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Association Of Snp8nrg241930 Polymorphism in The Neuregulin 1 (Nrg1) Gene with Schizophrenia Susceptibility and Clinical Symptom Improvement Following Risperidone Treatment

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ABSTRACT: Evidence linking neuregulin 1 (NRG1) polymorphisms with schizophrenia susceptibility and antipsychotic response remains inconsistent. This analytical observational study combined a case–control genetic analysis with prospective longitudinal assessment to evaluate SNP8NRG241930 (NRG1 rs62510682) in relation to schizophrenia and symptom changes during risperidone treatment. A total of 200 participants were included: 100 patients with schizophrenia and 100 healthy controls. Genotyping was performed using polymerase chain reaction–restriction fragment length polymorphism. Patients with schizophrenia were followed for 8 weeks during risperidone treatment, and psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) at baseline, week 4, and week 8. Genotype distribution differed significantly between groups (Fisher–Freeman–Halton exact P=0.013), whereas allele frequencies did not (P=0.313); the T allele was not significantly associated with schizophrenia (OR 1.23, 95% CI 0.83–1.82). The control group deviated significantly from Hardy–Weinberg equilibrium (P<0.001). Generalized estimating equation analysis showed significant improvement over time in all PANSS domains (all P<0.001), but no significant time-by-genotype interactions were observed. SNP8NRG241930 showed a case–control difference in genotype distribution but was not associated with differential symptom trajectories during risperidone treatment. The Hardy–Weinberg disequilibrium in controls warrants cautious interpretation of the susceptibility finding.

1. INTRODUCTION

Schizophrenia is a severe psychiatric disorder associated with persistent symptoms, cognitive dysfunction, functional impairment, and substantial global disease burden. From 1990 to 2019, its absolute prevalence and disability-adjusted life-years increased markedly, whereas age-standardized estimates changed relatively little [1]. Its genetic architecture is highly polygenic.

A large genome-wide association study identified 287 distinct loci, with implicated genes enriched in neuronal and synaptic processes, including synaptic organization, differentiation, and transmission [2]. Exome sequencing additionally identified rare coding variants in ten genes conferring substantial risk, several involved in neuronal and synaptic function [3]. Integration of genetic data with single-nucleus transcriptomic profiles further showed enrichment of schizophrenia liability in developing neuronal populations of the prenatal human brain, supporting a prenatal neurodevelopmental component [4].

Within this broader architecture, neuregulin 1 (NRG1) remains biologically relevant because NRG1–ErbB signaling participates in neuronal development, synaptic regulation, and cortical circuit formation. In mice, *Nrg1* deletion impaired callosal axon development, whereas intracellular *Nrg1* signaling promoted axonal outgrowth in cortical neurons, supporting a role in long-range cortical connectivity [5]. Human studies also suggest altered peripheral NRG1 biology. Serum NRG1β1 was lower in first-episode, drug-naïve patients than in healthy controls and was associated with selected cognitive measures [6]. Lower NRG1β1 concentrations were also observed in male patients with chronic schizophrenia, although no significant associations with psychopathology or cognitive performance were detected [7].

NRG1 may also contribute to variability during antipsychotic treatment, although evidence remains inconsistent. In a four-week study involving several atypical antipsychotics, serum NRG1β1 increased as PANSS scores decreased, with a significant increase among responders [8]. More directly, a six-week risperidone-monotherapy study found that NRG1 rs35753505 and rs3924999 genotypes were associated with selected PANSS outcomes and risperidone dose requirements, although neither variant significantly distinguished responders from non-responders [9]. A randomized trial also found greater symptom improvement with multigene pharmacogenomics-guided antipsychotic treatment than with treatment as usual, supporting pharmacogenomic stratification as a general concept rather than the predictive value of any single NRG1 variant [10].

Contemporary NRG1 pharmacogenetic studies have focused largely on variants other than SNP8NRG241930. Earlier evidence for SNP8NRG241930 was mixed; however, a meta-analysis of 25 studies reported a modest association of its G allele with schizophrenia (OR 1.10, 95% CI 1.01–1.20), with moderate heterogeneity [11]. Its relationship with risperidone-associated symptom change remains insufficiently characterized, particularly in Indonesian populations. This study therefore investigated the association of SNP8NRG241930 with schizophrenia susceptibility and with changes in PANSS-defined clinical symptoms during eight weeks of risperidone treatment.

2. MATERIALS AND METHODS

2.1 Study Design, Setting, Participants, and Sample-Size Determination

This analytical observational study comprised two complementary components: a case–control study evaluating the association between the SNP8NRG241930 polymorphism in the neuregulin 1 (NRG1) gene and schizophrenia susceptibility, and a prospective longitudinal study evaluating genotype-related changes in clinical symptoms among patients with schizophrenia receiving risperidone.

Participants with schizophrenia were recruited and clinically followed at the inpatient psychiatric wards of Dadi Regional Special Hospital, South Sulawesi Province, Makassar, Indonesia, from November 2025 to February 2026. Healthy controls were recruited from the general population. Molecular laboratory analyses, including genomic DNA extraction, PCR amplification, and PCR-RFLP genotyping, were performed at the Hasanuddin University Medical Research Center (HUMRC), Hasanuddin University, Makassar, Indonesia. Genotyping was performed in both patients with schizophrenia and healthy controls, whereas longitudinal PANSS assessments were conducted only in the schizophrenia group.

The study included 200 participants, comprising 100 patients with schizophrenia and 100 healthy controls. Patients had an established diagnosis of schizophrenia made by the treating psychiatrist during routine clinical care, consistent with ICD-10/Indonesian Classification and Diagnostic Guidelines for Mental Disorders III (PPDGJ-III) criteria, and were undergoing inpatient treatment at the study hospital. Patients were eligible if they were aged 18–55 years, provided written informed consent, and were receiving risperidone as part of their routine clinical management. Patients with severe organic or medical conditions that could interfere with participation or clinical assessment were excluded.

Healthy controls were healthy individuals recruited from the general population with no known history of schizophrenia or other psychiatric disorders. They participated only in the case–control genetic component and did not undergo PANSS

assessment or receive risperidone treatment. Participants were recruited consecutively until the required sample size was achieved.

The minimum sample size for the case–control component was estimated based on genotype frequencies reported by Shariati et al. [12], who observed the GG genotype of SNP8NRG241930 in 54% of patients with schizophrenia and 26% of healthy controls. Assuming a two-sided α level of 0.05, 80% statistical power, and a 1:1 allocation ratio, the minimum required sample size was approximately 47 participants per group. The present study included 100 participants in each group, yielding a total sample of 200 participants.

2.2 Clinical Assessment and Risperidone Follow-up

Patients with schizophrenia continued to receive risperidone during the 8-week observation period according to the individualized prescriptions of their treating psychiatrists. Risperidone dose selection and dose adjustments were determined according to clinical needs as part of routine psychiatric care and were not standardized by the study protocol.

Psychopathological symptoms were assessed using the 30-item Positive and Negative Syndrome Scale (PANSS), comprising seven positive-symptom items, seven negative-symptom items, and 16 general psychopathology items. Higher scores indicate greater symptom severity. Assessments were performed by trained clinicians at baseline (week 0), week 4, and week 8. Positive, negative, general psychopathology, and total PANSS scores were analyzed separately. Changes in PANSS scores from baseline were calculated to evaluate clinical symptom improvement during risperidone treatment.

2.3 Blood Collection, DNA Extraction, and SNP8NRG241930 Genotyping

Peripheral venous blood samples were obtained from all participants for genetic analysis. Genomic DNA was extracted from 200 μL of whole blood using the gSYNC™ DNA Extraction Kit (Geneaid) according to the manufacturer's column-based protocol. Briefly, blood samples were treated with proteinase K and GSB buffer for cell lysis. Ethanol was subsequently added to facilitate DNA binding to the GS column. The column was sequentially washed with W1 Buffer and Wash Buffer, and purified genomic DNA was eluted with 100 μL of preheated elution buffer. The resulting DNA was used as the template for polymerase chain reaction (PCR) amplification.

The genomic region containing SNP8NRG241930 was amplified using PCR. Oligonucleotide primers were synthesized by Integrated DNA Technologies (IDT). The primer sequences were forward 5'-AGAAGGGGAAGATTCAAGATGG-3' and reverse 5'-TCATGGACTGATGTGGCAATG-3', producing an expected amplicon of 897 base pairs (bp). Each PCR reaction had a total volume of 25 μL and contained 12.5 μL of GoTaq® Green Master Mix 2× (Promega), 0.5 μL of 10-μM forward primer, 0.5 μL of 10-μM reverse primer, 6.5 μL of nuclease-free water, and 5 μL of genomic DNA. Amplification was performed using a CFX96 system (Bio-Rad Laboratories).

The cycling protocol consisted of initial denaturation at 94°C for 3 minutes, followed by 35 cycles of denaturation at 94°C for 50 seconds, annealing at 56°C for 45 seconds, and extension at 72°C for 70 seconds. A final extension was performed at 72°C for 10 minutes. PCR products were evaluated using 2% agarose gel electrophoresis in 0.5× TBE buffer with ethidium bromide staining. A 100-bp DNA ladder was used as a molecular-size marker, and positive and negative PCR controls were included. Successful amplification was identified by the presence of an 897-bp band.

PCR products were subsequently subjected to restriction fragment length polymorphism analysis using ScaI restriction endonuclease (Thermo Scientific; Cat. No. ER0431). Each 20-μL digestion mixture contained 5 μL of PCR product, 1 μL of ScaI, 2 μL of 10× H buffer, and 12 μL of sterile purified water. Digestion was performed at 37°C for 1 hour. The digested products were subsequently separated by agarose gel electrophoresis and visualized under ultraviolet illumination. Genotypes were determined according to the resulting restriction-fragment patterns: GG, 576, 174, and 147 bp; GT, 750, 576, 174, and 147 bp; and TT, 750 and 147 bp.

2.4 Statistical Analysis

Continuous variables were summarized as mean ± standard deviation or median with interquartile range according to their distribution, whereas categorical variables were presented as frequencies and percentages. Normality of continuous variables was assessed using the Shapiro–Wilk test. Genotype and allele frequencies were calculated separately for patients with schizophrenia and healthy controls. Differences in genotype distribution between groups were evaluated using the Fisher–

Freeman–Halton exact test because of small expected cell counts. Allele distributions were compared using the Pearson chi-square test, and the strength of association with schizophrenia was expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Hardy–Weinberg equilibrium was assessed in the healthy-control group.

Longitudinal changes in positive, negative, general psychopathology, and total PANSS scores were analyzed using generalized estimating equations with a normal distribution, identity link function, exchangeable working-correlation structure, and robust covariance estimation. The models included time, genotype, and the time-by-genotype interaction. Because no patient with schizophrenia carried the TT genotype, longitudinal analyses were restricted to the GG and GT groups. Estimated marginal means with 95% Wald CIs were reported.

As secondary analyses, differences in PANSS change scores from baseline between the GG and GT groups at weeks 4 and 8 were evaluated using the Mann–Whitney U test. Negative change scores represented reductions in symptom severity. All tests were two-sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics.

3. RESULTS AND DISCUSSION

3.1 Participant Characteristics

A total of 200 participants were included, comprising 100 patients with schizophrenia and 100 healthy controls. All 100 patients with schizophrenia had complete PANSS assessments at baseline, week 4, and week 8. The schizophrenia group had a higher mean age and was predominantly male and unmarried, with moderate or low educational attainment being most common. In contrast, the healthy-control group was predominantly female and had a substantially higher proportion of participants with higher education. Bugis and Makassar were the predominant ethnic groups in both study groups. Participant characteristics are summarized in Table 1.

Table 1. Characteristics of Patients with Schizophrenia and Healthy Controls

Characteristics	Schizophrenia (n=100)	Healthy controls (n=100)
Age, years, mean ± SD	35.6 ± 7.4	31.7 ± 7.9
Sex, n (%)		
Male	86 (86.0)	33 (33.0)
Female	14 (14.0)	67 (67.0)
Marital status, n (%)		
Married	26 (26.0)	56 (56.0)
Unmarried	74 (74.0)	44 (44.0)
Education level, n (%)		
High	1 (1.0)	90 (90.0)
Moderate	52 (52.0)	10 (10.0)
Low	47 (47.0)	0 (0.0)
Ethnicity, n (%)		
Bugis	54 (54.0)	45 (45.0)
Makassar	31 (31.0)	28 (28.0)
Javanese	0 (0.0)	5 (5.0)
Kaili	0 (0.0)	4 (4.0)

Chinese	0 (0.0)	7 (7.0)
Others	15 (15.0)	11 (11.0)
Family history of schizophrenia, n (%)		
Yes	12 (12.0)	10 (10.0)
No	88 (88.0)	90 (90.0)

Note: Continuous data are presented as mean ± standard deviation, and categorical data as n (%). Participant characteristics are presented descriptively. SD, standard deviation.

3.2 SNP8NRG241930 Genotype and Allele Distribution

The overall distribution of SNP8NRG241930 genotypes differed significantly between patients with schizophrenia and healthy controls using the Fisher–Freeman–Halton exact test (P=0.013). In contrast, allele frequencies did not differ significantly between groups (P=0.313), and the T allele was not significantly associated with schizophrenia (OR 1.23, 95% CI 0.83–1.82). The genotype distribution among healthy controls deviated significantly from Hardy–Weinberg equilibrium (P<0.001). Genotype and allele distributions are presented in Table 2.

Table 2. Distribution of SNP8NRG241930 Genotypes and Alleles in Patients With Schizophrenia and Healthy Controls

Genetic variable	Schizophrenia (n=100)	Healthy controls (n=100)	OR (95% CI)	*P*
Genotype, n (%)				0.013*[a]
GG	9 (9.0)	21 (21.0)	—	
GT	91 (91.0)	77 (77.0)	—	
TT	0 (0.0)	2 (2.0)	—	
Allele, n (%)				
G	109 (54.5)	119 (59.5)	Reference	
T	91 (45.5)	81 (40.5)	1.23 (0.83–1.82)	0.313[b]

Note: Data are presented as n (%). [a] Fisher–Freeman–Halton exact test for the overall genotype distribution. [b] Pearson chi-square test. OR represents the odds of schizophrenia for the T allele relative to the G allele. The genotype distribution among healthy controls deviated from Hardy–Weinberg equilibrium (P<0.001). *P value <0.05 was considered statistically significant. CI, confidence interval; OR, odds ratio.

3.3 Longitudinal PANSS Changes According to Genotype

Longitudinal analysis included the 100 patients with schizophrenia, of whom 91 carried the GT genotype and nine carried the GG genotype; no TT carriers were identified in the schizophrenia group. GEE analysis demonstrated significant changes over time in positive, negative, general psychopathology, and total PANSS scores (all P<0.001). However, none of the time-by-genotype interactions were statistically significant, indicating no detectable difference in PANSS trajectories between the GG and GT genotypes during the 8-week observation period (Table 3). The trajectory of total PANSS scores is illustrated in Figure 1.

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Table 3. Longitudinal PANSS Scores According to SNP8NRG241930 Genotype

PANSS domain	Genotype	Baseline, estimated mean (95% CI)	Week 4, estimated mean (95% CI)	Week 8, estimated mean (95% CI)	Time *P*	Genotype *P*	Time × genotype *P*
Positive	GG	19.44 (15.86–23.02)	18.89 (15.41–22.37)	13.78 (12.07–15.49)	<0.001*	0.258	0.744
	GT	17.87 (16.84–18.90)	17.74 (16.90–18.57)	11.91 (11.43–12.39)			
Negative	GG	19.00 (16.58–21.43)	18.78 (16.81–20.74)	15.22 (13.82–16.63)	<0.001*	0.517	0.329
	GT	19.16 (17.84–20.49)	18.74 (17.86–19.61)	13.40 (12.86–13.93)			
General psychopathology	GG	39.22 (31.75–46.70)	38.22 (31.15–45.30)	29.22 (26.21–32.24)	<0.001*	0.737	0.283
	GT	39.16 (36.66–41.67)	39.08 (37.80–40.36)	25.59 (24.84–26.35)			
Total PANSS	GG	77.67 (65.19–90.14)	75.89 (64.12–87.66)	58.22 (53.66–62.79)	<0.001*	0.507	0.284
	GT	76.20 (72.05–80.35)	75.55 (73.35–77.75)	50.90 (49.61–52.19)			

Notes: Values are estimated marginal means with 95% Wald confidence intervals derived from generalized estimating equation models with an exchangeable working-correlation structure and robust covariance estimation. The time-by-genotype interaction was the principal test of genotype-related differences in longitudinal symptom trajectories. *P value <0.05 was considered statistically significant. CI, confidence interval; PANSS, Positive and Negative Syndrome Scale.

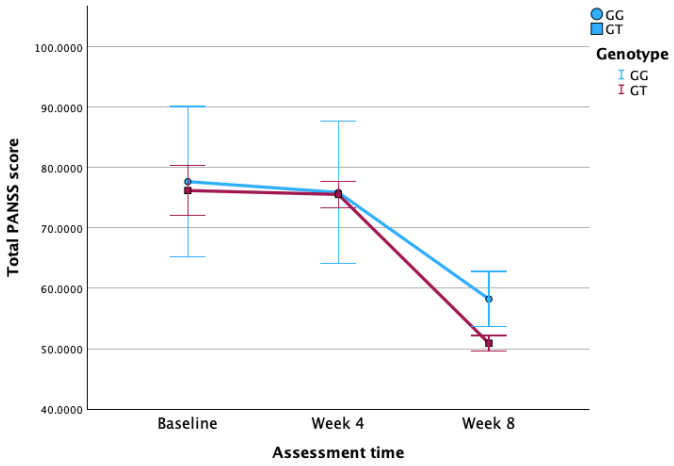

Figure 1. Longitudinal changes in total PANSS scores according to SNP8NRG241930 genotype.

3.4 Changes in PANSS Scores from Baseline

Change-score analyses supported the longitudinal GEE findings. No significant differences between the GG and GT genotypes were observed in changes from baseline in positive, negative, general psychopathology, or total PANSS scores at either week 4 or week 8 (all *P*>0.05). Detailed changes according to genotype are presented in Table 4.

Table 4. Changes in PANSS Scores from Baseline According to SNP8NRG241930 Genotype

Change in PANSS score	GG (n=9)	GT (n=91)	*P*
Positive, week 4 − baseline	−1 (−2 to 0.5)	−1 (−3 to 2)	0.985[a]
Negative, week 4 − baseline	0 (−1.5 to 0.5)	−1 (−3 to 2)	0.510[a]
General psychopathology, week 4 − baseline	0 (−3.5 to 0.5)	0 (−6 to 6)	0.833[a]
Total PANSS, week 4 − baseline	−3 (−4 to 0.5)	0 (−11 to 9)	0.651[a]
Positive, week 8 − baseline	−6 (−10.5 to −0.5)	−5 (−9 to −3)	0.870[a]
Negative, week 8 − baseline	−3 (−6.5 to −0.5)	−4 (−10 to −2)	0.371[a]
General psychopathology, week 8 − baseline	−14 (−20 to −1)	−12 (−20 to −6)	0.470[a]
Total PANSS, week 8 − baseline	−22 (−38.5 to −4.5)	−21 (−36 to −13)	0.485[a]

Note: Data are presented as median (Q1-Q3) [a] Mann–Whitney U test. Negative change scores indicate reductions in symptom severity relative to baseline. *P value <0.05 was considered statistically significant. PANSS, Positive and Negative Syndrome Scale.

3.5 Discussion

The present study found a significant difference in the overall distribution of SNP8NRG241930 (NRG1 rs62510682) genotypes between patients with schizophrenia and healthy controls, whereas allele frequencies did not differ significantly. The GT genotype was more frequent and GG less frequent among patients, but the T-versus-G allele comparison was null. This pattern does not support a straightforward additive allele-dose interpretation. Schizophrenia has a highly polygenic architecture in which thousands of common variants have individually small effects [2,13]. Functional genomic studies further demonstrate that statistical association alone does not establish a causal regulatory effect and that the activity of schizophrenia-associated noncoding variants can depend strongly on cellular and developmental context [14].

Evidence specifically for SNP8NRG241930 has also been modest and heterogeneous. A meta-analysis of 25 studies identified the G allele of rs62510682 as associated with schizophrenia, but the effect was small (OR 1.10, 95% CI 1.01–1.20; P=0.018) and heterogeneity was moderate (I^2=54.3%) [11]. The present allele-level analysis did not replicate that association. The discrepancy may reflect differences in sampling and population genetic context, but these factors cannot be established from the present data. Cross-ancestry studies nevertheless demonstrate the importance of evaluating the generalizability of schizophrenia genetic findings across diverse populations [15,16].

The most important qualification to the case–control finding is the marked deviation from Hardy–Weinberg equilibrium among healthy controls. HWE testing is widely used in genetic quality control because deviations can signal technical artifacts or genotype-calling error; however, population structure and genotype uncertainty can also produce departures from HWE [17]. In the present controls, the deviation was characterized by a pronounced excess of heterozygotes. Accordingly, the significant genotype-distribution difference should be considered hypothesis-generating rather than definitive evidence that SNP8NRG241930 confers schizophrenia susceptibility. Independent confirmation of genotype calls and replication in a larger, ancestry-characterized cohort are needed before any genotype is interpreted as conferring increased risk.

The biological relevance of NRG1 nevertheless remains plausible at the pathway level. In a mouse model, *Nrg1* overexpression in GABAergic interneurons produced reversible cortical disinhibition and behavioral abnormalities [18]. Another mouse study showed that deletion of *Nrg1* impaired callosal axon development and that intracellular *Nrg1* signaling promoted axonal development, further linking this pathway to cortical connectivity [5].

Human biomarker studies likewise suggest altered NRG1 biology, although its clinical correlates are inconsistent. Serum NRG1β1 was reduced in first-episode drug-naïve schizophrenia and associated with selected cognitive measures [6]. Lower NRG1β1 concentrations were also observed in male patients with chronic schizophrenia, but NRG1β1 was not associated with

psychopathological symptoms or cognitive deficits [7]. These findings support pathway-level relevance without establishing a functional consequence specifically for rs62510682.

Longitudinally, positive, negative, general psychopathology, and total PANSS scores improved significantly over eight weeks, but no PANSS domain showed a significant time-by-genotype interaction. Thus, the data did not demonstrate different symptom trajectories between GG and GT carriers during risperidone treatment.

This contrasts partly with a six-week risperidone-monotherapy study in which other NRG1 variants, rs35753505 and rs3924999, were associated with selected PANSS outcomes and risperidone dose requirements [9]. A separate 12-week risperidone study also reported associations of these variants with changes in selected neurocognitive measures, further suggesting that NRG1-related treatment effects may be variant- and outcome-specific [19]. Serum NRG1β1 has also been reported to increase during antipsychotic treatment as PANSS scores declined, with a significant increase among responders; however, that study involved several antipsychotic regimens and did not evaluate SNP8NRG241930 as a response marker [8]. The present findings therefore do not exclude a role for the broader NRG1 pathway in antipsychotic response; they indicate that a genotype-specific PANSS trajectory for rs62510682 was not detected in this cohort.

Antipsychotic outcomes are unlikely to be determined by a single candidate polymorphism. At a broader treatment-outcome level, treatment-resistant schizophrenia has a detectable polygenic component, with common-variant heritability estimated at approximately 1–4% [20]. Guo et al. [21] developed and externally validated a treatment-response model integrating clinical information, polygenic risk, genetic risk, and methylation proxies, achieving an external-validation AUC of 0.851. In a randomized clinical trial, multigenetic pharmacogenomics-guided treatment produced greater PANSS improvement than treatment as usual [10].

Nevertheless, an umbrella systematic review and meta-analysis found that many reported antipsychotic pharmacogenetic associations were weak at the unadjusted nominal level and highlighted important limitations in reproducibility and standardization [22]. Pharmacogenetic factors affecting risperidone disposition may add further heterogeneity: CYP2D6 phenotype influences exposure to risperidone and its active metabolite, and DPWG recommendations differ for selected CYP2D6 metabolizer phenotypes [23]. Because risperidone doses in the present study were individualized by treating psychiatrists and were not standardized by protocol, between-patient variation in dose and drug exposure may have reduced sensitivity to small genotype-related differences.

This study combined case–control genetic assessment with prospective repeated PANSS measurements and used a longitudinal model that directly tested genotype-by-time interaction. Its interpretation is constrained by the single-center design, small GG subgroup, absence of TT carriers among patients, marked HWE deviation in controls, lack of genomic adjustment for ancestry or population structure, and non-standardized risperidone dosing.

Future studies should prioritize independent genotype confirmation, larger multicenter and ancestry-characterized cohorts, standardized assessment of antipsychotic exposure, and multigene or multiomics approaches rather than reliance on a single candidate variant [17,21,22]. Within these constraints, SNP8NRG241930 should not yet be regarded as a reliable standalone marker of either schizophrenia susceptibility or risperidone-associated symptom improvement.

4. CONCLUSION

SNP8NRG241930 (NRG1 rs62510682) showed a significant difference in genotype distribution between patients with schizophrenia and healthy controls, whereas allele frequencies were not significantly different. Among patients receiving risperidone, PANSS scores improved significantly over eight weeks, but symptom trajectories did not differ between GG and GT genotypes. The marked deviation from Hardy–Weinberg equilibrium in controls and the small number of GG carriers warrant cautious interpretation of the genetic association. These findings suggest that SNP8NRG241930 alone cannot yet be considered a reliable marker of schizophrenia susceptibility or risperidone-associated clinical improvement. Larger, ancestry-characterized studies with independent genotype validation and better control of antipsychotic exposure are needed to clarify its potential clinical relevance.

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AUTHOR CONTRIBUTIONS

ANK: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Project Administration, and Writing – Original Draft.

SS: Conceptualization, Methodology, Supervision, Validation, and Writing – Review & Editing.

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All authors critically reviewed and revised the manuscript, approved the final version, and agreed to be accountable for the accuracy and integrity of the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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This research received no external funding.

ETHICS STATEMENT

The study protocol was approved by the Research Ethics Committee of Hasanuddin University, Makassar, Indonesia (Approval No. 860/UN4.6.4.5.31/PP36/2025; Protocol No. UH25100800) on October 28, 2025. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable ethical standards for research involving human participants. Written informed consent was obtained from all participants before enrollment.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable ethical and institutional restrictions.

REFERENCES

[1] Solmi, M., Seitidis, G., Mavridis, D., Correll, C.U., Dragioti, E., Guimond, S., et al., 2023. Incidence, prevalence, and global burden of schizophrenia—data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. *Molecular Psychiatry* 28(12), 5319–5327.

[2] Trubetskoy, V., Pardiñas, A.F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T.B., et al., 2022. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 604(7906), 502–508.

[3] Singh, T., Poterba, T., Curtis, D., Akil, H., Al Eissa, M., Barchas, J.D., et al., 2022. Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nature* 604(7906), 509–516.

[4] Cameron, D., Mi, D., Vinh, N.N., Webber, C., Li, M., Marín, O., et al., 2023. Single-nuclei RNA sequencing of 5 regions of the human prenatal brain implicates developing neuron populations in genetic risk for schizophrenia. *Biological Psychiatry* 93(2), 157–166.

[5] Rodríguez-Prieto, Á., Mateos-White, I., Aníbal-Martínez, M., Navarro-González, C., Gil-Sanz, C., Domínguez-Canterla, Y., et al., 2024. Nrg1 intracellular signaling regulates the development of interhemispheric callosal axons in mice. *Life Science Alliance* 7(9), e202302250.

[6] Yang, H., Xiao, W., Yang, M., Wang, Y., Zhang, X., 2021. Decreased neuregulin1β1 in first episode and drug-naïve patients with schizophrenia: Negative correlation with cognitive impairment. *Psychiatry Research* 304, 114164.

[7] Chen, P., Chen, W., Xu, L., Luan, L., Peng, R., Zhang, X., et al., 2024. Decreased serum VEGF and NRG1β1 levels in male patients with chronic schizophrenia: VEGF correlation with clinical symptoms and cognitive deficits. *Journal of Psychiatric Research* 176, 85–92.

[8] Yang, H., Pan, W., Xiao, W., Yang, M., Xu, J., Li, J., et al., 2022. Antipsychotic drugs increase Neuregulin1β1 serum levels in first-episode drug-naïve patients and chronic schizophrenia with suggestions for improving the treatment of psychotic symptoms. *BMC Psychiatry* 22(1), 217.

[9] Bondrescu, M., Dehelean, L., Farcas, S.S., Papava, I., Nicoras, V., Mager, D.V., et al., 2024. COMT and Neuregulin 1 markers for personalized treatment of schizophrenia spectrum disorders treated with risperidone monotherapy. *Biomolecules* 14(7), 777.

[10] Kang, Z., Qin, Y., Sun, Y., Lu, Z., Sun, Y., Chen, H., et al., 2023. Multigenetic pharmacogenomics-guided treatment vs treatment as usual among hospitalized men with schizophrenia: A randomized clinical trial. *JAMA Network Open* 6(10), e2335518.

[11] Mostaid, M.S., Mancuso, S.G., Liu, C., Sundram, S., Pantelis, C., Everall, I.P., et al., 2017. Meta-analysis reveals associations between genetic variation in the 5' and 3' regions of Neuregulin-1 and schizophrenia. *Translational Psychiatry* 7(1), e1004.

[12] Shariati, S.A.M., Behmanesh, M., Galehdari, H., 2011. A study of the association between SNP8NRG241930 in the 5' end of Neuregulin 1 gene with schizophrenia in a group of Iranian patients. *Cell Journal* 13(2), 91–96.

[13] Smeland, O.B., Frei, O., Dale, A.M., Andreassen, O.A., 2020. The polygenic architecture of schizophrenia—rethinking pathogenesis and nosology. *Nature Reviews Neurology* 16(7), 366–379.

[14] Rummel, C.K., Gagliardi, M., Ahmad, R., Herholt, A., Jimenez-Barron, L., Murek, V., et al., 2023. Massively parallel functional dissection of schizophrenia-associated noncoding genetic variants. *Cell* 186(23), 5165–5182.e33.

[15] Bigdeli, T.B., Fanous, A.H., Li, Y., Rajeevan, N., Sayward, F., Genovese, G., et al., 2021. Genome-wide association studies of schizophrenia and bipolar disorder in a diverse cohort of US veterans. *Schizophrenia Bulletin* 47(2), 517–529.

[16] Liu, D., Meyer, D., Fennessy, B., Feng, C., Cheng, E., Johnson, J.S., et al., 2023. Schizophrenia risk conferred by rare protein-truncating variants is conserved across diverse human populations. *Nature Genetics* 55(3), 369–376.

[17] Kwong, A.M., Blackwell, T.W., LeFaive, J., de Andrade, M., Barnard, J., Barnes, K.C., et al., 2021. Robust, flexible, and scalable tests for Hardy-Weinberg equilibrium across diverse ancestries. *Genetics* 218(1), iyab044.

[18] Wang, Y.Y., Zhao, B., Wu, M.M., Zheng, X.L., Lin, L., Yin, D.M., 2021. Overexpression of neuregulin 1 in GABAergic interneurons results in reversible cortical disinhibition. *Nature Communications* 12(1), 278.

[19] Yang, J.Z., Kang, C.Y., Wu, C., Lin, Y., Zeng, L., Yuan, J., et al., 2021. Pharmacogenetic associations of NRG1 polymorphisms with neurocognitive performance and clinical symptom response to risperidone in the untreated schizophrenia. *Schizophrenia Research* 231, 67–69.

[20] Pardiñas, A.F., Smart, S.E., Willcocks, I.R., Holmans, P.A., Dennison, C.A., Lynham, A.J., et al., 2022. Interaction testing and polygenic risk scoring to estimate the association of common genetic variants with treatment resistance in schizophrenia. *JAMA Psychiatry* 79(3), 260–269.

[21] Guo, L.K., Su, Y., Zhang, Y.Y.N., Yu, H., Lu, Z., Li, W.Q., et al., 2023. Prediction of treatment response to antipsychotic drugs for precision medicine approach to schizophrenia: Randomized trials and multiomics analysis. *Military Medical Research* 10(1), 24.

[22] Teng, Y., Sandhu, A., Liemburg, E.J., Naderi, E., Alizadeh, B.Z., 2023. The progress and pitfalls of pharmacogenetics-based precision medicine in schizophrenia spectrum disorders: A systematic review and meta-analysis. *Journal of Personalized Medicine* 13(3), 471.

[23] Beunk, L., Nijenhuis, M., Soree, B., de Boer-Veger, N.J., Buunk, A.M., Guchelaar, H.J., et al., 2024. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4 and CYP1A2 and antipsychotics. *European Journal of Human Genetics* 32(3), 278–285.