RESEARCH PAPER

Association Between the Neuregulin 1 (NRG1) SNP8NRG241930 Polymorphism and Quality of Life in Patients with Schizophrenia: A Case-Control Study

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ABSTRACT

BACKGROUND: Schizophrenia is a chronic, severe mental disorder with substantial impact on psychosocial functioning and quality of life. Neuregulin 1 (NRG1), located on chromosome 8p12, is among the most extensively studied candidate genes for schizophrenia susceptibility, yet findings for the SNP8NRG241930 polymorphism remain inconsistent across populations, and its relationship with patient-reported quality of life is rarely examined.

METHODS: This case-control study enrolled 100 patients with schizophrenia and 100 healthy controls in Makassar, Indonesia. SNP8NRG241930 genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using ScaI digestion. Quality of life was assessed with the WHOQOL-BREF instrument. Associations between genotype/allele and schizophrenia status, and between genotype/allele and WHOQOL-BREF domain scores, were analyzed using chi-square and Mann-Whitney U tests, with significance set at $p<0.05$.

RESULTS: Genotype distribution differed significantly between groups ($\chi^2=3.829$, $p=0.050$): the GT genotype was more frequent among cases (91.0%) than controls (77.0%), whereas GG was more common in controls (21.0%) than cases (9.0%); the TT genotype was rare and absent among cases. Allele frequencies did not differ significantly between groups ($p=0.313$). Among patients, WHOQOL-BREF scores were low-to-moderate across all domains. GT carriers had significantly higher psychological ($p=0.021$) and social ($p=0.005$) domain scores than GG carriers; physical and environmental domains did not differ significantly. No allele-level differences in quality of life were observed in any domain.

CONCLUSIONS: The SNP8NRG241930 genotype, but not allele, of the NRG1 gene was associated with both schizophrenia occurrence and with psychological and social quality-of-life domains among patients, suggesting that NRG1 genetic variation may influence not only disease susceptibility but also functional outcomes in schizophrenia.

KEY WORDS: Schizophrenia, Neuregulin-1, Polymorphism, Single Nucleotide, Quality of Life, Genotype

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INTRODUCTION

Schizophrenia is a chronic, severe mental disorder characterized by hallucinations, delusions, disorganized thinking, and progressive decline in social and occupational functioning.[1] Globally, mental disorders affected nearly one in eight people in 2019, with anxiety and depressive disorders the most prevalent, and the burden of these conditions was estimated to have risen further during the COVID-19 pandemic.[2,3] In Indonesia, national health survey data indicate that 7.1% of households include a member with a mental disorder, corresponding to an estimated 450,000 cases of severe mental illness nationwide.[4] Despite available preventive and therapeutic options, most affected individuals lack access to effective care and continue to face substantial stigma and discrimination.

Although environmental exposures contribute to schizophrenia risk, twin studies estimate its heritability at more than 80%, underscoring a strong genetic component.[5] Linkage analyses have implicated several chromosomal loci, including 8p, 13q, 22q, and 6p, harboring candidate genes such as DISC1, DTNBP1, RGS4, COMT, and Neuregulin 1 (NRG1).[6] Among these, NRG1, located at chromosome 8p12, has been one of the most consistently investigated candidate genes for schizophrenia since Stefansson et al. first identified a core risk haplotype in an Icelandic cohort comprising five single nucleotide polymorphisms (SNPs), including

SNP8NRG241930.[7,8] NRG1 encodes a signaling protein that interacts with ErbB receptors to regulate neuronal migration, myelination, synaptogenesis, and glutamatergic and dopaminergic neurotransmission, processes central to the neurodevelopmental hypothesis of schizophrenia.[9,10]

Despite extensive investigation, the association between SNP8NRG241930 and schizophrenia risk has produced heterogeneous results across populations. Studies among Iranian, Chinese, Japanese, and Saudi Arabian cohorts have reported variable genotype distributions and, in some instances, opposing risk alleles, while large consortium analyses in European and American populations have failed to replicate a significant association.[11] This inconsistency likely reflects population-specific allele frequencies, ethnic stratification, and gene-environment interactions, highlighting the need for genetic data from previously unstudied populations, including Indonesia.

Beyond disease susceptibility, schizophrenia substantially impairs patients' quality of life, encompassing physical health, psychological well-being, social relationships, and environmental functioning, with patients consistently reporting lower quality of life than the general population.[12] The WHOQOL-BREF, a validated four-domain instrument, is widely used to capture this multidimensional construct in cross-cultural health research.[13] While most genetic studies of NRG1 have focused on disease risk, clinical symptom severity, or cognitive endophenotypes, few have examined whether NRG1 polymorphisms also influence patient-reported quality of life, an outcome of direct relevance to rehabilitation planning and long-term clinical management.

To address these gaps, we conducted a case-control study in Makassar, Indonesia, to determine the distribution of the SNP8NRG241930 genotype and allele among patients with schizophrenia and healthy controls, to evaluate the association between this polymorphism and schizophrenia occurrence, and to examine whether genotype or allele status is associated with quality of life, assessed using WHOQOL-BREF, among patients with schizophrenia.

MATERIALS AND METHODS

Study design and setting

This was an observational analytic study using a case-control design, conducted at the inpatient ward of Rumah Sakit Khusus Daerah (RSKD) Dadi, South Sulawesi Province, and at the Hasanuddin University Medical Research Center (HUMRC) laboratory, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia, between April and June 2025.

Study population and case/control definitions

The source population comprised all patients with schizophrenia (ICD-10 code F20) admitted to RSKD Dadi during the study period. Cases were patients aged 18–55 years diagnosed with schizophrenia according to ICD-10/PPDGJ-III criteria who (or whose family) provided written informed consent. Controls were physically and mentally healthy individuals aged 18–55 years, screened using the Mini-ICD-10, who provided written informed consent. Individuals with comorbid organic disease were excluded. Drop-out criteria were withdrawal of consent, inability to complete study procedures due to illness, or death during the study period.

Sample size and sampling technique

The minimum required sample size, calculated using the two-independent-proportions formula ($Z\alpha$=1.96, $Z\beta$=0.84, P1=0.504, P2=0.154, based on prior data from Shariati et al.[8]), was 28 participants per group.[14] To enhance statistical power, 100 cases and 100 controls were enrolled using consecutive sampling, in which all eligible individuals presenting during the study period were included.[15]

DNA extraction and PCR-RFLP genotyping

Genomic DNA was extracted from peripheral venous blood samples using a commercial extraction kit involving proteinase K digestion, cell lysis, ethanol-based column binding, sequential washing, and elution. The SNP8NRG241930 locus was amplified by PCR using forward primer 5′-AGAAGGGGAAGATTCAAGATGG-3′ and reverse primer 5′-TCATGGACTGATGTGGCAATG-3′, in a 25 µL reaction containing GoTaq Master Mix Green (12.5 µL), each primer (0.5 µL), nuclease-free water (6.5 µL), and template DNA (5.0 µL). Thermal cycling consisted of initial denaturation at 94°C for 3 minutes, followed by 35 cycles of denaturation (94°C, 50 s), annealing (56°C, 45 s), and extension (72°C, 70 s), with a final extension at 72°C for 10 minutes. The 897-bp amplicon was confirmed by 2% agarose gel electrophoresis with ethidium bromide staining. Restriction digestion was performed using ScaI endonuclease (1 µL enzyme, 2 µL 10× H buffer, 5 µL PCR product, 12 µL sterile water) at 37°C for 1 hour. Genotypes were assigned according to fragment size: GG, 576/174/147 bp; GT, 750/576/174/147 bp; and TT, 750/147 bp.

Quality of life assessment

Quality of life among patients was assessed using the validated Indonesian-language WHOQOL-BREF instrument, comprising 26 items across four domains: physical health, psychological well-being, social relationships, and environment. Items were rated on a 5-point Likert scale and transformed to a 0–100 scale, with higher scores indicating better quality of life.

Outcome and independent variables

The primary outcomes were schizophrenia case status and WHOQOL-BREF domain scores. The primary independent variable was SNP8NRG241930 genotype (TT, GT, GG) and allele (T, G). Demographic and clinical covariates included age, sex, marital status, education level, ethnicity, and family history of schizophrenia.

Statistical analysis

Categorical variables were summarized as frequencies and percentages and compared between groups using the chi-square test. Genotype distribution between case and control groups was compared using the Kruskal-Wallis test. Because WHOQOL-BREF domain scores were not normally distributed, the Mann-Whitney U test was used to compare scores between genotype and allele groups; the chi-square test was used to compare categorized (poor/moderate/good) overall quality-of-life scores across genotype and allele groups. Statistical significance was set at $p<0.05$, with 95% confidence intervals reported where applicable.

Ethics approval and informed consent

This study was approved by the Ethics Committee of Hasanuddin University, Hasanuddin University State Higher Education Hospital (RSPTN) (approval no. 225/UN4.6.4.5.31/PP36/2025; date: April 11, 2025). Written informed consent was obtained from all participants or their legal representatives prior to enrollment.

RESULTS

Participant characteristics

A total of 200 participants were analyzed, comprising 100 patients with schizophrenia (cases) and 100 healthy controls. Mean age was higher among cases (35.6±7.4 years) than controls (31.7±7.9 years). Cases were predominantly male (86.0%), whereas controls were predominantly female (67.0%). Most cases were unmarried (74.0%), whereas most controls were married (56.0%). Educational attainment differed markedly between groups: 90.0% of controls had a high level of education, compared with only 1.0% of cases, among whom moderate (52.0%) and low (47.0%) education levels predominated. The most common ethnic groups in both samples were Bugis (49.5%) and Makassar (29.5%). A family history of schizophrenia was reported by 12.0% of cases and 10.0% of controls (Table 1).

Across genotype subgroups, the GT genotype showed a similar demographic skew to the overall case group, with male predominance, lower educational attainment, and unmarried status more common among cases than controls, while the small number of patients carrying the GG genotype precluded detailed stratified demographic comparison.

SNP8NRG241930 genotype and allele distribution

Three genotypes (TT, GT, GG) were identified among controls, whereas only GT and GG were observed among cases, with no TT genotype detected in this group. The GT genotype was more frequent among cases (91.0%) than controls (77.0%), while the GG genotype was more frequent among controls (21.0%) than cases (9.0%). Genotype distribution differed significantly between groups ($\chi^2=3.829$, $p=0.050$) (Table 2). At the allele level, the G allele was more frequent than the T allele in both groups (57.0% vs. 43.0% overall), but the difference in allele frequency between cases and controls did not reach statistical significance ($p=0.313$).

Quality of life by genotype among patients with schizophrenia

Descriptive analysis of WHOQOL-BREF domain scores among patients showed consistently higher mean scores for GT carriers than GG carriers across all four domains: physical (53.10±11.03 vs. 47.62±10.10), psychological (49.63±12.23 vs. 39.82±9.34), social (45.60±12.99 vs. 33.33±9.32), and environmental (44.64±11.37 vs. 40.63±5.85) (Table 3).

Association between genotype/allele and WHOQOL-BREF domains

Mann-Whitney U tests confirmed that GT carriers had significantly higher scores than GG carriers in the psychological ($p=0.021$) and social ($p=0.005$) domains; differences in the physical ($p=0.153$) and environmental ($p=0.198$) domains were not statistically significant (Table 4). No significant differences in any domain were observed when patients were compared by allele (T vs. G; all $p>0.05$). When quality of life was instead categorized into poor, moderate, and good overall scores, no statistically significant association was found with genotype ($\chi^2=5.203$, $p=0.074$) or allele ($\chi^2=0.859$, $p=0.651$), although a numerically larger proportion of GG carriers fell into the poor category (44.4%) compared with GT carriers (15.4%).

Table 1. Demographic and Clinical Characteristics of Case and Control Groups

Characteristic	Control (n=100)	Case (n=100)	Total (n=200)
Age, years, mean ± SD	31.7 ± 7.9	35.6 ± 7.4	33.6 ± 7.9
Sex			
Male	33 (33.0%)	86 (86.0%)	119 (59.5%)
Female	67 (67.0%)	14 (14.0%)	81 (40.5%)
Marital status			

Married	56 (56.0%)	26 (26.0%)	82 (41.0%)
Unmarried	44 (44.0%)	74 (74.0%)	118 (59.0%)
Education level			
High	90 (90.0%)	1 (1.0%)	91 (45.5%)
Moderate	10 (10.0%)	52 (52.0%)	62 (31.0%)
Low	0 (0.0%)	47 (47.0%)	47 (23.5%)
Ethnicity			
Bugis	45 (45.0%)	54 (54.0%)	99 (49.5%)
Makassar	28 (28.0%)	31 (31.0%)	59 (29.5%)
Other	27 (27.0%)	15 (15.0%)	42 (21.0%)
Family history of schizophrenia			
Present	10 (10.0%)	12 (12.0%)	22 (11.0%)
Absent	90 (90.0%)	88 (88.0%)	178 (89.0%)

SD: standard deviation. Percentages are column percentages within each group.

Table 2. Distribution of SNP8NRG241930 Genotype and Allele in Case and Control Groups

Variable	Control (n=100)	Case (n=100)	Total / p-value
Genotype			
TT	2 (2.0%)	0 (0.0%)	2 (1.0%)
GT	77 (77.0%)	91 (91.0%)	168 (84.0%)
GG	21 (21.0%)	9 (9.0%)	30 (15.0%)
Total	**100 (100%)**	**100 (100%)**	**χ^2=3.829; p=0.050***
Allele (n=200 per group)			
T	81 (40.5%)	91 (45.5%)	172 (43.0%)
G	119 (59.5%)	109 (54.5%)	228 (57.0%)
Total	**200 (100%)**	**200 (100%)**	**p=0.313**

**Kruskal-Wallis test for genotype distribution; chi-square test for allele distribution. p<0.05 considered statistically significant.*

Table 3. WHOQOL-BREF Domain Scores by SNP8NRG241930 Genotype among Patients with Schizophrenia (n=100)

Domain	Genotype	Min–Max	Mean ± SD	Median
Physical	GT	28.57 – 75.00	53.10 ± 11.03	53.57
	GG	35.71 – 64.29	47.62 ± 10.10	46.43
Psychological	GT	20.83 – 79.17	49.63 ± 12.23	50.00
	GG	29.17 – 54.17	39.82 ± 9.34	37.50
Social	GT	16.67 – 75.00	45.60 ± 12.99	41.67
	GG	25.00 – 50.00	33.33 ± 9.32	33.33
Environmental	GT	25.00 – 78.13	44.64 ± 11.37	43.75
	GG	34.38 – 53.13	40.63 ± 5.85	40.63

SD: standard deviation. No patient carried the TT genotype; analysis restricted to GT and GG carriers.

Table 4. Association between SNP8NRG241930 Genotype/Allele and WHOQOL-BREF Domain Scores among Patients with Schizophrenia

Domain	Category	n	U	p-value
By genotype				
Physical	GT / GG	91 / 9	291.5	0.153
Psychological	GT / GG	91 / 9	218.5	0.021 *
Social	GT / GG	91 / 9	182.5	0.005 *
Environmental	GT / GG	91 / 9	303.5	0.198
By allele				
Physical	T / G	91 / 109	4723.5	0.560
Psychological	T / G	91 / 109	4577.5	0.345
Social	T / G	91 / 109	4505.5	0.255
Environmental	T / G	91 / 109	4747.5	0.600

*Mann-Whitney U test. *p<0.05 considered statistically significant.*

DISCUSSION

Main findings

This case-control study found that the SNP8NRG241930 genotype, but not allele frequency, differed significantly between patients with schizophrenia and healthy controls, with the heterozygous GT genotype overrepresented among cases. Among patients, GT carriers reported significantly better psychological and social quality-of-life scores than GG carriers, while physical and environmental domains and allele-level comparisons showed no significant differences.

Comparison with previous studies

The demographic profile of patients in this study male predominance, younger and largely unmarried status, and lower educational attainment relative to controls mirrors patterns reported across Asian, European, and North American cohorts, suggesting that these sociodemographic correlates of schizophrenia are broadly generalizable even as genetic findings vary by population.[16,17]

The predominance of the GT genotype among cases is consistent with findings from Iran, where Shariati et al. used the same PCR-RFLP/ScaI approach to demonstrate an association between SNP8NRG241930 and schizophrenia risk, although the specific risk genotype identified differed (GG). In China, Kang et al. reported an association between NRG1 polymorphisms and auditory P300 abnormalities, a schizophrenia endophenotype, supporting a functional role for this genomic region.[18] Conversely, studies among Japanese and Saudi Arabian populations have reported divergent genotype distributions, and large Western consortium analyses have found no significant association between NRG1 variants and schizophrenia.[19,20,21] A meta-analysis by Mostaid et al. similarly concluded that associations between 5′ and 3′ NRG1 variants and schizophrenia are population-dependent rather than universal. These discrepancies likely reflect differences in linkage disequilibrium structure, allele frequencies, and ethnic background across study populations, reinforcing the value of population-specific genetic data, including the data generated here from an Indonesian cohort.

Biological mechanisms

NRG1 signals through ErbB4 receptors to regulate cortical GABAergic interneuron development, synapse formation, and glutamatergic and dopaminergic neurotransmission.[22,23] Disruption of NRG1-ErbB4 signaling alters excitatory-inhibitory synaptic balance in the mature cortex, a mechanism consistent with the neurodevelopmental hypothesis of schizophrenia. Because SNP8NRG241930 lies near the 5′ regulatory region of NRG1, this variant may influence transcriptional activity or isoform expression, providing a plausible biological basis for its association with both disease risk and downstream functional outcomes such as quality of life.[24,25]

Clinical implications

The association between genotype and the psychological and social domains of quality of life, independent of its association with disease risk, suggests that NRG1 variation may have a dual role as both a susceptibility factor and a modifier of functional prognosis. This finding supports the emerging concept of personalized psychiatry, in which genetic information could eventually complement clinical assessment in tailoring psychosocial interventions and anticipating which patients may be at greater risk of poor psychological and social functioning after disease onset.

Public health implications

The pattern of low-to-moderate quality of life across all WHOQOL-BREF domains observed in this Indonesian cohort mirrors findings from outpatient

and community samples elsewhere in Indonesia, where psychological and social domains are consistently the most affected.[26,27,28] Comparable patterns have been reported elsewhere in Asia, including in South Korea, where negative symptoms and impaired interpersonal functioning were identified as key determinants of quality of life.[29] These convergent findings underscore the importance of stigma reduction, community-based psychosocial rehabilitation, and family support programs as complements to pharmacological treatment in resource-limited settings such as Indonesia.

Strengths

To our knowledge, this is the first study to jointly examine SNP8NRG241930 genotype distribution and its association with patient-reported quality of life in an Indonesian population, combining molecular genotyping with a validated, cross-culturally adapted outcome measure in a reasonably large sample of 200 participants.

Limitations

This study has several limitations. The number of patients with the GG genotype was small, and no patient carried the TT genotype, limiting the precision and generalizability of genotype-stratified comparisons. Recruitment from a single center within a predominantly Bugis and Makassar ethnic population raises the possibility of population stratification, and Hardy-Weinberg equilibrium testing was not performed. PCR-RFLP, while validated and cost-effective, is susceptible to technical artifacts such as incomplete digestion. Finally, quality of life was assessed by self-report, which may be influenced by symptom severity and insight at the time of assessment.

Future research

Larger, multi-center studies incorporating Hardy-Weinberg equilibrium testing, haplotype-based analyses, and more advanced genotyping platforms are needed to confirm these findings. Longitudinal designs that integrate clinical severity, cognitive function, and treatment adherence would help clarify the mechanisms linking NRG1 genotype to functional outcomes in schizophrenia.

CONCLUSIONS

In this Indonesian case-control study, the SNP8NRG241930 genotype of the NRG1 gene, but not allele frequency, was associated with schizophrenia occurrence, with the GT genotype overrepresented among patients. Among patients with schizophrenia, GT carriers reported significantly better psychological and social quality of life than GG carriers. These findings suggest that NRG1 genetic variation may influence both susceptibility to schizophrenia and functional outcomes after disease onset, supporting further investigation of genetic factors in personalized approaches to schizophrenia management.

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NOTES

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in this manuscript.

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Authors' contributions

Concept: N.F.W.N., S.T.L.; Design N.F.W.N., S.T.L.; Supervision: S.T.L.; Resources: S.T.L., A.A.Z.; Materials: R.R.; Data collection and/or processing: N.F.W.N., R.R.; Analysis and/or interpretation: N.F.W.N., S.T.L.; Literature search : N.F.W.N.; Writing manuscript: N.F.W.N.; Critical review: S.T.L., S.S., A.A.Z. All authors read and approved the final version of the manuscript.

Ethics approval

Ethical approval was obtained from the Ethics Committee of Hasanuddin University, Hasanuddin University State Higher Education Hospital (RSPTN) (approval no. 225/UN4.6.4.5.31/PP36/2025; date: April 11, 2025).

Informed consent

Written informed consent was obtained from all subjects or their legal representatives prior to participation.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Artificial intelligence usage statement

The authors used an artificial intelligence tool solely for grammar editing during the preparation of this

manuscript. The tool was not used for data analysis, interpretation, or generation of scientific content. All intellectual content, including study design, analysis, and conclusions, was developed entirely by the authors.

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