

# Correlation of Four Single Nucleotide Polymorphisms of the *RELN* Gene With Schizophrenia

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\* Equal contribution

## Abstract

**Objective:** This study aims to determine the association between single-nucleotide polymorphisms (SNPs) of the *RELN* gene and schizophrenia.

**Methods:** 134 patients aged 16 to 58 (mean, 38.0) years who were diagnosed with acute or chronic schizophrenia at the Zhongshan Third People's Hospital between January 2018 and April 2020 were recruited, as were 64 healthy controls aged 22 to 59 (mean, 45.6) years who matched with the age and sex of the patients. MassARRAY mass spectrometry genotyping technology was used to determine the genotypes of four SNPs of *RELN* (rs2073559, rs2229864, rs362691, and rs736707).

**Results:** There were no significant between-group or between-sex differences in terms of genotype, allele frequency, or haplotype frequency of the SNPs (all  $p > 0.05$ ). In the association analysis between genotypes and quantitative traits in the Positive and Negative Syndrome Scale, rs2229864 and rs736707 were associated with the scores for items P3 (hallucinatory behaviour) and G11 (attention disorder), and rs362691 was associated with G10 (disorientation). However, the associations did not remain significant after Bonferroni correction.

**Conclusion:** Multiple pathogenic polymorphisms of *RELN* might be associated with hallucinatory behaviour and attention disorder in Chinese patients with schizophrenia.

**Key words:** Alleles; Genotype; Hallucinations; Polymorphism, single nucleotide; Reelin protein; Schizophrenia

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## Introduction

Schizophrenia is a complex genetically based psychiatric disorder characterised by auditory hallucinations, delusions,

and cognitive impairment. The onset of schizophrenia usually occurs in late adolescence or early adulthood.<sup>1</sup> Schizophrenia is one of the ten most common causes of disability in young people. Its prevalence is approximately 1%. According to the 2019 mental health epidemiological survey in China, the lifetime prevalence of schizophrenia is 0.7%.<sup>2</sup> Schizophrenia impacts patients' social relations and employment opportunities and is a heavy economic burden.<sup>3,4</sup> Family, twin, and adoption studies have reported that schizophrenia has a strong genetic tendency and that its heritability can reach 80% to 85%.<sup>5</sup> However, finding a susceptibility gene is difficult. At least 100 genes have been reported to be associated with schizophrenia, but only a few have consistently shown such an association in multiple regions and ethnic groups.<sup>6</sup> Genome-wide association studies that investigate single-nucleotide polymorphisms (SNPs) and copy number variation have been used to provide genetic evidence for the aetiology of schizophrenia. Multiple functional variants of genes in neurodevelopmental pathways may be involved in the development of the illness.<sup>7,8</sup>

Brain-structure and animal experiments have revealed that aberrations in neurodevelopment may be a factor in the aetiology of schizophrenia. Moreover, molecular genetic studies have confirmed several repeatable chromosomal

locations and susceptibility genes, suggesting that genetic variations in multiple neurodevelopmental pathways are involved in the disease progress.<sup>9</sup>

A number of susceptibility genes are implicated for schizophrenia, including several short repetitive sequences in the *RELN* gene, which is located on chromosome 7q22.1 and encodes the protein reelin.<sup>10</sup> rs7341475 polymorphism increases the risk of schizophrenia by 1.4-fold in women.<sup>11</sup> Genetic variants in *RELN* are associated with working memory, situational memory, and executive function in core symptoms of patients with schizophrenia.<sup>10</sup> SNPs in some *RELNs* may mediate schizophrenia pathogenesis and clinical symptom severity.<sup>12-14</sup>

Reelin is a serine protease located in the extracellular matrix. During brain development, reelin plays an important role in the migration of neurons and formation of the sebaceous layer. In mice, spontaneous deletion of *RELN* leads to abnormal brain function, causing uncoordinated movement. Reelin is also important for brain function after birth and throughout adulthood. Adult reelin signal interruption causes changes in synaptic signalling and plasticity, leading to neuropsychiatric diseases.<sup>15</sup> In a Finnish population, loci in the 7q22 region, including *RELN*, are associated with the endophenotype of schizophrenia.<sup>16</sup>

It remains controversial whether the genetic polymorphism of *RELN* is associated with psychiatric disorders. Some found evidence for the association between *RELN* polymorphism and schizophrenia; others reported dissimilar conclusions. In a meta-analysis of SNPs of *RELN*, the rs736707 locus was associated with schizophrenia in the Asian population.<sup>17</sup> In a study of 103 schizophrenic patients and 169 healthy controls in Guangdong province, China, the A-C-T-T-A and A-C-T-T-G haplotypes in the rs362814-rs39339-rs540058-rs661575-rs727708 haplotype system of *RELN* were associated with increased susceptibility to schizophrenia.<sup>18</sup> In contrast, in a study of 761 schizophrenic patients and 775 healthy controls in Jilin province, China, no association was found between the *RELN* rs736707 locus and schizophrenia.<sup>19</sup> The diverse findings may be due to the small sample size and/or patient heterogeneity (including sex differences or family history of illness). The present study aims to investigate associations between the rs2073559, rs2229864, rs362691, and rs736707 loci of *RELN* and schizophrenia in a population in Zhongshan, Guangdong, China.

## Methods

This study was approved by the ethics committee of Zhongshan Third People's Hospital (reference: SSYLL20180301). Written informed consent was obtained from each participant or his guardian. 134 patients (92 males and 42 females) of Han ethnicity aged 16 to 58 (mean, 38.0) years who were diagnosed with acute or chronic schizophrenia based on the DSM-5 by two attending psychiatrists at the Zhongshan Third People's Hospital between January 2018 and April 2020 were

recruited. Those with major physical diseases (eg, diabetes, hypertension, cancer), nervous system diseases, or other psychiatric diseases were excluded. In addition, 64 healthy controls (38 males and 26 females) aged 22 to 59 (mean, 45.6) years who matched with the age and sex of the patients were recruited. They were workers, nurses, volunteers, and physical examinees from the Zhongshan Third People's Hospital. Those who were adopted or from single-parent families with an unknown family history, with a history of major physical diseases (such as diabetes, hypertension, or cancer), or with a personal history or family history of mental illness were excluded.

For each participant, 5 mL peripheral venous blood was collected. Genomic DNA was extracted using a Tiangen Blood Genomic DNA Extraction Kit (Tiangen Biotech, Beijing, China) and stored at -80°C. The MassARRAY SNP genotyping platform was used for *RELN* genotyping. The loci rs2073559, rs2229864, rs362691, and rs736707 were input into the Agena website (<http://agenacx.com/>) for primer design, and the primers were ordered.

Statistical analysis was performed using SPSS (Windows version 20; IBM Corp, Armonk [NY], US). The Hardy-Weinberg equilibrium was tested using the Chi square test. The online software SHEsis was used for the pairwise SNP linkage disequilibrium, unit point, and haplotype association analyses. A p value of <0.05 was considered statistically significant.

Differences in the frequency distribution of the alleles, genotypes, and haplotypes of linkage disequilibrium in each SNP locus between the schizophrenia and healthy control groups were determined, as were their association with schizophrenia. The degree of linkage disequilibrium between each pair of SNPs was expressed as  $D'$  value ranging from 0 to 1. Higher values indicate higher linkage disequilibrium between the two loci. Then, the polymorphic loci were grouped according to the  $D'$  value, and the SNPs with high linkage disequilibrium were combined into a group for haplotype analysis to determine the 'pair local  $D'/r^2$  value'.

The expectation maximisation calculation method was used to estimate the haplotype frequency, and the threshold was set at 0.03. For the haplotypes, the allele combination with the highest frequency was used as a reference and compared with other allele combinations. The significance of association between a haplotype and schizophrenia was determined by the overall p value.

The optical density of the genomic DNA was measured. All DNA concentrations were >20 ng/μL; optical density of 260/280 was between 1.6 and 2.2 and optical density of 260/230 was >0.6. There was no absorption peak at 230 nm. The DNA bands were intact without serious degradation.

## Results

According to the Hardy-Weinberg genetic equilibrium, there was no significant difference in the gene frequency

of the rs2073559, rs2229864, rs362691, and rs736707 loci of *RELN* between the schizophrenia and healthy control groups or between sexes (Tables 1 and 2). Thus, the two groups are representative of the regional population.

As the genetic distance was long between the four studied polymorphic loci of the *RELN* gene, the  $R^2$  value was relatively low. Therefore, the  $D'$  value was used to represent the linkage disequilibrium between the loci. The  $D'$  values were large between rs2073559 and rs362691 ( $D' = 0.790$ ) and between rs2229864 and rs736707 ( $v = 0.923$ ), whereas the  $D'$  values were low between other pairs of loci ( $D' < 0.5$ ).

Only common haplotypes with a frequency of  $\geq 3\%$  were selected to determine the association between each haplotype and schizophrenia. There were significant differences between the schizophrenia and healthy control groups in rs2073559/rs2229864 (TA\*), rs2073559/rs2229864/rs362691 (TAG\*), and rs2073559/rs2229864/rs362691/rs736707 (TAGA\*), but the difference became

not significant in a pairwise comparison (Table 3).

In the association analysis between genotypes and quantitative traits in the Positive and Negative Syndrome Scale, rs2229864 and rs736707 were associated with both P3 (hallucinatory behaviour) and G11 (attention disorder) [both  $p < 0.05$ ], and rs362691 was associated with G10 (disorientation) [ $p < 0.05$ ]. However, these associations became not significant after Bonferroni correction (Table 4).

## Discussion

Reelin is a member of the glycoprotein family and is involved in neuronal migration, construction of brain structure, and synapse formation and stability during the neurodevelopmental period.<sup>20</sup> Schizophrenia is considered a result of abnormal neurodevelopment; abnormal expression of genes involved in neurodevelopment may contribute to its pathogenesis.<sup>21</sup> Indeed, dysfunction of the

**Table 1. Comparison of rs2073559, rs2229864, rs362691, and rs736707 genotypes between the schizophrenia and healthy control groups**

Group	Sex	rs2073559			rs2229864			rs362691			rs736707		
		CC	TC	TT	AA	GA	GG	CC	CG	GG	AA	GA	GG
Schizophrenia	Male (n = 92)	32	51	9	5	28	59	0	21	71	27	49	16
Healthy control	Male (n = 38)	10	20	8	2	16	20	0	4	34	14	16	8
<b>p Value</b>		<b>0.197</b>			<b>0.434</b>			<b>0.081</b>			<b>0.511</b>		
Schizophrenia	Female (n = 42)	13	14	15	3	14	25	1	7	34	15	20	7
Healthy control	Female (n = 26)	10	10	6	2	10	14	0	7	19	11	12	3
<b>p Value</b>		<b>0.544</b>			<b>0.897</b>			<b>0.457</b>			<b>0.788</b>		
<b>p Value</b>		<b>Schizophrenia vs healthy control</b>			<b>0.798</b>			<b>0.415</b>			<b>0.642</b>		

**Table 2. Comparison of allele frequency of rs2073559, rs2229864, rs362691, and rs736707 between the schizophrenia and healthy control groups**

Group	Sex	rs2073559		rs2229864		rs362691		rs736707	
		C	T	A	G	C	G	A	G
Schizophrenia	Male (n = 92)	115	69	38	146	21	163	103	91
Healthy control	Male (n = 38)	40	36	20	56	4	72	44	32
<b>p Value</b>		<b>0.091</b>		<b>0.201</b>		<b>0.093</b>		<b>0.283</b>	
Schizophrenia	Female (n = 42)	40	44	20	64	9	75	50	34
Healthy control	Female (n = 26)	30	22	14	38	7	45	34	18
<b>p Value</b>		<b>0.167</b>		<b>0.416</b>		<b>0.411</b>		<b>0.309</b>	
<b>p Value</b>		<b>Schizophrenia vs healthy control</b>		<b>0.314</b>		<b>0.169</b>		<b>0.272</b>	

Table 3. Haplotype association analysis

Haplotype	No. (frequency)		p Value	Odds ratio (95% confidence interval)
	Schizophrenia	Healthy control		
rs2073559/rs2229864				
CA*	33 (0.125)	13 (0.102)	0.505	1.259 (0.639-2.480)
CG*	122 (0.453)	57 (0.445)	0.875	1.035 (0.677-1.580)
TA*	25 (0.092)	21 (0.164)	0.035	0.514 (0.275-0.916)
TG*	88 (0.330)	37 (0.289)	0.414	1.211 (0.765-1.916)
rs2073559/rs362691				
CC*	26 (0.098)	11 (0.086)	0.669	1.175 (0.562-2.457)
CG*	129 (0.480)	59 (0.461)	0.628	1.110 (0.727-1.695)
TG*	109 (0.408)	58 (0.453)	0.457	0.851 (0.556-1.302)
rs2073559/rs736707				
CA*	92 (0.345)	42 (0.326)	0.708	1.089 (0.696-1.704)
CG*	63 (0.234)	28 (0.221)	0.783	1.074 (0.648-1.777)
TA*	61 (0.226)	36 (0.284)	0.213	0.738 (0.457-1.192)
TG*	52 (0.195)	22 (0.169)	0.534	1.191 (0.686-2.068)
rs2229864/rs362691				
AG*	53 (0.199)	34 (0.265)	0.159	0.702 (0.428-1.150)
GC*	25 (0.094)	11 (0.086)	0.744	1.132 (0.538-2.379)
GG*	185 (0.689)	83 (0.649)	0.290	1.274 (0.813-1.996)
rs2229864/rs736707				
AA*	55 (0.206)	34 (0.266)	0.201	0.726 (0.444-1.187)
GA*	98 (0.365)	44 (0.344)	0.623	1.117 (0.718-1.738)
GG*	112 (0.418)	50 (0.391)	0.542	1.143 (0.743-1.759)
rs362691/rs736707				
CA*	17 (0.063)	8 (0.059)	0.880	1.071 (0.441-2.598)
GA*	136 (0.508)	70 (0.551)	0.429	0.843 (0.553-1.287)
GG*	102 (0.380)	47 (0.364)	0.753	1.073 (0.693-1.660)
rs2073559/rs2229864/rs362691				
CAG*	28 (0.106)	12 (0.093)	0.630	1.192 (0.584-2.430)
CGC*	21 (0.080)	10 (0.086)	0.914	0.959 (0.448-2.052)
CGG*	100 (0.374)	47 (0.368)	0.729	1.080 (0.698-1.674)
TAG*	25 (0.092)	21 (0.164)	0.028	0.503 (0.271-0.934)
TGG*	85 (0.317)	36 (0.281)	0.351	1.247 (0.784-1.985)
rs2073559/rs2229864/rs736707				
CAA*	29 (0.109)	13 (0.101)	0.765	1.111 (0.556-2.220)
CGA*	62 (0.235)	28 (0.221)	0.708	1.101 (0.665-1.824)
CGG*	60 (0.223)	29 (0.226)	0.998	1.000 (0.604-1.657)
TAA*	25 (0.092)	21 (0.165)	0.054	0.547 (0.295-1.016)
TGA*	35 (0.130)	16 (0.123)	0.826	1.074 (0.568-2.030)
TGG*	523 (0.195)	21 (0.165)	0.440	1.245 (0.714-2.171)
rs2073559/rs362691/rs736707				
CCA*	17 (0.064)	8 (0.059)	0.828	1.103 (0.455-2.673)
CGA*	76 (0.280)	34 (0.269)	0.749	1.080 (0.673-1.734)
CGG*	53 (0.199)	25 (0.192)	0.822	1.063 (0.624-1.810)
TGA*	60 (0.227)	36 (0.282)	0.263	0.761 (0.471-1.229)
TGG*	49 (0.182)	22 (0.171)	0.758	1.091 (0.626-1.901)
rs2229864/rs362691/rs736707				
AGA*	50 (0.188)	34 (0.265)	0.106	0.663 (0.403-1.093)
GCA*	12 (0.045)	7 (0.051)	0.837	0.903 (0.341-2.393)
GCG*	13 (0.049)	4 (0.034)	0.473	1.496 (0.495-4.524)
GGA*	86 (0.320)	37 (0.292)	0.464	1.188 (0.750-1.882)
GGG*	99 (0.370)	46 (0.357)	0.648	1.108 (0.714-1.720)
rs2073559/rs2229864/rs362691/rs736707				
CAGA*	24 (0.089)	12 (0.093)	0.982	1.008 (0.485-2.095)
CGCA*	12 (0.044)	7 (0.051)	0.838	0.903 (0.339-2.406)
CGCG*	9 (0.034)	3 (0.035)	0.952	1.036 (0.327-3.278)
CGGA*	50 (0.191)	22 (0.173)	0.537	1.189 (0.685-2.064)
CGGG*	50 (0.190)	25 (0.196)	0.951	1.017 (0.596-1.734)
TAGA*	25 (0.092)	21 (0.164)	0.046	0.540 (0.293-0.995)
TGGA*	34 (0.130)	15 (0.120)	0.661	1.154 (0.607-2.194)
TGGG*	49 (0.181)	21 (0.160)	0.478	1.227 (0.697-2.162)

**Table 4. Associations between single-nucleotide polymorphism genotypes and quantitative traits in the Positive and Negative Syndrome Scale (PANSS) of the schizophrenia group**

PANSS item	rs2073559		rs2229864		rs362691		rs736707	
	$\chi^2$	p Value	$\chi^2$	p Value	Z	p Value	$\chi^2$	p Value
P1	2.088	0.352	1.574	0.455	0.320	0.749	1.709	0.426
P2	0.290	0.865	0.569	0.752	1.205	0.228	1.483	0.476
P3	1.695	0.429	11.184	<b>0.004</b>	0.482	0.630	6.683	<b>0.035</b>
P4	2.171	0.338	0.085	0.958	0.650	0.516	1.395	0.498
P5	2.473	0.290	2.769	0.250	0.521	0.620	1.942	0.379
P6	0.546	0.761	2.177	0.337	0.669	0.503	4.588	0.101
P7	1.291	0.524	0.707	0.702	0.353	0.724	2.288	0.319
N1	1.652	0.438	1.192	0.551	1.548	0.122	0.005	0.997
N2	3.570	0.168	2.965	0.227	1.001	0.317	0.245	0.884
N3	3.016	0.221	0.217	0.897	0.585	0.558	0.838	0.658
N4	3.633	0.163	2.176	0.337	1.372	0.170	0.788	0.675
N5	1.455	0.483	0.830	0.660	1.478	0.139	1.083	0.582
N6	0.523	0.770	1.064	0.587	1.211	0.226	0.689	0.708
N7	1.298	0.522	2.404	0.301	0.643	0.521	0.091	0.955
G1	2.298	0.317	0.884	0.643	1.281	0.200	0.079	0.961
G2	1.232	0.540	1.371	0.504	1.134	0.257	0.008	0.996
G3	0.292	0.864	2.436	0.296	0.629	0.529	3.190	0.203
G4	0.067	0.967	1.010	0.604	1.127	0.260	2.139	0.343
G5	0.649	0.723	0.508	0.776	1.260	0.208	0.640	0.739
G6	0.453	0.797	0.008	0.996	0.480	0.631	0.650	0.723
G7	0.147	0.929	1.665	0.435	1.654	0.098	0.888	0.643
G8	3.818	0.148	2.277	0.320	0.297	0.767	0.087	0.957
G9	0.843	0.656	4.686	0.096	0.187	0.851	1.941	0.379
G10	1.942	0.379	1.219	0.544	2.162	<b>0.041</b>	0.182	0.913
G11	0.008	0.996	6.475	<b>0.039</b>	0.220	0.826	7.358	<b>0.035</b>
G12	4.292	0.117	1.869	0.393	1.474	0.140	0.133	0.936
G13	0.060	0.970	0.978	0.613	0.000	1.000	1.534	0.464
G14	0.213	0.899	0.751	0.687	0.609	0.542	0.487	0.784
G15	0.424	0.809	3.433	0.180	1.324	0.186	0.329	0.848
G16	0.552	0.759	3.228	0.199	0.410	0.682	0.562	0.755

reelin signalling pathway has been found in people with schizophrenia.<sup>22</sup> Our results provide further evidence for the hypothesis that deficits of neurodevelopment are the underlying mechanisms of schizophrenia.

According to our genetic risk analysis, rs2073559, rs2229864, rs362691, and rs736707, which are SNPs in *RELN*, showed no significant association with schizophrenia. Similarly, no significant association was found between

the rs2073559, rs2229864, rs362691, and rs736707 in 165 autistic trios, 67 sporadically autistic children, and 283 healthy controls of Han Chinese ethnicity.<sup>23</sup> In a study of *RELN* between patients with schizophrenia or bipolar disorder and controls, no association was found between rs2229864 and *RELN* gene expression, but allele disequilibrium expression of rs2229864 in patients with schizophrenia was observed,<sup>24</sup> which is consistent with

the findings of the present study. In a meta-analysis of *RELN* SNPs and putatively *RELN*-linked neuropsychiatric disorders (schizophrenia, autistic spectrum disorders, attention-deficit hyperactivity disorder, Alzheimer disease, and bipolar disorders), no association was found between the SNPs (rs2073559, rs2229864, rs362691) and the disorders.<sup>17</sup> However, *RELN* rs736707 was significantly associated with schizophrenia in an Asian group.<sup>17</sup> This is not consistent with our findings. The discrepancy may be related to sample size, which affects the estimation accuracy in populations with high genetic diversity.

The present study revealed strong linkage disequilibrium between rs2073559 and rs362691 and between rs2229864 and rs736707. Consistently, two studies also revealed strong linkage disequilibrium between rs736707 and rs2229864 in a Chinese population.<sup>23,25</sup> Further studies are warranted to determine the functional interaction among rs736707 and other gene polymorphisms, such as rs2229864, in patients with schizophrenia.

Our findings suggest that the investigated haplotypes might be associated with schizophrenia, but the SNPs of *RELN* were not associated with the pathogenesis of schizophrenia after Bonferroni correction. Although *RELN* is 160 kb long and consists of 65 exons, only four SNPs that are evenly distributed across *RELN* were selected for the genetic polymorphism analysis. The small number of selected loci may limit the extent to which the results are indicative of the whole gene. Therefore, additional SNPs should be included for analysis to achieve more representative and reliable information about the association between *RELN* and schizophrenia. In addition, the sample size was small.

## Conclusion

The SNPs rs2073559, rs2229864, rs362691, and rs736707 of *RELN* were not associated with the pathogenesis of schizophrenia. However, three of them (rs2229864, rs362691, and rs736707) might affect the clinical manifestations of schizophrenia. Considering the strong linkage disequilibrium (0.923) between rs2229864 and rs736707, we speculate that the haplotype composed of rs2229864-rs736707 is associated with hallucinatory behaviour and attention impairment in patients with schizophrenia.

## Contributors

BGD and TYJ designed the study. JW, CYH, and JMY acquired the data. JJP and JZ analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. AB critically revised the manuscript. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

## Conflicts of Interest

All authors have disclosed no conflicts of interest.

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## Data Availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

## Ethics Approval

The study was approved by the ethics committee of the Third People's Hospital of Zhongshan (reference: SSYLL20180301). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The participants or their guardians provided written informed consent for all treatments and procedures and for publication.

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