Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Association Analysis Between SNPs in the Promoter Region of *RGS4* and Schizophrenia in the Northern Chinese Han Population

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Background: Abnormal *RGS4* gene expression may cause neurotransmitter disorders, resulting in schizophrenia. The association between *RGS4* and the risk of schizophrenia is controversial, and there has been little research on the SNPs in the promoter region of *RGS4*.

Purpose: The present study was performed to detect the association between SNPs in the promoter region of the *RGS4* gene and the risk of schizophrenia.

Materials and Methods: In this study, the 1757-bp fragment (−1119–+600, TSS+1) of *RGS4* was amplified and sequenced in 198 schizophrenia patients and 264 healthy controls of the northern Chinese Han population. Allele, genotype and haplotype frequencies were analyzed by chi-square test.

Results: Four SNPs were detected in the region. LD analysis determined that rs7515900 was linked to rs10917671 (D' = 1, r^2 = 1). Therefore, the data for rs10917671 were eliminated from further analysis. Genotype TT of rs12041948 (P = 0.009, OR = 1.829, and 95% CI = 0.038–0.766) was significantly different between the two groups in the northern Chinese Han population. In males, genotype GG of rs6678136 (P = 0.009, OR = 2.292, and 95% CI = 1.256–4.18) and CC of rs7515900 (P = 0.003, OR = 2.523, and 95% CI = 1.332–4.778) were significantly different.

Conclusion: The results of this study suggested that genotype TT of rs12041948 in the pooled male and female samples and GG of rs6678136 and CC of rs7515900 in the male samples could be risk factors for schizophrenia. The present study is the first to detect an association between SNPs in the promoter region of the *RGS4* gene and the risk of schizophrenia in the northern Chinese Han population. Functional studies are required to confirm these findings.

Keywords: *RGS4*, schizophrenia, promoter region, SNPs

Introduction

Schizophrenia is a chronic mental disorder characterized by fantasies, delusions, altered emotional responses, behavioral disorders, social isolation, and cognitive impairment.[1,2] The clinical manifestations of this disease in different patients are divergent, and the pathogenesis remains unknown.[3] Studies of schizophrenic twins found that the incidence in monozygotic twins was four to six times higher than that in dizygotic twins.[4] Studies on the relationship between twins and adoptees and schizophrenia suggested that both genetic and environmental factors could influence the onset of schizophrenia.[5] Associations between genes and the risk of schizophrenia are controversial.[6–8] Regulators of G-protein signaling (*RGS*) negatively modulate G-protein signaling by acting as GTPase-activating proteins that shorten, sharpen, or otherwise attenuate signals

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http://doi.org/10.2147/NDT.S250282

transduced by heterotrimeric G-protein-coupled receptors.[9,10] The *RGS* gene has been associated with many disorders, including schizophrenia[11] and neuroglioma.[12] *RGS4* has attracted more attention than other *RGS*. The *RGS4* gene is highly expressed in the brain, especially in the cerebral cortex. *RGS4* is expressed in a highly regulated manner in subclasses of developing neurons.[13] *RGS4* plays an important role in pre- and post-synaptic neurotransmitter transmission, such as opioid, serotoninergic dopaminergic, and acetylcholine signaling.[10,14] The relationship between *RGS4* and the risk of schizophrenia is controversial based on epidemiological surveys and meta-analyses.[15,16] One hypothesis is that abnormal *RGS4* expression would cause neurotransmitter disorders, resulting in schizophrenia.[17,18] The current study is the first to investigate the association between SNPs in the promoter region of the *RGS4* gene and the risk of schizophrenia in the northern Chinese Han population.

Materials and Methods

Samples

The study included venous blood specimens from 198 schizophrenia patients (case group, 87 males and 111 females) and 264 healthy subjects of the northern Chinese Han population (control group, 133 males and 131 females). The inclusion criteria for the case group were as follows: (1) recruited from the Third People's Hospital of Liaoning Province; (2) northern Chinese Han population; (3) fully met DSM-IV criteria. The inclusion criteria for the control group were as follows: (1) recruited from blood donors; (2) northern Chinese Han population; (3) unaffected by mental disorder through at least three generations. Participants were excluded if they had other mental diseases or serious physiological diseases or were relatives of other participants. The case group (mean age ± standard deviation [SD], 43.1 ± 6.1 years; range 21–65 years) and control group (mean age ± SD, 40.7 ± 6.4 years; range 24–65 years) were matched for ethnicity, age, gender, and geographical region.

This study was conducted in accordance with the Declaration of Helsinki. All participants provided written consent after being informed of the study procedures and implications. Sample collection and analysis were approved by the Ethics Committee of China Medical University.

Table 1 Primers in the Study

Primer	Sequence
F	5′ TAACTCATGACAAATCAGGCTTCTC 3′
R	5′ GATGAGGAAGAAAAGACTGACGC 3′
CXF	5′ GATGAGGAAGAAAAGACTGACGC 3′
CXR	5′ TCTGAACACCTAGACAATCAGTATC 3′

DNA Extraction, Amplification, and Sequencing

Genomic DNA was extracted using the phenol-chloroform method previously described.[19] The primers for amplification (F and R) and sequencing (CXF and CXR) were designed using the Premier 5 Design Program (www.premierbiosoft.com) (Table 1). The 1757-bp fragment (−1119–+600, TSS+1) was amplified using primers F and R. The 20 μL PCR reaction contained 2.0 μL 10×buffer, 2 μL 2.5 mM dNTP mix, 0.2 μL of LA Taq (5.0 U/μL), 1.5 μL each primer (5 pM), and 20 ng of template DNA. PCR was conducted according to the following cycle conditions: initial denaturation of 94°C for 5 min; 30 cycles of 94°C denaturation for 30 s, 64°C annealing for 30 s, and 72°C elongation for 60 s; final extension at 72°C for 10 min.

Sequencing was performed with an ABI 377 DNA automatic sequencer by the Taihe Biotechnology Co. (Beijing, China).

Data Analysis

The generated sequences were aligned with reference sequences in the National Center for Biotechnology Information database to identify polymorphisms. Allele, genotype and haplotype frequencies were calculated using Microsoft Excel. The Hardy–Weinberg equilibrium (HWE) test, haplotype verification, and linkage disequilibrium (LD) were performed using Haploview 4.1 software (Broad Institute, Cambridge, MA, USA).[19] The differences between case and control groups were determined by the chi-square test using SPSS PASW Statistics v. 20.0 (IBM, Chicago, IL). A $p < 0.05$ was statistically significant. The Bonferroni correction was conducted for multiple independent tests ($p < 0.05/4$ as statistically significant).[20]

Results

Genotype TT of Rs12041948 Was a Risk Factor in the Northern Chinese Han Population

There were four SNPs (rs6678136, rs12041948, rs7515900, and rs10917671) detected in the 1757-bp fragment of the *RGS4* gene. The frequencies of the alleles and genotypes of the four SNPs are shown in Table 2. The LD block is presented in Figure 1 (rs6678136 and rs12041948 D' = 0.722, $r^2 = 0.167$;

Table 2 Genotype and Allele Distributions of the *RGS4* Gene in Patients and Controls

	SNP	Case		Control		P_{HWE}
		n	%	n	%	
All	rs6678136					
(Case 198, Control 264)	GG	70	35.35	82	31.06	0.425
	AG	87	43.94	137	51.89	
	AA	41	20.71	45	17.05	
	G allele	227	57.32	301	57.01	
	rs12041948					
	TT	146	73.74	175	66.29	0.170
	CT	50	25.25	75	28.41	
	CC	2	1.01	14	5.30	
	T allele	342	86.36	425	80.49	
	rs7515900					
	CC	56	28.28	62	23.48	0.088
	AC	97	48.99	147	55.68	
	AA	45	22.73	55	20.83	
	C allele	209	52.78	271	51.33	
	rs10917671					
	GG	56	28.28	62	23.48	0.088
	AG	97	48.99	147	55.68	
	AA	45	22.73	55	20.83	
	G allele	209	52.78	271	51.33	
Male	rs6678136					
(Case 87, Control 133)	GG	33	37.93	28	21.05	
	AG	33	37.93	80	60.15	
	AA	21	24.14	25	18.80	
	G allele	99	56.90	136	51.13	
	rs12041948					
	TT	64	73.56	79	59.40	
	CT	22	25.29	46	34.59	
	CC	1	1.15	8	6.02	
	T allele	150	86.21	204	76.69	
	rs7515900					
	CC	29	33.33	22	16.54	
	AC	37	42.53	80	60.15	
	AA	21	24.14	31	23.31	
	C allele	95	54.60	124	46.62	
	rs10917671					
	GG	29	33.33	22	16.54	
	AG	37	42.53	80	60.15	
	AA	21	24.14	31	23.31	
	G allele	95	54.60	124	46.62	
Female	rs6678136					
(Case 111, Control 131)	GG	37	33.33	54	41.22	
	AG	54	48.65	57	43.51	
	AA	20	18.02	20	15.27	
	G allele	128	57.66	165	62.98	
	rs12041948					
	TT	82	73.87	96	73.28	
	CT	28	25.23	29	22.14	
	CC	1	0.90	6	4.58	
	T allele	192	86.49	221	84.35	
	rs7515900					
	CC	27	24.32	40	30.53	
	AC	60	54.05	67	51.15	
	AA	24	21.62	24	18.32	
	C allele	114	51.35	147	56.11	
	rs10917671					
	GG	27	24.32	40	30.53	
	AG	60	54.05	67	51.15	
	AA	24	21.62	24	18.32	
	G allele	114	51.35	147	56.11	

Abbreviation: P_{HWE}, P value of Hardy–Weinberg equilibrium.

rs12041948 and rs7515900 D' = 0.806, r^2 = 0.166; rs7515900 and rs10917671 D' = 1, r^2 = 1). LD analysis determined that rs7515900 was linked to rs10917671. Therefore, the data for rs10917671 were excluded from further analysis. In the control group, the four SNPs satisfied the HWE for the northern Chinese Han population (Table 2).

No association was observed between rs6678136 or rs7515900 and the risk of schizophrenia (Table 3). However, the T allele of rs12041948 was associated with the risk of schizophrenia (P = 0.021, odds ratio (OR) = 1.535, and 95% confidence interval (CI) = 1.072–2.197). In the homozygous codominant model, genotype TT (P = 0.009, OR = 5.840, and 95% CI = 1.306–26.115) was significantly different between the two groups. In the dominant model, the genotype TT +TC was significantly different (P = 0.018, OR =

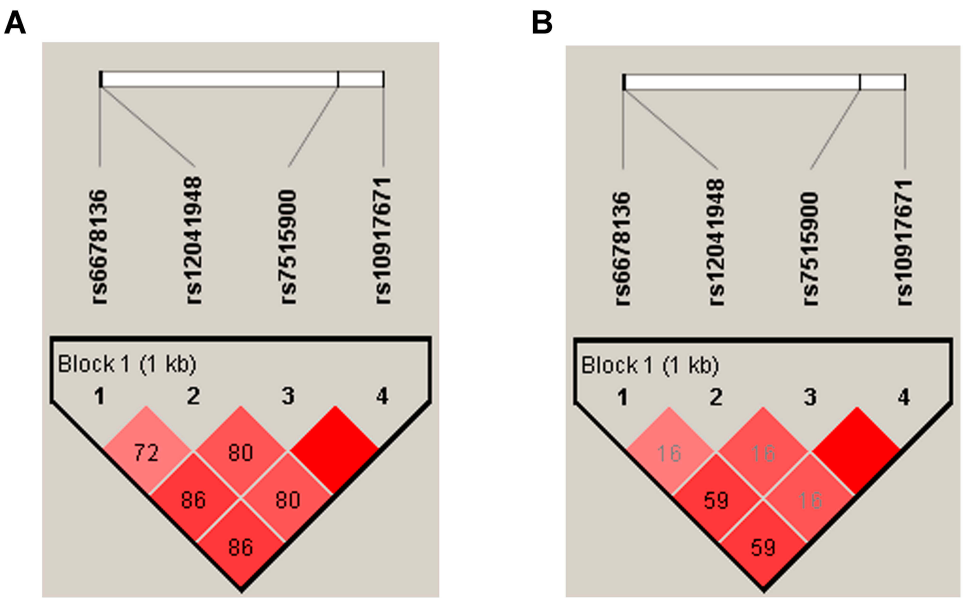

Figure 1 Linkage disequilibrium block composed of rs6678136, rs12041948, rs7515900, and rs10917671. The numbers indicate the value of multiallelic D′ in (**A**) and r^2 in (**B**), which represents the level of recombination between the two blocks.

1.818, and 95% CI = 0.041–0.811); however, this difference disappeared following the Bonferroni correction.

Genotype GG of Rs6678136 and CC of Rs7515900 Were Risk Factors in the Male Northern Chinese Han Population

Relationships between the three SNPs and the risk of schizophrenia were detected in the male population (Table 4). Genotype GG of rs6678136 was significantly different between case and control groups in the heterozygous codominant model (P = 0.002, OR = 2.857, and 95% CI = 1.497–5.454) and recessive model (P = 0.009, OR = 2.292, and 95% CI = 1.256–4.18). The differences were also significant after the Bonferroni correction. In the recessive model, genotype TT of rs12041948 (P = 0.043, OR = 1.902, and 95% CI = 1.056–3.427) was significantly different between the two groups; however, the difference was not significant after the Bonferroni correction. In the heterozygous codominant and recessive models, genotype CC of rs7515900 was associated with the risk of schizophrenia (P = 0.003, OR = 2.850, and 95% CI = 1.448–5.611; P = 0.003, OR = 2.523, and 95% CI = 1.332–-4.778, respectively). These differences remained after the Bonferroni correction.

No Association Was Detected Between RGS4 and the Risk of Schizophrenia in the Female Northern Chinese Han Population

No significant differences were found between rs6678136, rs12041948, and rs7515900 and the risk of schizophrenia in the female northern Chinese Han population (Table 5).

No Associations Were Detected Between Haplotypes and the Risk of Schizophrenia

Eight haplotypes composed of the three SNPs (rs6678136, rs12041948, and rs7515900) were found in the northern Chinese Han population. Three haplotypes (ATC, GCA, GCC) were only detected in the control group (Table 6). Haplotype GTC was the most frequent haplotype. No significant differences were detected between any of the haplotypes and the risk of schizophrenia.

Table 3 Analysis of *RGS4* Polymorphisms and Schizophrenia in Cases and Controls

Model		*P*	OR	95% CI
rs6678136				
Allele contrast	G VS A	0.924	1.013	0.759–1.318
Homozygous codominant	GG VSAA	0.893	0.937	0.552–1.592
Heterozygous codominant	GG VSGA	0.168	1.344	0.886–2.040
Dominant	GG+GA VS AA	0.335	0.787	0.492–1.259
Recessive	GG VS GA +AA	0.368	1.214	0.821–1.794
rs12041948				
Allele contrast	T VS C	0.021	1.535	1.072–2.197
Homozygous codominant	TT VS CC	0.009*	5.84	1.306–26.115
Heterozygous codominant	TT VS TC	0.339	1.251	0.822–1.904
Dominant	TT+TC VS CC	0.018	1.818	0.041–0.811
Recessive	TT VS TC +CC	0.102	1.428	0.951–2.144
rs7515900				
Allele contrast	C VS A	0.690	1.057	0.727–1.225
Homozygous codominant	CC VSAA	0.785	1.104	0.647–1.884
Heterozygous codominant	CC VSCA	0.175	1.369	0.879–2.132
Dominant	CC+CA VS AA	0.649	0.895	0.573–1.397
Recessive	CC VS CA +AA	0.281	1.285	0.844–1.956

Note: *P < 0.05/4 (indicates statistical significance).
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Table 4 Analysis of *RGS4* Polymorphisms and Schizophrenia in Male Cases and Controls

Model		*P*	OR	95% CI
rs6678136				
Allele contrast	G VS A	0.243	1.262	0.859–1.853
Homozygous codominant	GG VSAA	0.438	1.403	0.651–3.025
Heterozygous codominant	GG VSGA	0.002*	2.857	1.497–5.454
Dominant	GG+GA VS AA	0.397	0.728	0.378–1.402
Recessive	GG VS GA +AA	0.009*	2.292	1.256–4.180
rs12041948				
Allele contrast	T VS C	0.014	1.900	1.134–3.183
Homozygous codominant	TT VS CC	0.079	6.481	0.790–53.181
Heterozygous codominant	TT VS TC	0.100	1.694	0.924–3.104
Dominant	TT+TC VS CC	0.091	5.504	0.676–44.808
Recessive	TT VS TC +CC	0.043	1.902	1.056–3.427
rs7515900				
Allele contrast	C VS A	0.119	1.377	0.938–2.021
Homozygous codominant	CC VSAA	0.116	1.946	0.889–4.260
Heterozygous codominant	CC VSCA	0.003*	2.850	1.448–5.611
Dominant	CC+CA VS AA	1.000	0.955	0.506–1.802
Recessive	CC VS CA +AA	0.003*	2.523	1.332–4.778

Note: *P < 0.05/4 (indicates statistical significance).
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Discussion

In previous studies, five target SNPs (rs10917670, rs951436, rs951439, rs2661319, and rs10759) in the *RGS4* gene were intensively studied to determine the association between the *RGS4* gene and the risk of schizophrenia.[21–23] However, there has been little study of the 1757-bp fragment (−1119–+600, TSS+1) analyzed in the current study. Moreover, the relationships between the three SNPs (rs6678136, rs12041948, and rs7515900) and the risk of schizophrenia were not previously studied in the northern Chinese Han population. In the present study, there was no association between rs6678136 or rs7515900 and the risk of schizophrenia in the northern Chinese Han population. These findings were consistent with a previous study of a population in the United States.[24] Furthermore, in male subgroup analysis, both genotype GG of rs6678136 and genotype CC of rs7515900 were identified as risk factors for schizophrenia. It was previously shown that gender might affect the outcome of schizophrenia and influence the correlation between candidate genes and schizophrenia.[25] The genotype TT of rs12041948 was a risk factor for schizophrenia in the northern Chinese Han population; however, a significant difference was not detected by gender subgroup analysis. Finally, the haplotypes composed of the three SNPs were not associated with the risk of schizophrenia.

Table 5 Analysis of *RGS4* Polymorphisms and Schizophrenia in Female Cases and Controls

Model		*P*	OR	95% CI
rs6678136				
Allele contrast	G VS A	0.263	0.801	0.555–1.154
Homozygous codominant	GG VSAA	0.324	0.685	0.324–1.447
Heterozygous codominant	GG VSGA	0.320	0.723	0.413–1.266
Dominant	GG+GA VS AA	0.605	0.820	0.416–1.617
Recessive	GG VS GA +AA	0.232	0.713	0.421–1.207
rs12041948				
Allele contrast	T VS C	0.522	1.187	0.714–1.975
Homozygous codominant	TT VS CC	0.132	5.125	0.605–43.447
Heterozygous codominant	TT VS TC	0.761	0.885	0.487–1.607
Dominant	TT+TC VS CC	0.129	5.280	0.626–44.540
Recessive	TT VS TC +CC	1.000	1.031	0.581–1.830
rs7515900				
Allele contrast	C VS A	0.315	0.826	0.577–1.182
Homozygous codominant	CC VSAA	0.344	0.675	0.320–1.425
Heterozygous codominant	CC VSCA	0.367	0.754	0.414–1.373
Dominant	CC+CA VS AA	0.268	0.813	0.432–1.531
Recessive	CC VS CA +AA	1.000	0.960	0.535–1.720

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

The association between *RGS4* and the risk of schizophrenia was controversial in different ethnic groups,[15,26] geographical locations,[27] and sample number.[16] It was reported that some marker SNPs within the *RGS4* gene were associated with a more severe baseline for the Positive and Negative Syndrome Scale (PANSS) total score.[28] *RGS4* gene variants were associated with risperidone antipsychotic treatment response in schizophrenia.[29] The clinical manifestation of schizophrenia and treatment response can be influenced by the SNPs in the *RGS4* gene, suggesting that the *RGS4* gene might play a role in the fundamental process of disease pathophysiology.[30] In addition, *RGS4* mRNA expression was decreased in the prefrontal region of post-mortem brains from schizophrenic patients.[31]

Transcription factors acting as critical activators or repressors regulate transcription by targeting cis-acting elements in the promoter region of genes.[32] *RGS4* expression was regulated by some transcription factors,[33,34] such as C/EBP, Bcl6,[35] and GATA-6.[34] The SNPs identified in this study might affect the binding of specific transcription factors, leading to altered gene expression. Functional assays are needed to address these possibilities. The transcription factors that could bind to the *RGS4* promoter region were predicted in JASPAR (http://jaspar.genereg.net/). Rs6678136 might be located at the binding site of activating transcription factor 2 (*ATF2*), which was associated with depression and schizophrenia.[36,37] *ATF2* overexpression in the nucleus accumbens caused an increase in emotional reactivity and antidepressant-like responses.[38] Rs12041948 might be located at the binding site for aristaless-like homeobox 3 (*ALX3*). Garcia-Sanz et al found that *ALX3* caused congenital craniofacial and neural tube defects.[39] Rs7515900 might be located at the androgen receptor (*AR*) binding site. One SNP, which was functional for *AR* binding and transcription, represented a risk-associated allele for schizophrenia.[40]

The present study is the first to detect an association between SNPs in the promoter region of the *RGS4* gene

Table 6 Haplotype Distribution of Rs6678136, Rs12041948, and Rs7515900 of the *RGS4* Gene

Haplotype			Case (n)	Control (n)	*P*	OR	95% CI
G	T	C	103	124	0.302	1.224	0.846–1.770
A	T	A	57	63	0.240	1.290	0.849–1.959
A	C	A	25	43	0.291	0.743	0.436–1.264
G	T	A	10	19	0.439	0.686	0.312–1.510
A	C	C	2	2	1.000	1.337	0.187–9.573
A	T	C	0	6			
G	C	A	0	4			
G	C	C	0	3			

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

and the risk of schizophrenia in the northern Chinese Han population. The association we observed should be viewed with caution. First, the sample number was not large enough to represent the northern Chinese Han population. Second, only SNPs in the *RGS4* promoter region were analyzed. Third, interaction of gene-gene, which might influence the occurrence of schizophrenia, was not detected.[41,42] In addition, functional assays are needed to confirm the results. The findings of this study have implications for future molecular genetic studies and personalized medicine.

Acknowledgment

All authors of the study were worthy of appreciation.

Disclosure

The authors declare no conflicts of interest in this work.

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