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# *NR3C1* Polymorphisms for Genetic Susceptibility to Schizophrenia

**Joo Seok Park, MD,[1] Sang Min Lee, MD,[1,2] Jong Woo Kim, MD,[1,2] Won Sub Kang, MD[1,2]**

[1]*Department of Psychiatry, Kyung Hee University Hospital, Seoul, Korea*
[2]*Department of Psychiatry, College of Medicine, Kyung Hee University, Seoul, Korea*

**Objectives** Psychological stress has been known to increase the risk of schizophrenia. Because stress responses are mainly mediated by cortisol, the action of the glucocorticoid receptors (Nuclear Receptor Subfamily 3 Group C Member 1, NR3C1) is possibly related to the pathogenesis of schizophrenia. In this study, we investigated the associations between polymorphisms of *NR3C1* and schizophrenia.
**Methods** Four single nucleotide polymorphisms (SNPs) (rs17100236, rs2963155, rs9324924, and rs7701443) of *NR3C1* were genotyped in 208 patients with schizophrenia and 339 healthy individuals. A chi-square test was performed to test differences in allele distributions among groups. A multiple logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), and multiple inheritance models to analyze the associations between schizophrenia and SNPs (the dominant, recessive and additive models).
**Results** The minor allele frequencies of two SNPs were significantly higher in the schizophrenia group than in those of the control group (rs2963155 G > A : 0.25 vs. 0.18, p = 0.0066 ; rs7701443 A > G : 0.40 vs. 0.33, p = 0.012). The genotype frequencies of two SNPs were found to be significantly different between patients with schizophrenia and controls in the dominant model (rs2963155 : AG/GG vs. AA, OR = 1.66, 95% CI = 1.16−2.38, p = 0.0055, rs7701443 : AG/AA vs. GG, OR = 1.61, 95% CI = 1.11−2.34, p = 0.01) and the log-additive model (rs2963155 : AG vs. GG vs. AA, OR = 1.54, 95% CI = 1.13−2.10, p = 0.0067).
**Conclusions** This study showed significant associations between *NR3C1* polymorphisms and schizophrenia. It suggests that *NR3C1* may play a role in the pathogenesis of schizophrenia.

**Key Words** NR3C1 gene · Schizophrenia · Genetic polymorphisms.

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**Address for correspondence:** Won Sub Kang, MD
Department of Psychiatry, College of Medicine, Kyung Hee University, 26 Kyung Hee dae-ro, Dongdaemun-gu, Seoul 02447, Korea
**Tel:** +82-2-958-8551, **Fax:** +82-2-957-1997, **E-mail:** menuhinwskang@khu.ac.kr

## Introduction

Schizophrenia is one of the most common, serious mental disorders and often has a long-lasting, deteriorating course. The exact cause of schizophrenia is yet to be clarified, but the interaction of various biological and environmental factors is known to be associated with the development of the disorder.[1)] Although stressful life events are related to the onset of schizophrenia, and patients with schizophrenia tend to report greater subjective stress and negative emotions to stressors,[2)3)] they do not seem to experience more stressful life events than the general population.[2)] This suggests that psychological stress increases the risks of developing schizophrenia, especially in individuals with genetic susceptibility. However, little is known about how stress affects the pathogenesis of schizophrenia.[1)4)]

The hypothalamic-pituitary-adrenal axis (HPA axis) is a major neuroendocrine system that mediates stress responses. The HPA axis is considered to be the main system that explains the link between stress and psychosis, and dysregulation of the HPA axis in schizophrenia has widely been demonstrated.[5)] In patients with schizophrenia, a blunted cortisol awakening response[6)] and a non-suppression in the dexamethasone suppression test[7)] were reported. Several studies have shown cortisol hyper-secretion regardless of stress events in schizophrenia,[6)8)] and reduction in cortisol levels after antipsychotic treatment was also observed.[9)] Moreover, the severity of schizophrenia symptoms tends to be positively related to cortisol levels.[10)] In addition, the difference in expression of the glucocorticoid receptor (Nuclear Receptor Subfamily 3 Group C Member 1, NR3C1) gene was reported. NR3C1 mRNA expression has been shown to be decreased in the frontal cortex, inferior temporal cortex, entorhinal cortex, and hippocampus in the brains of patients with schizophre-

 

nia.[11] Other studies also showed that NR3C1 mRNA expression in schizophrenia was decreased in the dorsolateral prefrontal cortex than controls, and those differences in mRNA expression were related to particular polymorphisms of *NR3C1*.[12]

Stress responses by the HPA axis are controlled mainly by cortisol, which acts on various target cells. These actions of cortisol are mediated by an intracellular protein, the glucocorticoid receptor (GR).[13] GR, also known as NR3C1, exists in almost all cells of a human body. GR can function both as a transcription factor that binds to glucocorticoid response elements in the promoters of glucocorticoid responsive genes to activate their transcription, and as a regulator of other transcription factors. That is, when cortisol binds to GR, the cortisol-GR complex moves into the nucleus and activates gene transcription of anti-inflammatory proteins, or represses the expression of pro-inflammatory proteins by interacting other transcription factors such as NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells).[14] *NR3C1* contains 10 exons coding for 777 amino acids and is located on chromosome 5q,[15] on which several other susceptibility loci linked to schizophrenia were demonstrated.[16-19]

In light of the above, it can be hypothesized that genetic variations of *NR3C1* may be associated with a predisposition to schizophrenia. However, the relationship between *NR3C1* polymorphism and schizophrenia has been little studied before. Therefore, the aim of this study was to investigate the associations between *NR3C1* polymorphisms and schizophrenia.

## Methods

### Subjects

Inpatients diagnosed with schizophrenia [n = 208, mean age ± standard deviation (SD) : 37.2 ± 10.6 years] and healthy control individuals (n = 339, mean age ± SD : 44.4 ± 6.4 years) were recruited from the Department of Psychiatry of Kyung Hee University Hospital in Korea. Each patient's consensus diagnosis of schizophrenia was made by at least two experienced psychiatrists using interviews, clinical records and family history according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria. We excluded patients diagnosed with schizophreniform disorder, schizoaffective disorder, substance-induced psychotic disorder, major depressive disorder with psychotic features, bipolar disorder, or mental retardation. The control subjects were recruited from individuals visiting the hospital for routine health checkup. The controls were screened with a general health examination program to exclude any major psychiatric illnesses. We also excluded subjects with serious medical conditions or neurological diseases, such as organic brain disease. This study was carried out as recommended in the Helsinki Declaration. All participants signed an informed consent form, and the study received approval by the Ethical Review Committee of the Medical Research Institute of Kyung Hee University Medical Center, Seoul, Korea (IRB No. 2004-09-15).

### Genotyping

We searched the single nucleotide polymorphism (SNP) database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP) for SNP of *NR3C1* candidates. We considered the presence of Asian genotype frequency data and the positions of the polymorphisms in the gene, and SNPs with a heterozygosity ≤ 0.2 or a minor allele frequency ≤ 0.2 were excluded. Finally, the following four SNPs (rs17100236, rs2963155, rs9324924, and rs7701443) were selected to be analyzed (Fig. 1).

After extracting genomic DNA from peripheral blood samples with DNA isolation kit (Roche, Indianapolis, IN, USA), direct sequencing of four SNPs was performed to determine genotypes of SNPs (MACROGEN, Seoul, Korea). For direct sequencing, DNA samples were amplified by polymerase chain reaction (PCR) using the following primers for each SNP. : rs17100236 (forward primer, 5'-CAGTCTGTGGGCAAACA CAA-3'; reverse primer, 5'-AAGCCATGGGGCCATT TACC-3'), rs2963155 (forward primer, 5'-ACAGCGGGAAAG AACTGTGG-3'; reverse primer, 5'-AGCAGGCCTACCT GACTTTC-3'), rs9324924 (forward primer, 5'-ATGTCTC CACATTCACCCACC-3'; reverse primer, 5'-GCCTTAT ACTGGGGCCTAACA-3'), and rs7701443 (forward primer, 5'-AGGCCCCAGTATAAGGCTGC-3'; reverse primer, 5'-CCTCTAGGAAACCCTCCGTGA-3') The PCR products were sequenced by ABI PRISM 3730XL analyzer (PE Applied

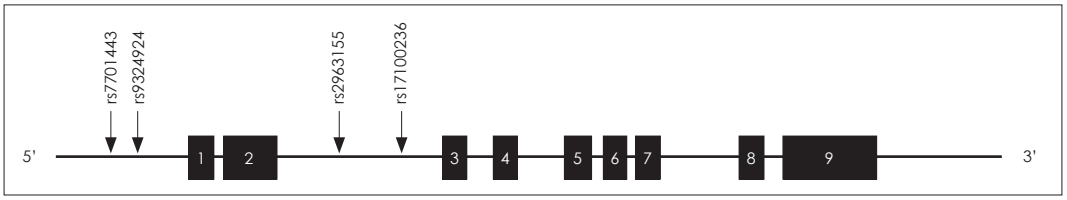


**Fig. 1.** Gene map and location of single nucleotide polymorphisms (SNPs) in *NR3C1*. Black boxes and white numbers represent exons with each exon numbers. Arrow indicates the location of each SNP.

Biosystems, Foster City, CA, USA), and analyzing the sequenced data was done by SeqManII software (DNASTAR Inc., Madison, WI, USA).

### Statistical analysis

We assessed genotype frequencies using SNPAnalyzer Pro (ISTECH Inc., Goyang, Korea) and SNPStats (http:// bioinfo.iconcologia.net/index.php), and also checked genotypes for agreement with the Hardy-Weinberg equilibrium. A chi-square test was used to examine the differences of the allele frequencies between groups with Haploview 4.2. To analyze the associations between schizophrenia and each SNP, a multiple logistic regression model was performed to calculate odds ratios (ORs) and the 95% confidence intervals (CIs) and p-values, correcting for age and gender. Then, we determined whether the polymorphism follows specific inheritance models such as the dominant model (minor allele homozygote genotype and heterozygote genotype have a similar risk for the disease), the recessive model (only minor allele homozygote genotype has an increased risk of the diseases), or the additive model (the risk of minor allele homozygote genotype is twice as high as that of heterozygote).

We evaluated the linkage disequilibrium (LD) block and haplotypes using Haploview 4.2 (Daly Lab, Cambridge, MA, USA). Bonferroni correction was applied to avoid the problem of multiple testing. Statistical significance was evaluated using SPSS statistics version 24 (IBM Corp., Armonk, NY, USA). A Bonferroni corrected p-value < 0.0125 (0.05/a number of tested SNPs) was regarded as statistically significant.

## Results

Tested SNPs in both patients with schizophrenia and the control showed genotype distributions in agreement with Hardy-Weinberg equilibrium ($p > 0.05$). The allele frequencies of each SNPs of schizophrenia and the control are listed in Table 1. Significant differences in the allele frequencies of two SNPs (rs2963155 and rs7701443) between patients with schizophrenia and controls were demonstrated. The minor G allele frequency of the rs2963155 and the minor A allele frequency of the rs7701443 were higher in the schizophrenia group than in the control group (G allele of rs2963155 : 0.25 vs. 0.18, $p = 0.0066$ ; A allele of rs7701443 : 0.40 vs. 0.33, $p = 0.012$).

In the genotype frequency analysis, two SNPs (rs2963155 and rs7701443) showed a significant difference between schizophrenia and controls (Table 2). The genotype frequencies of rs2963155 of *NR3C1* were significantly different between patients with schizophrenia and controls in the dominant (AG/GG vs. AA, OR = 1.66, 95% CI = 1.16-2.38, $p = 0.0055$) and in the log-additive model (AG vs. GG vs. AA, OR = 1.54, 95% CI = 1.13−2.10, $p = 0.0067$) (Table 2). In the dominant model, the frequency of genotypes carrying G allele (AG/GG) of rs2963155 was higher in the schizophrenia group (45.7%) than in the control group (33.3%). The rs7701443 also showed a significant association with schizophrenia in the dominant model (AG/AA vs. GG, OR = 1.61, 95% CI = 1.11-2.34, $p = 0.01$) (Table 2). Carrying the A allele (AG/AA) was significantly more frequent in the schizophrenia group (68.3%) than in the control group (56.3%).

We tested a LD block of the SNPs according to Gabriel et al.[20] but no meaningful LD block was constructed. Results of haplotype analysis in the SNPs were not significant either.

## Discussion

There were several studies on the associations between *NR3C1* and psychiatric illnesses. It is widely studied that epigenetic changes of *NR3C1* were related to trauma- or stress-related disorder, such as post-traumatic stress disorder, depression, borderline personality disorder.[21][22] The relationship between *NR3C1* polymorphisms and other psychiatric illnesses also have been

**Table 1.** Allele frequencies of *NR3C1* polymorphisms in schizophrenia and controls

| SNP | Alleles | Frequency | Schizophrenia | | Control | | p |
|---|---|---|---|---|---|---|---|
| | | | n | f | n | f | |
| rs17100236 | T | 0.82 | 332 | 0.80 | 567 | 0.84 | 0.109 |
| | C | 0.18 | 84 | 0.20 | 111 | 0.16 | |
| rs2963155 | A | 0.79 | 312 | 0.75 | 555 | 0.82 | 0.0066* |
| | G | 0.21 | 104 | 0.25 | 123 | 0.18 | |
| rs9324924 | G | 0.57 | 228 | 0.55 | 400 | 0.59 | 0.174 |
| | T | 0.43 | 188 | 0.45 | 278 | 0.41 | |
| rs7701443 | G | 0.64 | 248 | 0.60 | 455 | 0.67 | 0.012* |
| | A | 0.36 | 168 | 0.40 | 223 | 0.33 | |

* : A significant association after Bonferroni correction ($p < 0.0125$). NR3C1 : Nuclear receptor subfamily 3 group C member 1, SNP : Single nucleotide polymorphism, n : Number, f : Frequency

**Table 2.** Genotype frequencies of *NR3C1* polymorphisms in schizophrenia and controls

| SNP | Genotype | Schizophrenia | | Control | | Model | OR (95% CI) | p |
|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | | |
| rs17100236 | T/T | 133 | 63.9 | 236 | 69.6 | Dominant (CT/CC vs. TT) | 1.35 (0.93−1.96) | 0.11 |
| | C/T | 66 | 31.7 | 95 | 28.0 | Recessive (CC vs. TT/CT) | 2.09 (0.78−5.64) | 0.14 |
| | C/C | 9 | 4.3 | 8 | 2.4 | Log-additive | 1.35 (0.98−1.87) | 0.07 |
| rs2963155 | A/A | 113 | 54.3 | 226 | 66.7 | Dominant (AG/GG vs. AA) | 1.66 (1.16−2.38) | 0.0055* |
| | A/G | 86 | 41.4 | 103 | 30.4 | Recessive (GG vs. AA/AG) | 1.56 (0.61−3.97) | 0.35 |
| | G/G | 9 | 4.3 | 10 | 2.9 | Log-additive | 1.54 (1.13−2.10) | 0.0067* |
| rs9324924 | G/G | 63 | 30.3 | 115 | 33.9 | Dominant (GT/TT vs. GG) | 1.21 (0.83−1.77) | 0.31 |
| | G/T | 102 | 49.0 | 170 | 50.1 | Recessive (TT vs. GG/GT) | 1.41 (0.90−2.21) | 0.14 |
| | T/T | 43 | 20.7 | 54 | 15.9 | Log-additive | 1.21 (0.94−1.56) | 0.13 |
| rs7701443 | G/G | 66 | 31.7 | 148 | 43.7 | Dominant (AG/AA vs. GG) | 1.61 (1.11−2.34) | 0.01* |
| | A/G | 116 | 55.8 | 159 | 46.9 | Recessive (AA vs. GG/AG) | 1.26 (0.72−2.20) | 0.41 |
| | A/A | 26 | 12.5 | 32 | 9.4 | Log-additive | 1.38 (1.05−1.81) | 0.021 |

* : Statistically significant values after Bonferroni correction ($p < 0.0125$). NR3C1 : Nuclear receptor subfamily 3 group C member 1, SNP : Single nucleotide polymorphism, OR : Odds ratio, CI : Confidence interval

studied. It has been reported that the BclI and ER22/23EK polymorphisms of *NR3C1* were associated with an increased risk of major depressive disorder and the ER22/23EK carrier showed more favorable antidepressant response.[23] Other studies demonstrated that *NR3C1* polymorphisms were associated with an increased risk of developing depressive disorders,[24] hospitalization for depressive disorder,[25] and major mood episodes in bipolar disorder.[26][27] Manenschijn et al.[28] reported homozygous carriage of the BclI-TthIIII haplotype of *NR3C1* were associated with a decreased risk of delirium. Some *NR3C1* polymorphisms, including rs244465 were associated with early onset of alcohol abuse, which implies *NR3C1* polymorphism might contribute to susceptibility to addiction.[29]

There was one report testing the possible association of *NR3C1* polymorphism and the risks of schizophrenia. Feng et al.[30] scanned DNA samples from 100 patients with schizophrenia and 40 puerperal psychosis and reported no association between the five missense variants of *NR3C1* (R23K, F29L, L112F, D233N, and N363S) and the diagnosis puerperal psychosis or schizophrenia. However, in our study, two SNPs (rs2963155 and rs7701443) showed a significant association with the risks of schizophrenia. In the allele frequency analysis, the minor G allele of rs2963155 and the minor A allele of rs7701443 were more frequent in the patient group compared to controls. Genotype frequencies of two SNPs (rs2963155 and rs7701443) also showed a significant difference between schizophrenia and controls. Genotypes carrying G allele (AG/GG) of rs2963155 were more frequent in the schizophrenia group than in the control group. The significant association of carrying G allele of rs2963155 with the risks of schizophrenia was demonstrated in both the dominant and additive model (dominant model : $p = 0.0055$ ; additive model : $p = 0.0067$) (Table 2). Genotypes carrying A allele(AG/AA) of rs7701443 showed a significant association with the risks of schizophrenia in the dominant model ($p = 0.01$) (Table 2).

Focusing on the two SNPs which showed a significant association in the present study, previous studies showed that rs2963155 was associated with corticosteroid dependence in Crohn's disease of pediatric onset,[31] and the risk of infantile spams.[32] Several studies revealed that rs7701443 was related to systolic blood pressure and body-mass index,[33] and systemic lupus erythematosus.[34] Moreover, rs7701443 was also found to have associations with steroid treatment responses in medical illnesses, including corticosteroid resistance in Crohn's disease of pediatric,[31] poor prednisone response in childhood acute lymphoblastic leukemia,[35] a decreased risk of glucocorticoid resistance in pemphigus vulgaris treatment.[36]

As above, among SNPs we investigated, rs7701443 was more frequently reported to be significantly associated with response to steroid treatment. Because rs7701443 is located in the promoter region of *NR3C1*, the polymorphism may be associated with transcriptional change. To find whether alleles of rs7701443 were related to transcription factors, we used the program "AliBaba 2.1" (http://www.gene-regulation.com/pub/programs/alibaba2). At rs7701443 SNP site, transcription factor NF-κB and NF-1 were able to bind to A allele carrying sequences, but NF-κB did not bind to G allele carrying sequence. Therefore, this SNP may regulate gene expressions by controlling the binding of transcription factors.

Mizoguchi et al.[37] demonstrated that endogenous glucocorticoid deficiency in rats was related to impaired working memory, probably through the hypodopaminergic state in the prefrontal cortex, which means glucocorticoids are essential for

prefrontal cortex cognitive function. And also in several human genetic studies, *NR3C1* polymorphisms were associated with working memory performance.[38)39)] With these result, Kumsta et al.[38)] speculated NR3C1 might be associated with working memory impairments in stress-related psychiatric disorders, and other researchers described that impaired working memory related to the HPA dysregulation might explain one of the negative symptoms of schizophrenia.[40)]

Due to the moderate sample size, there may exist type I errors. Also, since all participants were Korean, further validations using larger samples of other ethnic groups may be required. Future research including functional investigations is needed to explain the role of *NR3C1* in the pathogenesis of schizophrenia. Despite the limitations, the results of the present study show possible associations of schizophrenia pathogenesis and NR3C1, which has been underestimated.

In conclusion, we demonstrated two SNPs (rs2963155 and rs7701443) of *NR3C1* were associated with the risks of schizophrenia. This result suggests that these *NR3C1* polymorphisms may be related to the susceptibility of schizophrenia. To confirm this, future studies with larger number of cases will be required.

## Conflicts of interest

The authors have no financial conflicts of interest.

## Author Contributions

Conceptualization: Joo Seok Park, Jong Woo Kim, Won Sub Kang. Data curation: Sang Min Lee, Won Sub Kang. Formal analysis: Joo Seok Park, Won Sub Kang. Investigation: Sang Min Lee, Won Sub Kang. Methodology: Joo Seok Park, Jong Woo Kim, Won Sub Kang. Project administration: Jong Woo Kim, Won Sub Kang. Resources: Jong Woo Kim. Software: Joo Seok Park, Won Sub Kang. Supervision: Jong Woo Kim, Won Sub Kang. Validation: Jong Woo Kim, Won Sub Kang. Visualization: Joo Seok Park. Writing—original draft: Joo Seok Park, Won Sub Kang. Writing—review & editing: Joo Seok Park, Sang Min Lee, Jong Woo Kim, Won Sub Kang.

## ORCID iDs


| | |
|---|---|
| Won Sub Kang | https://orcid.org/0000-0003-0495-2861 |
| Joo Seok Park | https://orcid.org/0000-0002-0511-2840 |
| Jong Woo Kim | https://orcid.org/0000-0001-7004-3792 |
| Sang Min Lee | https://orcid.org/0000-0002-7834-8272 |


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