism results in a substitution of valine (Val) with methionine (Met) at codon 66 and has been shown to disrupt activity-dependent BDNF secretion, thereby affecting hippocampal and prefrontal cortical circuits involved in cognition and emotional regulation [5,6]. Previous studies have linked this variant to smaller hippocampal volume, poorer episodic memory, reduced executive function, and variability in clinical presentation [6,8], although the direction and magnitude of these associations have varied across populations [9-11].

Beyond its potential role in schizophrenia susceptibility and clinical phenotype, the *BDNF* Val66Met polymorphism may also influence treatment-related outcomes. Patients with schizophrenia have been reported to have reduced circulating BDNF levels, and changes in BDNF levels may occur during antipsychotic treatment [12,13]. Early increases in serum BDNF levels during risperidone treatment have also been associated with short-term clinical improvement in first-episode schizophrenia [14]. However, evidence from systematic reviews and meta-analyses remains heterogeneous, suggesting that BDNF and the Val66Met polymorphism may act as modifiers of treatment response rather than deterministic predictors [13,15]. Pharmacological treatment of schizophrenia commonly involves second-generation antipsychotics such as risperidone [16], sometimes accompanied by short-term benzodiazepine use for agitation, anxiety, or sleep-related symptoms [17]. Despite relatively standardized treatment strategies, substantial inter-individual variability in symptom improvement and cognitive recovery persists, supporting the need to explore pharmacogenetic markers that may help explain differences in clinical response [18].

Cognitive impairment is a core manifestation of schizophrenia and is strongly associated with functional disability, poor social recovery, and reduced quality of life. A growing body of evidence has examined the relationship between *BDNF* Val66Met polymorphism and cognitive function in schizophrenia [18]. Met-allele carriers, particularly individuals with the Met/Met genotype, may have poorer cognitive performance, lower serum BDNF levels, and impaired synaptic plasticity [18]. Other evidence suggests that Val66Met polymorphism may interact with neurophysiological markers such as mismatch negativity and N-methyl-D-aspartate receptor-dependent mechanisms involved in working memory capacity [19]. However, findings remain inconsistent, and relatively few studies have examined clinical symptoms, cognitive function, and treatment-related changes within the same cohort [20]. Integrated analyses are therefore needed to clarify whether Val66Met polymorphism is associated not only with baseline clinical and cognitive profiles but also with early improvement after antipsychotic treatment.

Despite increasing global evidence, data from Indonesia remain limited, particularly among genetically diverse populations such as the Acehnese. The Acehnese population has a distinct geographic, historical, and genetic background that may influence genetic variability and disease expression. Located at the westernmost part of Indonesia, Aceh has historically been exposed to population interactions through regional migration and maritime trade, which may have shaped genetic patterns that differ from those of other Indonesian populations. A previous Indonesian study from East Java reported genotype-specific differences in schizophrenia symptom domains, but the sample size was limited and cognitive outcomes were not comprehensively evaluated [21]. Therefore, further population-specific studies are needed to determine whether the *BDNF* Val66Met polymorphism is associated with clinical and cognitive outcomes in Indonesian patients with schizophrenia, especially in regions where local genetic backgrounds may differ from those of previously studied populations. The aim of this study was to examine the role of the *BDNF* Val66Met polymorphism in schizophrenia among individuals from the Acehnese population. Specifically, this study assessed: (1) the genotypic distribution of *BDNF* Val66Met polymorphism; (2) its association with clinical symptom severity and cognitive function; and (3) its influence on clinical and cognitive improvement after antipsychotic treatment. The findings are expected to provide population-specific evidence on the clinical relevance of this polymorphism in schizophrenia and to support further development of precision psychiatry approaches in Indonesia.

Methods

Study design and setting

A prospective cohort study was conducted at Aceh Mental Hospital, Banda Aceh, Indonesia, in 2025. Aceh Mental Hospital is the main psychiatric referral hospital in Aceh Province and provides specialist mental health services for patients from urban and rural districts across the region. This setting enabled recruitment of clinically diagnosed patients with schizophrenia from a population with relatively specific ethnic and geographic characteristics. The study focused on Acehnese individuals to reduce potential population stratification in the genetic analysis and to provide population-specific evidence.

The study was designed to evaluate the association of *BDNF* Val66Met polymorphism with clinical symptom severity, cognitive function, and short-term response to antipsychotic therapy among individuals with schizophrenia from the Acehnese population. Clinical and cognitive outcomes were assessed longitudinally at three time points: baseline assessment on Day 0 (before treatment initiation), on Day 14 (early treatment phase), and after 42 days of therapy. The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians before enrolment and data collection.

Participants and criteria

Participants were recruited from individuals with schizophrenia who were receiving inpatient or outpatient care at Aceh Mental Hospital. Eligible participants were Acehnese aged 18–45 years who had been clinically diagnosed with schizophrenia by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the International Classification of Diseases, Tenth Revision (ICD-10), or the Indonesian *Pedoman Penggolongan dan Diagnosis Gangguan Jiwa III* (PPDGJ-III). Participants were required to have recurrent schizophrenia, have a medication-free interval of at least two weeks before enrolment, and plan for treatment with risperidone with adjunctive anxiolytic therapy.

Patients were excluded if they had a history of major neurological disorders, including epilepsy, stroke, or neurodegenerative disease; clinically relevant sensory impairment that could interfere with assessment; severe systemic illness that could confound psychiatric or genetic findings; intellectual disability likely to compromise cognitive testing; comorbid with major psychiatric disorders including bipolar disorder or major depressive disorder; current substance use disorder other than nicotine use; or pregnancy and breastfeeding.

Sample size and sampling method

The minimum sample size was estimated based on expected differences in *BDNF* Val66Met genotype distribution and allele frequency patterns reported in Asian populations with schizophrenia [22,23]. The calculation indicated that a minimum of 90 participants were required to provide adequate statistical power to detect genotype-related differences in clinical and cognitive outcomes. The minimal sample size was increased to enhance the robustness of the analysis and to allow comparisons across different genetic inheritance models, resulting in a final analytical sample of 207 participants.

Participants were selected using a consecutive sampling method. All patients with schizophrenia who attended or were admitted to Aceh Mental Hospital were screened for eligibility. Those who fulfilled the inclusion criteria, had no exclusion criteria, and provided written informed consent, either personally or through their legal guardian, were recruited.

Study variables

The main independent variable was the *BDNF* Val66Met polymorphism, and its genotypes are classified as Val/Val, Val/Met, and Met/Met. The genotype data were also analyzed to examine the consistency of genotype–outcome associations under different inheritance assumptions using five genetic models: dominant model (Met/Met + Val/Met vs Val/Val), recessive model (Met/Met vs Val/Met + Val/Val), heterozygous model (Val/Met vs Val/Val), homozygous model (Met/Met vs Val/Val), and allelic model (Met vs Val).

Clinical symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS), a clinician-rated instrument for evaluating symptom burden in schizophrenia [24]. The PANSS consists of 30 items assessing three domains: positive symptoms, negative symptoms, and general psychopathology. Each PANSS item is scored from 1 to 7, where 1 indicates absent symptoms and 7 indicates extreme symptom severity. The positive and negative subscale scores each range from 7 to 49, while the general psychopathology subscale ranges from 16 to 112. The total PANSS score was calculated by summing all 30 items and ranged from 30 to 210, with higher scores indicating more severe clinical symptoms [25].

Cognitive function was assessed using the Montreal Cognitive Assessment–Indonesian version (MoCA-INA) [26,27]. The MoCA-INA evaluates global cognitive performance across several domains, including visuospatial and executive function, naming, attention, language, abstraction, delayed recall, and orientation. The total score ranges from 0 to 30, with higher scores indicating better cognitive performance. MoCA remains among the most accessible and scalable cognitive screening instruments in resource-limited settings [28].

Other variables such as age, sex, educational attainment, occupation, and duration of illness were also collected. These variables were collected through structured interviews and medical record review and were used to assess baseline comparability across genotype groups.

Treatments

All participants received a standardized antipsychotic treatment regimen during the 42-day follow-up period. Risperidone was used as the primary antipsychotic therapy at a therapeutic dose of 1–2 mg/day, initiated after baseline assessment, and adjusted according to clinical response and tolerability to 1–4 mg/day. Adjunctive anxiolytic therapy with benzodiazepines was permitted at a dose of 2–6 mg/day to manage agitation, anxiety, or sleep-related symptoms when clinically indicated. The concomitant use of other antipsychotics or mood stabilizers was not permitted to minimize treatment-related confounding during the study period.

Study outcomes

The study had two main outcomes: clinical symptom improvement and cognitive function improvement after treatment. Both outcomes were assessed using change scores from baseline to follow-up, including Day 14 vs Day 0, Day 42 vs Day 0, and Day 42 vs Day 14. Clinical symptom improvement was defined as a reduction in PANSS scores, with larger reductions indicating greater improvement. Cognitive function improvement was defined as an increase in MoCA-INA scores, with higher positive changes indicating greater cognitive recovery. Both outcomes were compared across the three genotype groups and across the dominant, recessive, heterozygous, homozygous, and allelic genetic models.

Study procedures

Potential participants were screened among individuals with schizophrenia receiving care at Aceh Mental Hospital during the study period. After eligibility confirmation, written informed consent was obtained. At baseline, demographic and clinical information were collected through structured interviews and review of medical records. These data included age, sex, educational attainment, occupation, and duration of illness. Clinical symptom severity was assessed using the PANSS, and cognitive function was evaluated using the MoCA-INA before treatment initiation on Day 0. Peripheral venous blood was collected for *BDNF* Val66Met genotyping; genomic DNA was extracted from blood samples and analyzed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP).

After baseline assessment, participants received standardized treatment with risperidone, with adjunctive benzodiazepines when clinically indicated. Follow-up assessments were conducted on Day 14 and Day 42 using the same clinical and cognitive instruments. PANSS scores were used to quantify clinical symptom improvement, while MoCA-INA scores were used to quantify cognitive function improvement. Changes were calculated for Day 14 vs Day 0, Day 42 vs Day 0, and Day 42 vs Day 14. Clinical and cognitive assessments were performed to reduce measurement variability by trained clinicians using standardized procedures.

BDNF Val66Met polymorphism genotyping

The *BDNF* Val66Met polymorphism was determined using PCR-RFLP. Briefly, peripheral venous blood was collected from each participant into EDTA-containing tubes and processed for DNA extraction. Genomic DNA was isolated from the buffy coat fraction using the Wizard Genomic DNA Purification Kit according to the manufacturer's protocol (Promega, Madison, WI, USA). Extracted DNA was stored at −20°C until further molecular analysis. The *BDNF* Val66Met polymorphism was amplified using specific primers: forward 5′-ATCCGAGGACAAGGTGGC-3′ and reverse 5′-CCTCATGGACATGTTTGCAG-3′. PCR amplification generated a 300-bp product, which was subsequently digested using the *Eco72I/PmlI* restriction enzymes (Thermo Scientific, Waltham, MA, USA). The digested products were separated by electrophoresis on a 2% agarose gel stained with GelRed (Biotium, Fremont, CA, USA) and visualized under ultraviolet illumination. Genotypes were determined according to the restriction fragment pattern and classified as Val/Val, Val/Met, or Met/Met.

Statistical analysis

The distribution of numerical variables was assessed using the Kolmogorov–Smirnov test. Baseline demographic and clinical characteristics were compared across genotype groups (Val/Val, Val/Met, and Met/Met) using the chi-squared test, independent-sample t-test, or Mann–Whitney U test, as appropriate. The independent-sample t-test was used to compare baseline clinical symptom severity (assessed using PANSS total score) and baseline cognitive function (assessed using MoCA-INA score) across *BDNF* Val66Met genetic models. Linear regression analysis was used to assess the association between *BDNF* Val66Met genetic models and baseline PANSS total score and MoCA-INA score. Regression coefficients (B), standard errors (SE), 95% confidence intervals (95%CIs), *p*-values, and adjusted R^2 values were reported. An independent-sample t-test was used to compare clinical symptom improvement and cognitive function improvement across *BDNF* Val66Met genetic models. Improvements were assessed using delta of PANSS total scores and MoCA-INA scores for Day 14 vs Day 0, Day 42 vs Day 0, and Day 42 vs Day 14. A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 31.0 (IBM Corp., Armonk, NY, USA).

Results

Participant characteristics and genotypic distribution of *BDNF* Val66Met polymorphism

A total of 207 individuals with schizophrenia were included in the analysis. The most frequent genotype was Val/Met, observed in 108 participants (52.2%), followed by Val/Val in 58 (28.0%) and Met/Met in 41 (19.8%) (**Table 1**). The baseline demographic and clinical characteristics were

generally comparable across genotype groups (**Table 1**). Mean age did not differ significantly between groups, and the duration of illness was also similar across genotypes. Most participants in each genotype group were male, had primary-level education, and were unemployed, reflecting the substantial functional burden in this schizophrenia cohort. No statistically significant differences were observed across genotype groups for age (p=0.463), sex (p=0.133), duration of illness (p=0.084), education (p=0.837), and occupation (p=0.699) (**Table 1**).

Table 1. Baseline demographic and clinical characteristics of individuals with schizophrenia across *BDNF* Val66Met genotypes (n=207)

Characteristics	*BDNF* Val66Met polymorphism genotypes			*p*-value
	Val/Val (n=58)	Val/Met (n=108)	Met/Met (n=41)	
	n (%)	n (%)	n (%)	
Age (years), mean±SD	35.63±6.60	34.20±6.72	35.09±6.33	0.463[a]
Sex				0.133[b]
Male	50 (86.2)	93 (86.1)	30 (73.2)	
Female	8 (13.8)	15 (13.9)	11 (26.8)	
Duration of illness (years), median (min–max)	6 (2–10)	7 (3–15)	6 (3–10)	0.084[c]
Education				0.837[b]
Primary school	35 (60.3)	70 (64.8)	24 (58.5)	
Junior high school	8 (13.8)	8 (7.4)	5 (12.2)	
Senior high school	14 (24.1)	30 (27.8)	12 (29.3)	
University (Bachelor's degree)	1 (1.7)	0 (0.0)	0 (0.0)	
Occupation				0.699[b]
Farmer	1 (1.7)	7 (6.5)	0 (0.0)	
Private employee	1 (1.7)	2 (1.9)	2 (4.9)	
Housewife	1 (1.7)	0 (0.0)	0 (0.0)	
Student	1 (1.7)	1 (0.9)	0 (0.0)	
Unemployed	54 (93.1)	98 (90.7)	39 (95.1)	

[a] Analyzed with independent-sample t-test
[b] Analyzed with chi-squared test
[c] Analyzed with the Mann-Whitney test

Comparison of baseline symptom severity across *BDNF* Val66Met polymorphism genetic models

Baseline symptom severity across *BDNF* Val66Met polymorphism genetic models is presented in **Table 2**. PANSS total score was significantly different across all genetic models. In the dominant model, participants carrying the Met allele had higher PANSS total scores than those with the Val/Val genotype (184.38±8.04 vs 160.24±0.62; p<0.001). In the recessive model, PANSS total score was also significantly different between the Met/Met genotype and the combined Val/Val + Val/Met group (173.24±3.34 vs 178.69±14.03; p<0.001), although the higher symptom burden was observed in the combined Val/Val + Val/Met group rather than in the Met/Met group alone. Genotype-specific comparisons showed that both Val/Met and Met/Met genotypes had significantly higher PANSS total scores than the Val/Val genotype (**Table 2**). The Val/Met genotype had the highest PANSS total score, followed by Met/Met and Val/Val. In the allele model, the Met allele was associated with a higher PANSS total score than the Val allele (181.97±8.60 vs 173.91±14.54; p<0.001) (**Table 2**).

Table 2. Comparisons of clinical symptom severity, assessed using PANSS total score, according to *BDNF* Val66Met polymorphism (n=207)

Genotype and allele models	PANSS total score	*p*-value[a]
	Mean±SD	
Dominant model		<0.001
Met/Met + Val/Met, n=149	184.38±8.04	
Val/Val, n=58	160.24±0.62	
Recessive model		<0.001
Met/Met, n=41	173.24±3.34	
Val/Met + Val/Val, n=166	178.69±14.03	
Heterozygous		<0.001
Val/Met, n=108	188.61±4.43	
Val/Val, n=58	160.24±0.62	
Homozygous model		<0.001

Genotype and allele models	PANSS total score	*p*-value[a]
	Mean±SD	
Met/Met, n=41	173.24±3.34	
Val/Val, n=58	160.24±0.62	
Allele model		<0.001
Met, n=190	181.97±8.6	
Val, n=224	173.91±14.54	

[a] Analyzed with independent-sample t-test

Association between *BDNF* Val66Met polymorphism and baseline clinical symptom severity

Linear regression analyses confirmed significant associations between *BDNF* Val66Met polymorphism genetic models and baseline clinical symptom severity (**Table 3**). In the dominant model, Met-allele carriers had a 24.14-point higher PANSS total score than individuals with the Val/Val genotype (95%CI: 22.05–26.22; $p<0.001$; adjusted $R^2=0.716$). The recessive model also showed a significant association, although the explained variance was small (B=5.45; 95%CI: 1.09–9.81; $p=0.014$; adjusted $R^2=0.024$). In genotype-specific models, both heterozygous and homozygous comparisons were significantly associated with baseline PANSS total score. The heterozygous model showed the strongest model fit (adjusted $R^2=0.934$), followed by the homozygous model (adjusted $R^2=0.895$), indicating that Val/Met and Met/Met comparisons against Val/Val explained a substantial proportion of variation in baseline symptom severity. In the allele model, the Met allele was associated with an 8.05-point higher PANSS total score than the Val allele (95%CI: 5.69–10.42; $p<0.001$; adjusted $R^2=0.096$). These findings indicate that *BDNF* Val66Met was significantly associated with baseline clinical symptom severity, with the strongest explanatory patterns observed in the genotype-specific models (**Table 3**).

Table 3. Association between *BDNF* Val66Met polymorphism genetic models and baseline clinical symptom severity, assessed with PANSS total score

Genotype and allele models	B	SE	B (95%CI)	*p*-value [a]
Dominant model (Met/Met + Val/Met vs Val/Val), $aR^2=0.716$	24.14	1.05	22.05, 26.22	<0.001
Recessive model (Met/Met vs Val/Met + Val/Val), $aR^2=0.024$	5.45	2.21	1.09, 9.81	0.014
Heterozygous (Val/Met vs Val/Val), $aR^2=0.934$	-14.18	0.29	-14.76, -13.6	<0.001
Homozygous model (Met/Met vs Val/Val), $aR^2=0.895$	-13.00	0.44	-13.89, -12.11	<0.001
Allele model (Met vs Val), $aR^2=0.096$	8.05	1.20	5.69, 10.42	<0.001

aR^2: adjusted R-squared; B: unstandardized regression coefficient; PANSS: Positive and Negative Syndrome Scale; SE: standard error; 95%CI: 95% confidence interval
[a] Analyzed with a linear regression

Association between *BDNF* Val66Met polymorphism and clinical symptom improvement

Clinical symptom improvement after treatment, assessed using changes in PANSS total score, is presented in **Table 4**. Across all *BDNF* Val66Met polymorphism genetic models, the magnitude of PANSS reduction differed significantly at Day 14 vs Day 0, Day 42 vs Day 0, and Day 42 vs Day 14 ($p<0.001$ for all comparisons). In the dominant model, participants carrying the Met allele had smaller reductions in PANSS total score than those with the Val/Val genotype at Day 14 vs Day 0 (24.66±4.28 vs 51.24±0.62), Day 42 vs Day 0 (69.10±11.65 vs 110.24±0.62), and Day 42 vs Day 14 (44.43±9.24 vs 59.00±0.03) (**Table 4**). In the recessive model, participants with the Met/Met genotype also showed less improvement than the combined Val/Met + Val/Val group across all intervals, with the largest difference observed at Day 42 vs Day 0 (**Table 4**).

Genotype-specific comparisons showed a consistent pattern. The Val/Met group had smaller PANSS reductions than the Val/Val group at Day 14 vs Day 0, Day 42 vs Day 0, and Day 42 vs Day 14 (**Table 4**). Similarly, in the homozygous model, participants with the Met/Met genotype showed markedly smaller reductions than those with the Val/Val genotype, particularly at Day 42 vs Day 0 (51.80±5.08 vs 110.24±0.62). In the allele model, the Met allele was consistently associated with smaller PANSS reductions than the Val allele at all time intervals. These findings indicate that clinical symptom improvement was greatest among Val/Val participants, whereas Met-allele carriage was associated with weaker improvement during the 42-day treatment period (**Table 4**).

Table 4. Improvement in clinical symptom severity after treatment, assessed using delta of PANSS total score, according to *BDNF* Val66Met polymorphism genetic models

Genotype and allele models	Day 14 vs Day 0		Day 42 vs Day 0		Day 42 vs Day 14	
	PANSS total score Δ Mean±SD	*p*-value[a]	PANSS total score Δ Mean±SD	*p*-value[a]	PANSS total score Δ Mean±SD	*p*-value[a]
Dominant model		<0.001		<0.001		<0.001
Met/Met + Val/Met, n=149	24.66±4.28		69.10±11.65		44.43±9.24	
Val/Val, n=58	51.24±0.62		110.24±0.62		59.00±0.03	
Recessive model		<0.001		<0.001		<0.001
Met/Met, n=41	22.02±2.09		51.80±5.08		29.78±3.57	
Val/Met + Val/Val, n=166	34.60±12.75		87.74±16.92		53.14±4.3	
Heterozygous		<0.001		<0.001		<0.001
Val/Met, n=108	25.66±4.47		75.66±4.47		50.00±0.02	
Val/Val, n=58	51.24±0.62		110.24±0.62		59.00±0.01	
Homozygous model		<0.001		<0.001		<0.001
Met/Met, n=41	22.02±2.09		51.80±5.08		29.78±3.57	
Val/Val, n=58	51.24±0.62		110.24±0.62		59.00±0.01	
Allele models		<0.001		<0.001		<0.001
Met, n=190	24.09±4.05		65.36±12.75		41.27±10.30	
Val, n=224	38.91±18.18		93.57±17.56		54.66±4.50	

PANSS: Positive and Negative Syndrome Scale
[a] Analyzed with independent-sample t-test

Clinical symptom improvement across PANSS domains according to *BDNF* Val66Met polymorphism

Reductions in PANSS scores across all domains according to *BDNF* Val66Met polymorphism are illustrated in **Figure 1**, highlighting the aspects of clinical symptoms that showed the greatest improvement. Overall, the Val/Val group showed the most consistent improvement across negative symptoms, positive symptoms, and general psychopathology, particularly by Day 42. For negative symptoms, the Val/Val group had the lowest baseline score and showed progressive reductions during follow-up, whereas Val/Met and Met/Met participants had higher baseline scores and smaller reductions. For positive symptoms, baseline scores were relatively similar across genotypes, but the greatest decline was observed in the Val/Val group and the smallest in the Met/Met group. For general psychopathology, the Val/Met group had the highest baseline score, but improvement was again greatest in the Val/Val group (**Figure 1**). These findings indicate that Val/Val was associated with more favorable PANSS domain improvement, while Met-allele carriers showed weaker improvement, especially in negative symptoms and general psychopathology.

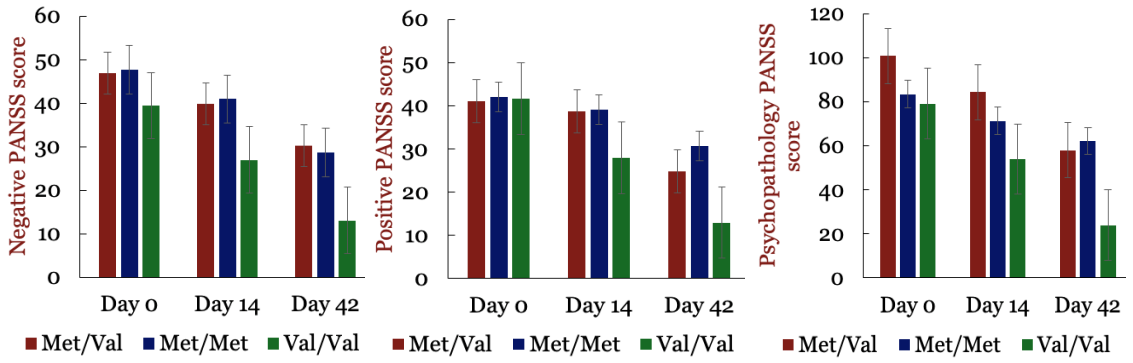

Figure 1. Changes in PANSS domain scores (negative symptoms, positive symptoms, and general psychopathology) from baseline to Day 14 and Day 42 according to *BDNF* Val66Met polymorphism genotypes among individuals with schizophrenia.

Comparison of baseline cognitive function across *BDNF* Val66Met polymorphism genetic models

Baseline cognitive function across *BDNF* Val66Met polymorphism genetic models is presented in **Table 5**. Data indicated that MoCA-INA scores were significantly different across all genetic models. In the dominant model, participants carrying the Met allele had lower MoCA-INA scores than those with the Val/Val genotype (12.68±2.19 vs 16.06±0.97; $p<0.001$), indicating poorer baseline cognitive function among Met-allele carriers. In the recessive model, participants with the Met/Met genotype had substantially lower MoCA-INA scores than the combined Val/Met + Val/Val group (9.75±1.44 vs 14.59±1.54; $p<0.001$) (**Table 5**). Genotype-specific comparisons showed that both Val/Met and Met/Met genotypes had lower MoCA-INA scores than the Val/Val genotype. The lowest cognitive score was observed in the Met/Met group, followed by Val/Met and Val/Val. In the allele model, the Met allele was associated with a lower MoCA-INA score than the Val allele (12.05±2.38 vs 14.97±1.55; $p<0.001$) (**Table 5**). These findings indicate that baseline cognitive function varied significantly according to *BDNF* Val66Met genetic models, with poorer cognitive performance consistently observed among participants carrying the Met allele, particularly those with the Met/Met genotype.

Table 5. Comparisons of baseline cognitive function, assessed using MoCA-INA score, according to *BDNF* Val66Met polymorphism (n=207)

Genotype and allele models	MoCA-INA scores Mean±SD	*p*-value[a]
Dominant model		<0.001
Met/Met + Val/Met, n=149	12.68±2.19	
Val/Val, n=58	16.06±0.97	
Recessive model		<0.001
Met/Met, n=41	9.75±1.44	
Val/Met + Val/Val, n=166	14.59±1.54	

Genotype and allele models	MoCA-INA scores Mean±SD	*p*-value[a]
Heterozygous		<0.001
Val/Met, n=108	13.79±1.15	
Val/Val, n=58	15.09±0.97	
Homozygous model		<0.001
Met/Met, n=41	9.75±1.44	
Val/Val, n=58	15.09±0.97	
Allele models		<0.001
Met, n=190	12.05±2.38	
Val, n=224	14.97±1.55	

MoCA-INA: Montreal Cognitive Assessment–Indonesian version
[a] Analyzed with independent-sample t-test

Association between *BDNF* Val66Met polymorphism and baseline cognitive function

Linear regression analyses confirmed significant associations between *BDNF* Val66Met polymorphism genetic models and baseline cognitive function, assessed using MoCA-INA score (**Table 6**). In the dominant model, Met-allele carriers had a 3.38-point lower MoCA-INA score than individuals with the Val/Val genotype (95%CI: −3.97 to −2.79; $p<0.001$), indicating poorer baseline cognitive function among participants carrying the Met allele. The recessive model also showed a significant association with baseline MoCA-INA score, with a 4.83-point difference between the Met/Met genotype and the combined Val/Met + Val/Val group (95%CI: 4.31–5.35; $p<0.001$). This finding is consistent with the markedly lower baseline cognitive performance observed in participants with the Met/Met genotype. In genotype-specific models, both heterozygous and homozygous comparisons were significantly associated with baseline MoCA-INA score.

The homozygous model showed the strongest model fit (adjusted $R^2=0.873$), followed by the recessive model, suggesting that Met/Met homozygosity explained a substantial proportion of variation in baseline cognitive function (**Table 6**). In the allele model, the Met allele was associated with a 2.92-point lower MoCA-INA score than the Val allele (95%CI: −3.31 to −2.54; $p<0.001$). These findings indicate that *BDNF* Val66Met genetic models were significantly associated with baseline cognitive function, with the strongest cognitive impairment observed among participants with the Met/Met genotype and among Met-allele carriers more broadly (**Table 6**).

Table 6. Association between *BDNF Val66Met* polymorphism genetic models and baseline cognitive function, assessed with MoCA-INA score

Genotype and allele models	B	SE	B (95%CI)	*p*-value [a]
Dominant model (Met/Met + Val/Met vs Val/Val), $aR^2=0.381$	-3.38	0.29	-3.97, -2.79	<0.001
Recessive model (Met/Met vs Val/Met + Val/Val), $aR^2=0.616$	4.83	0.26	4.31, 5.35	<0.001
Heterozygous (Val/Met vs Val/Val), $aR^2=0.494$	0.43	0.03	0.37, 0.51	<0.001
Homozygous model (Met/Met vs Val/Val), $aR^2=0.873$	0.13	0.01	0.12, 0.14	<0.001
Allele model (Met vs Val), $aR^2=0.351$	-2.92	0.19	-3.31, -2.54	<0.001

aR^2: adjusted R-squared; B: unstandardized regression coefficient; MoCA-INA: Montreal Cognitive Assessment–Indonesian version; SE: standard error; 95%CI: 95% confidence interval
[a] Analyzed with linear regression

Association between *BDNF* Val66Met polymorphism and cognitive function improvement

Cognitive function improvement after treatment, assessed using changes in MoCA-INA score, is presented in **Table 7**. At Day 14 vs Day 0, MoCA-INA score improvement was significantly different across all *BDNF* Val66Met polymorphism genetic models ($p<0.001$ for all comparisons). In the dominant model, participants carrying the Met allele had smaller increases in MoCA-INA score than those with the Val/Val genotype (5.93±1.37 vs 9.27±1.30; $p<0.001$), indicating weaker early cognitive improvement among Met-allele carriers (**Table 7**). In the recessive model, participants with the Met/Met genotype showed smaller MoCA-INA score improvement than the combined Val/Met + Val/Val group at Day 14 vs Day 0 (5.34±1.23 vs 7.25±1.99; $p<0.001$).

Table 7. Improvement in cognitive function after treatment, assessed using delta of MoCA-INA score, according to *BDNF* Val66Met genetic models

Genotype and allele models	Day 14 vs Day 0		Day 42 vs Day 0		Day 42 vs Day 14	
	MoCA-INA score Δ Mean±SD	*p*-value[a]	MoCA-INA score Δ Mean±SD	*p*-value[a]	MoCA-INA score Δ Mean±SD	*p*-value[a]
Dominant model		<0.001		<0.001		<0.001
Met/Met + Val/Met, n=149	5.93±1.37		10.34±1.51		4.40±1.13	
Val/Val, n=58	9.27±1.3		11.24±1.32		1.96±0.26	
Recessive model		<0.001		0.595		<0.001
Met/Met, n=41	5.34±1.23		10.70±1.70		5.36±1.04	
Val/Met + Val/Val, n=166	7.25±1.99		10.56±1.47		3.31±1.25	
Heterozygous		<0.001		<0.001		<0.001
Val/Met, n=108	6.16±1.35		10.20±1.41		4.03±0.94	
Val/Val, n=58	9.27±1.3		11.24±1.32		1.96±0.26	
Homozygous model		<0.001		0.083		<0.001
Met/Met, n=41	5.34±1.23		10.70±1.70		5.35±1.04	
Val/Val, n=58	9.27±1.3		11.24±1.32		1.96±0.26	
Allele models		<0.001		0.032		<0.001
Met, n=190	8.81±1.36		10.42±1.56		4.61±1.81	
Val, n=224	7.77±2.04		10.74±1.46		2.96±1.24	

MoCA-INA: Montreal Cognitive Assessment–Indonesian version
[a] Analyzed with independent-sample t-test

Genotype-specific comparisons showed a similar pattern, with both Val/Met and Met/Met genotypes having lower early cognitive improvement than the Val/Val genotype. In the allele model, the Met allele and Val allele also differed significantly at Day 14 vs Day 0, although the direction of the difference should be interpreted carefully in relation to the genotype-based findings (**Table 7**).

At Day 42 vs Day 0, the differences in cognitive improvement became less consistent across genetic models (**Table 7**). The dominant and heterozygous models remained significant, with greater improvement observed in the Val/Val group than in Met-allele carriers. However, the recessive model (10.70±1.70 vs 10.56±1.47; p=0.595) and homozygous model (10.70±1.70 vs 11.24±1.32; p=0.083) were no longer statistically significant, suggesting that cognitive improvement among Met/Met participants became more comparable by Day 42 (**Table 7**).

For Day 42 vs Day 14, significant differences were observed across all genetic models (p<0.001) (**Table 7**). Participants carrying the Met allele showed larger later-phase cognitive gains than those with the Val/Val genotype in the dominant model (4.40±1.13 vs 1.96±0.26), while the Met/Met genotype also showed greater change than Val/Val in the homozygous model (5.35±1.04 vs 1.96±0.26). These findings suggest that Val/Val participants had the greatest early cognitive improvement, whereas Met-allele carriers, particularly Met/Met participants, showed slower initial improvement followed by greater later-phase gains, leading to more comparable cognitive improvement by Day 42 (**Table 7**).

Discussion

This is the first genetic study in Aceh, and one of the very few in Indonesia, to explore the *BDNF* Val66Met polymorphism among individuals with schizophrenia. This study examined the association of *BDNF* Val66Met polymorphism with clinical symptom severity, cognitive function, and treatment-related improvement among Acehnese individuals with schizophrenia. The main findings indicate that *BDNF* Val66Met was significantly associated with both baseline clinical and cognitive profiles, as well as treatment-related improvements. The Val/Val genotype was consistently associated with milder clinical symptom severity, better cognitive function, and greater improvement in clinical symptoms after antipsychotic treatment. In contrast, Met-allele carriage was associated with more severe clinical symptoms, lower cognitive function, and smaller improvement in clinical symptoms during follow-up. For cognitive outcome, Val/Val participants showed greater early improvement, whereas Met-allele carriers showed slower initial improvement followed by larger later-phase gains, leading to more comparable cognitive improvement by Day 42 in some genetic models.

The genotype distribution was characterized by a predominance of Val/Met heterozygotes, followed by Val/Val and Met/Met genotypes. This pattern is broadly consistent with previous evidence indicating that *BDNF* Val66Met genotype frequencies vary substantially across ethnic and geographic populations in Southeast Asian populations [29], including in Indonesia [21]. The high proportion of Val/Met participants in this study may reflect the genetic background of the Acehnese population, which has been shaped by complex historical admixture across Island Southeast Asia [30-32]. This population-specific context is important because inconsistent findings across *BDNF* Val66Met studies may be partly explained by ethnic differences in allele frequency, linkage disequilibrium structure, environmental exposure, and clinical characteristics.

The baseline clinical symptom findings showed a consistent difference across all *BDNF* Val66Met genetic models. In the dominant model, Met-allele carriers had markedly higher PANSS total scores than Val/Val participants, suggesting that the presence of at least one Met allele may be associated with greater clinical symptom burden. This finding is consistent with previous reports linking the Met allele with more severe psychopathology in schizophrenia [18,33]. The biological plausibility of this association is supported by evidence that the Met substitution impairs intracellular trafficking and activity-dependent secretion of BDNF, which may reduce neuroplastic capacity in hippocampal and prefrontal circuits involved in emotion regulation, cognition, and psychotic symptom expression [34,35]. A previous study also reported that the *BDNF* Met variant may be associated with progressive frontal gray matter reduction and ventricular enlargement in schizophrenia, suggesting that Val66Met may influence structural brain vulnerability relevant to clinical expression [36].

Findings from the regression analyses further confirmed that *BDNF* Val66Met genetic models were significantly associated with baseline PANSS total score. The dominant model explained a substantial proportion of variation in baseline symptom severity, indicating that grouping Val/Met and Met/Met participants together as Met-allele carriers captured an important difference from the Val/Val group. However, the recessive model showed only a small explained variance, and the descriptive comparison showed that the combined Val/Val + Val/Met group had a higher mean PANSS score than the Met/Met group. This pattern suggests that baseline clinical symptom severity in this cohort did not follow a simple Met-allele dose-response pattern. Instead, the high PANSS total score among Val/Met participants appears to have influenced the recessive-model comparison. Therefore, the clinical severity findings should be interpreted as model-dependent, with the dominant and genotype-specific models providing stronger explanatory patterns than the recessive model. The heterozygous and homozygous models also showed significant associations with baseline PANSS total score, indicating that both Val/Met and Met/Met participants differed from Val/Val participants. In the genotype-specific comparisons, the Val/Met group showed the highest PANSS total score, followed by Met/Met and Val/Val. This finding suggests that heterozygosity may not simply represent an intermediate state between Val/Val and Met/Met for clinical symptom severity. Such non-linear genotype effects have been reported in genetic studies of neuropsychiatric phenotypes, where heterozygous effects may differ depending on population background, environmental exposure, illness stage, and interaction with other genetic variants. Therefore, while the Met allele appears relevant to clinical severity, the present findings also emphasize that *BDNF* Val66Met should not be interpreted as a deterministic marker of symptom severity.

The association between *BDNF* Val66Met and cognitive function was more consistent with a Met-related impairment pattern. In the dominant model, Met-allele carriers had lower MoCA-INA scores than Val/Val participants. In the recessive and homozygous models, Met/Met participants showed the lowest cognitive scores, suggesting that Met homozygosity may be particularly related to poorer baseline cognitive function. This is consistent with studies showing that BDNF polymorphisms are associated with cognitive performance in schizophrenia and that the Met allele may affect domains such as attention, executive function, and memory [37,38]. The finding also aligns with evidence that BDNF-related cognitive effects may vary by illness stage and cognitive domain [39]. Since MoCA-INA captures global cognitive function across multiple domains, the lower score among Met-allele carriers may reflect broad cognitive vulnerability rather than impairment in a single cognitive process.

The regression models for baseline MoCA-INA further support this interpretation. The homozygous model had the strongest model fit, followed by the recessive model, indicating that Met/Met homozygosity explained a substantial proportion of variation in baseline cognitive function. This pattern differs from the PANSS findings, where the dominant and heterozygous models were more informative. The difference between clinical and cognitive models suggests that the genetic architecture underlying symptom severity and cognitive impairment may not be identical. For cognitive function, the data suggest a stronger role of Met/Met homozygosity or Met-allele burden. This is biologically plausible because BDNF is directly involved in synaptic plasticity, hippocampal function, and learning-related neural adaptation [5,34,40]. Prior work has also shown that *BDNF* Val66Met can interact with neurophysiological markers of NMDAR-mediated plasticity and working memory capacity in schizophrenia [19]. Therefore, the cognitive findings in this study provide further evidence that *BDNF* Val66Met may be more closely related to cognitive impairment than to general clinical symptom severity alone.

The treatment-outcome analysis showed that clinical symptom improvement, measured by reductions in PANSS total score, differed significantly across all genetic models and all-time intervals. The Val/Val group had the largest PANSS reductions from Day 0 to Day 14, Day 0 to Day 42, and Day 14 to Day 42. In contrast, Met-allele carriers showed smaller reductions, indicating weaker clinical improvement during the 42-day treatment period. This pattern was observed in the dominant, heterozygous, homozygous, and allele models, suggesting that Val/Val genotype may be associated with a more favorable clinical response profile. Previous pharmacogenetic evidence has suggested that BDNF variants may contribute to variability in therapeutic response to risperidone among patients with schizophrenia [22]. This is also

consistent with evidence suggesting that BDNF levels may change during antipsychotic treatment and that higher or increasing BDNF levels may be associated with better clinical improvement [14].

The consistency of PANSS improvement across multiple genetic models is important. In the dominant model, Met-allele carriers had substantially smaller PANSS reductions than Val/Val participants, indicating that carrying at least one Met allele may be associated with reduced treatment-related clinical improvement. In the homozygous model, Met/Met participants showed markedly smaller improvement than Val/Val participants, supporting a less favorable response among individuals with two Met alleles. The allele model also showed smaller PANSS reductions for the Met allele than the Val allele, further supporting the direction of the genotype-based findings. Together, these results suggest that *BDNF* Val66Met may influence not only baseline symptom burden but also the magnitude of symptom reduction after antipsychotic treatment.

The PANSS domain patterns provide additional clinical meaning to the total-score findings. The Val/Val group showed the most consistent improvement across negative symptoms, positive symptoms, and general psychopathology, particularly by Day 42. In contrast, Val/Met and Met/Met participants showed higher baseline negative symptom scores and smaller reductions during follow-up. This is relevant because negative symptoms and general psychopathology are often more closely related to functional impairment and may be less responsive to antipsychotic treatment than positive symptoms. Previous studies have linked *BDNF* Val66Met with negative symptom severity [20,33], and altered BDNF signaling may contribute to impaired prefrontal and limbic plasticity involved in motivation, affective regulation, and social functioning [34,41]. The greater improvement in Val/Val participants may therefore reflect more efficient neuroplastic adaptation during treatment.

For cognitive outcomes, the pattern was more complex than for PANSS improvement. Val/Val participants showed the greatest early improvement in MoCA-INA score from Day 0 to Day 14, especially in the dominant and genotype-specific models. This suggests that the Val/Val genotype may support faster early cognitive recovery or better cognitive stabilization after initiation of antipsychotic treatment. This finding is compatible with the biological role of the Val allele in more efficient BDNF secretion and synaptic plasticity [34]. Evidence from neurophysiological studies also suggests that Val homozygotes may show better working memory capacity and stronger NMDAR-related cognitive plasticity than Met carriers [19]. Therefore, the early cognitive advantage observed in Val/Val participants may reflect a stronger capacity for early treatment-related neurocognitive adaptation.

However, by day 42, cognitive improvement became more comparable in some models. In the recessive and homozygous models, the Day 42 vs Day 0 differences were no longer statistically significant, suggesting that Met/Met participants partially caught up over time. The Day 42 vs Day 14 results showed larger later-phase MoCA-INA gains among Met-allele carriers and Met/Met participants than among Val/Val participants. This pattern may be explained by several possibilities. First, Val/Val participants had higher baseline MoCA-INA scores and greater early improvement, leaving less room for later improvement. Second, Met-allele carriers started with lower cognitive scores, which may have allowed greater later gains once acute symptoms improved. Third, cognitive recovery may depend not only on BDNF genotype but also on symptom stabilization, practice effects from repeated testing, medication adherence, psychosocial support, and rehabilitation exposure. Therefore, *BDNF* Val66Met appears to influence the timing of cognitive improvement more strongly than the final magnitude of improvement by Day 42.

The difference between clinical and cognitive treatment patterns is noteworthy. Clinical symptom improvement remained consistently greater among Val/Val participants across all follow-up intervals, whereas cognitive improvement showed an early Val/Val advantage followed by later gains among Met-allele carriers. This suggests that clinical symptom reduction and cognitive recovery may follow partly distinct trajectories. Antipsychotic treatment may rapidly reduce psychotic symptoms through dopaminergic and serotonergic mechanisms, while cognitive recovery may depend more heavily on neural plasticity, learning, environmental stimulation, and functional engagement. The *BDNF* Val66Met polymorphism may therefore be more relevant to

the rate and pattern of cognitive adaptation than to cognitive improvement as a fixed endpoint. Studies examining BDNF polymorphisms across different stages of schizophrenia also support the idea that BDNF effects on cognition may be domain-specific and stage-dependent [39].

These different trajectories for clinical and cognitive outcomes may be explained by the biological effects of the Val66Met polymorphism on BDNF-dependent neuroplasticity. From a mechanistic perspective, Val66Met modulates BDNF–TrkB signaling pathways, including ERK and PI3K–Akt cascades, which are critical for synaptic plasticity and neural circuit stabilization [34]. The Val/Val genotype is associated with more efficient BDNF secretion and signaling, which may facilitate neuroplastic adaptation during antipsychotic treatment and contribute to faster symptom improvement [42,43]. In contrast, the Met substitution impairs intracellular trafficking and activity-dependent release of BDNF, limiting neuroplastic responsiveness and contributing to slower recovery [20]. This mechanism is consistent with the greater early clinical and cognitive improvement observed among Val/Val participants and the slower initial recovery among Met-allele carriers. However, the influence of Val66Met appears to be most pronounced during the early phase of treatment, with diminishing predictive value over time as environmental and psychosocial factors become increasingly influential [41]. This may explain why cognitive improvement among Met-allele carriers became more comparable by Day 42 and why the findings should be interpreted in light of heterogeneity in the existing literature.

The findings should also be interpreted in light of heterogeneity in the existing literature. Some previous studies support an association between the Met allele and poorer cognition or more severe symptoms, whereas others have found no significant association between rs6265 and cognitive performance [9-11,20]. For example, a large study of BDNF polymorphisms reported that rs6265 did not have a significant effect on cognitive functioning, although other BDNF variants were related to specific cognitive domains [39]. These inconsistencies may arise from differences in ethnicity, sample size, illness duration, medication status, cognitive instruments, symptom severity, and genetic models. The present study contributes to this literature by examining multiple genetic inheritance models and by evaluating both baseline profiles and treatment-related changes in the same Acehnese cohort.

From a clinical perspective, the findings suggest that *BDNF* Val66Met may have potential value as a population-specific marker for identifying patients at risk of greater baseline impairment and weaker early clinical improvement. The Val/Val genotype was associated with a more favorable symptom and cognitive profile, while Met-allele carriage was associated with greater baseline impairment and weaker early PANSS reduction. However, the model-specific findings also indicate that *BDNF* Val66Met should not be used as a single deterministic biomarker. The recessive model for PANSS, the non-linear pattern in the Val/Met group, and the changing pattern of cognitive improvement over time all suggest that the clinical relevance of this polymorphism depends on the outcome assessed, the genetic model applied, and the phase of treatment evaluated.

This study has some strengths. This study focused on an underrepresented Indonesian population and examined a clinically relevant functional polymorphism using several genetic inheritance models. It also assessed both clinical symptoms and cognitive function longitudinally at three time points, allowing evaluation of baseline differences and treatment-related changes. The use of standardized treatment with risperidone reduced some treatment heterogeneity, and baseline demographic comparability across genotypes strengthened internal validity. The inclusion of PANSS domain patterns also provided additional insight into how symptom improvement differed across genotypes. Some limitations should be considered. The study was conducted in a single ethnic group from Aceh, which strengthens population-specific relevance but may limit generalizability to other Indonesian or Southeast Asian populations. The follow-up period was limited to 42 days; longer follow-up is needed to determine whether genotype-related differences persist, diminish, or re-emerge during maintenance treatment. Cognitive function was assessed using the MoCA-INA, which is a brief global cognitive screening instrument. Although useful for identifying overall cognitive impairment, it may not comprehensively capture domain-specific cognitive deficits that are clinically relevant in schizophrenia, such as working memory, processing speed, verbal learning, attention, and executive function. Therefore, the cognitive findings should be interpreted as reflecting global cognitive performance rather than

detailed neurocognitive profiles. Circulating BDNF levels were not measured, so the study could not directly link genotype with BDNF expression or treatment-induced BDNF changes. Neuroimaging and detailed domain-specific neuropsychological testing were not included, limiting mechanistic interpretation of the cognitive findings.

Conclusion

BDNF Val66Met polymorphism was significantly associated with clinical symptom severity, cognitive function, and treatment-related improvement among Acehnese individuals with schizophrenia. The Val/Val genotype was associated with a more favorable clinical and cognitive profile, including lower PANSS total score, higher MoCA-INA score, and greater clinical symptom improvement after antipsychotic treatment. In contrast, Met-allele carriage was associated with greater baseline symptom severity, poorer cognitive function, and weaker clinical improvement. The genetic models provided additional insight. The dominant model suggested that Met-allele carriage was associated with worse clinical and cognitive profiles, while the recessive and homozygous models indicated that Met/Met genotype was particularly related to poorer cognitive function. For treatment outcomes, Val/Val participants showed greater clinical improvement, whereas cognitive improvement among Met-allele carriers was slower initially but became more comparable by Day 42. Overall, *BDNF* Val66Met may be a relevant population-specific genetic marker for clinical and cognitive heterogeneity in schizophrenia. Its clinical applicability, however, remains preliminary, and this polymorphism should be interpreted only as a supportive marker within a broader clinical assessment rather than as a standalone predictor of treatment response. Further studies with larger, multiethnic cohorts, longer follow-up, and biological validation are needed before clinical implementation can be considered.

Ethics approval

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia (Approval No. 026/EA/FK/2025; 24 February 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians before enrolment and data collection.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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