

ORIGINAL ARTICLE

The rs11191580 variant of the *NT5C2* gene is associated with schizophrenia and symptom severity in a South Chinese Han population: evidence from GWAS

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Objective: Recent genome-wide association studies have identified a significant relationship between the *NT5C2* variant rs11191580 and schizophrenia (SCZ) in European populations. This study aimed to validate the association of rs11191580 polymorphism with SCZ risk in a South Chinese Han population. The relationship of this polymorphism with the severity of SCZ clinical symptoms was also explored.

Methods: A case-control study was performed in 462 patients with SCZ and 598 healthy controls. rs11191580 was genotyped by the Sequenom MassARRAY iPLEX platform. A total of 459 SCZ patients completed the Positive and Negative Syndrome Scale (PANSS) evaluation. Data were analyzed by PLINK software.

Results: We confirmed an association of the rs11191580 polymorphism with SCZ risk in South Chinese Han under a dominant genetic model ($OR_{adj} = 0.769$; $95\%CI_{adj} = 0.600-0.984$; $p_{adj} = 0.037$). PANSS scores showed a significant association between variant rs11191580 and total score ($p_{adj} = 0.032$), lack of response scale score ($p_{adj} = 0.022$), and negative scale score (additive: $p_{adj} = 0.004$; dominant: $p_{adj} = 0.016$; recessive: $p_{adj} = 0.021$) after data were adjusted for age and sex.

Conclusion: *NT5C2* variant rs11191580 conferred susceptibility to SCZ and affected the clinical symptoms of SCZ in a South Chinese Han population.

Keywords: Schizophrenia; susceptibility; clinical symptom; rs11191580; GWAS-supported genetic variant

Introduction

Schizophrenia (SCZ) is a complex psychiatric disorder characterized by cognitive dysfunction, disorganized behavior, and social withdrawal. These characteristics usually lead to problems in self-care, occupational and social functioning, and financial burdens.¹ The lifetime prevalence of SCZ is estimated to be 8.7 per 1,000 worldwide and 5.4 per 1,000 in mainland China.^{2,3} Although the actual cause of SCZ remains unclear, strong evidence suggests that the heritability of SCZ is approximately 81%.⁴ Numerous risk variants in candidate genes have been identified to clarify the genetic etiology of SCZ. The development of genome-wide association studies (GWASs), which facilitate the simultaneous testing of thousands of single nucleotide polymorphisms (SNPs), has stimulated development of the field of SCZ genetics. To date, 50 GWASs in SCZ have been implemented and some high-risk loci have met the genome-wide significance threshold (<http://www.genome.gov/gwastudies/>). However, these observations

should be validated in other genetically independent populations.

In 2011, the SCZ Psychiatric GWAS Consortium first reported that locus rs11191580 in the cytosolic 5'-nucleotidase II gene (*NT5C2*) gene was associated with SCZ in 29,839 individuals of European ancestry.⁵ *NT5C2* encodes a hydrolase that participates in the regulation of cellular purine metabolism.⁶ A replication study in 2012 provided further evidence that rs11191580 plays an important role in the genetic etiology of SCZ in a North Chinese Han population.⁷ Two subsequent GWASs showed that rs11191580 is the risk locus of SCZ.^{8,9} In 2012, a GWAS in a Swedish population observed that rs11191580 was significantly associated with SCZ susceptibility.⁸ In 2013, the Cross-Disorder Group of Psychiatric Genomics Consortium indicated that locus rs11191580 conferred susceptibility to five major psychiatric disorders (including SCZ) in a European population.⁹ Nevertheless, a replication study in a Japanese population suggested that rs11191580 polymorphism in the *NT5C2* gene was not associated with SCZ.¹⁰ Thus, the association between rs11191580 and SCZ risk remains controversial and should be validated in different populations.

In the present study, we used a case-control design to validate the association between GWAS-supported variant rs11191580 and SCZ susceptibility in a South Chinese Han population. SCZ is a complex disease with

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highly heterogeneous clinical symptoms. Numerous techniques have been employed to minimize clinical heterogeneity in SCZ studies. Intermediate phenotypes, for example, have been used as clinical symptoms to reflect the underlying genetic mechanism.¹¹ The Positive and Negative Syndrome Scale (PANSS) can assess the intermediate phenotype of SCZ.¹² Thus, we investigated the association between locus rs11191580 and intermediate phenotypes of SCZ as evaluated by the PANSS in this study.

Methods

Inclusion and exclusion criteria

The diagnosis of SCZ was confirmed independently by two experienced psychiatrists using DSM-IV criteria. SCZ patients were included if their diagnosis was confirmed by both psychiatrists. Exclusion criteria for case subjects were as follows: 1) mental retardation, 2) mental disorders caused by organic brain disease, somatopathy, or medication, 3) neurological disorders, such as epilepsy and stroke, 4) uncooperative patients with severe excitement or impulse control issues, 5) history of head injury, and 6) pregnant or breastfeeding women. Controls were included when they could be age- and gender-matched with an SCZ patient. Exclusion criteria for healthy controls included a family history of mental disorder and severe head injury.

Subjects

A total of 1,060 unrelated Han Chinese subjects (462 SCZ patients and 598 healthy controls) were recruited. All patients were recruited from the Guangxi Brain Hospital in Liuzhou; healthy controls were individuals undergoing regular checkups and medical staff at two general hospitals in the same region: the First Affiliated Hospital of Guangxi University of Chinese Medicine and Guangxi Liuzhou People's Hospital. All subjects gave their written informed consent for participation. This study was approved by the Ethics Committee of Guangxi Medical University.

PANSS assessment

Symptom severity of SCZ patients was assessed using the PANSS. PANSS interviews were performed by two experienced psychiatrists on the day the patient was admitted to hospital. The following PANSS scores were measured: total score, three subscale scores (positive, negative, and general psychopathology), and six syndrome scores (lack of response, thought disturbance, activation, paranoid, depression, and aggressivity scale scores).

DNA extraction and SNP genotyping

Peripheral blood samples (5 mL) were collected from each subject into Vacutainer EDTA tubes. A blood genotyping DNA kit (Tiangen Biotech, Beijing, China) was used to isolate genomic DNA from peripheral blood leukocytes. The extracted DNA samples were partially shipped in three tubes and stored at -80 °C for genotyping.

rs11191580 was genotyped using Sequenom Mass-ARRAY® technology (Sequenom Inc., San Diego, CA, USA). Primer design for the rs11191580 polymorphism was conducted using Sequenom Assay Designer 3.1 (Sequenom Inc.). The primer sequences for rs11191580 are listed in Table 1. Puji Biological Co., LGC Genomics Ltd. (Shanghai, China) was invited to conduct primer design and synthesis, as well as SNP genotyping. Genomic DNA (5%) samples were randomly chosen and retested and the concordance rate of the retest results was 100%.

Statistical analysis

Power was estimated using Quanto software. The characteristics of age and gender between SCZ patients and healthy controls were compared using SPSS version 16.0. PLINK version 1.9 software was used for the following genetic analyses. Hardy-Weinberg equilibrium (HWE) was assessed by using the chi-square (χ^2) goodness of fit test. Genetic associations between the rs11191580 polymorphism and SCZ risk were assessed through unconditional logistic regression analysis with the following genetic models: additive (TT+CC vs. TC), dominant (TT+TC vs. CC), and recessive (TT vs. TC+CC). The correlation between rs11191580 and symptom severity was evaluated through linear regression analysis. P-values were two tailed and $p < 0.05$ was deemed significant for all statistical analyses.

Results

Demographic characteristics of the subjects

A total of 717 males (67.6%) and 343 females (32.4%) were recruited for this study. The SCZ group consisted of 327 males and 135 females (mean age: 34.35 ± 13.34 years), while the healthy control group comprised 390 males and 208 females (mean age: 4.92 ± 8.45 years). No significant difference in gender ($\chi^2 = 3.684$, $p = 0.055$) or age ($t = 0.850$, $p = 0.396$) was observed between the groups.

A total of 459 SCZ patients (323 males and 136 females) completed the PANSS assessment. The average ages of male and female SCZ cases were 33.97 ± 13.47 and 35.64 ± 13.32 years, respectively. No difference in age ($t = -1.220$, $p = 0.223$) was found between the male and female cases.

Table 1 Primer sequence for rs11191580

SNP_ID	Primer	Sequence (5' → 3')	UEP_SEQ
rs11191580 (T/C)	1st-PCR	ACGTTGGATGTTTGCCCTCTCAAAAAGCAC	TGGGCTTGCATAATTACACA
	2nd-PCR	ACGTTGGATGTAGGAGCTGCTGGTGCAGG	

Association between rs11191580 polymorphism and SCZ risk

Table 2 shows that the genotypic distribution of rs11191580 polymorphism was in HWE in the control samples ($p_{\text{HWE}} > 0.050$). The genotypic ($\chi^2 = 4.926$, $p = 0.085$) and allelic ($\chi^2 = 2.656$, $p = 0.103$) frequencies of rs11191580 polymorphism did not differ significantly between patients and controls. However, variant rs11191580 was observed to be significantly associated with SCZ susceptibility in the dominant model after adjusting for age and sex (odds ratio [OR]_{adj} = 0.769; 95% confidence interval [95%CI]_{adj} = 0.600-0.984; $p_{\text{adj}} = 0.037$) (Table 3).

Association between rs11191580 polymorphism and PANSS scores

Table 4 shows that the rs11191580 polymorphism was significantly associated with total (recessive: $p_{\text{adj}} = 0.032$) and negative-scale (additive: $p_{\text{adj}} = 0.004$; dominant: $p_{\text{adj}} = 0.016$; recessive: $p_{\text{adj}} = 0.021$) PANSS scores. Regarding syndrome scores, the rs11191580 polymorphism was significantly associated with the lack of response scale score ($p_{\text{adj}} = 0.022$) in the recessive model (Table 5).

Discussion

We confirmed the association of GWAS-supported locus rs11191580 within the *NT5C2* gene with SCZ susceptibility (OR_{adj} = 0.769) and that the TT+TC genotype conferred a protective effect against SCZ in the South Chinese Han population. The rs11191580 polymorphism was also significantly associated with severity of SCZ clinical symptoms. Our samples had a power of 76.32% to detect a susceptibility locus with a genotypic relative risk of 0.77 in the present study.

Prior to this research, variant rs11191580 within the *NT5C2* gene had been identified to be significantly associated with SCZ susceptibility, but three GWASs conducted in Swedish or broader European populations had suggested that the T allele might increase SCZ

risk.^{5,8,9} Besides, the correlation between GWAS-supported locus rs11191580 and SCZ risk has been replicated, but the results also showed that the T allele might increase SCZ susceptibility (OR = 1.05) in a North Chinese Han population.⁷ One possible reason for this discrepancy is the genetic heterogeneity of SCZ in individuals of different ethnic groups and/or regions. HapMap data show that the minor allele frequency (MAF) differs significantly between European (0.075) and Han Chinese in Beijing (0.350), while our result showed that the MAF (0.243) in a South Chinese Han population differed from that in the above two populations. Therefore, it is possible that the T allele may act as a protective factor for SCZ in South Chinese Han and as a risk factor for SCZ in Europeans and the North Chinese Han population. However, the association between variant rs11191580 and SCZ susceptibility was not found in a Japanese population.¹⁰ The inconsistent results between Chinese and Japanese populations may also be explained by discrepancies in genetic heterogeneity among populations with different ethnicities. According to the HapMap database (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=11191580), the T-allele frequencies of the rs11191580 polymorphism are 0.350 in Han Chinese in Beijing and 0.285 in Japanese in Tokyo. Thus, a differential MAF of rs11191580 might exert a disproportionate influence on SCZ susceptibility in the Chinese and Japanese populations. We also note that the sample size of the study including the Japanese population was relatively small; thus, it may have been underpowered to observe a statistically significant association.

The rs11191580 polymorphism is located in an intron region about 2 kB upstream of the *NT5C2* gene. In addition to GWAS-supported locus rs11191580, a family-based study proved that the rs17094683 polymorphism within *NT5C2* gene is significantly associated with SCZ.¹³ Moreover, the *NT5C2* gene was indicated to be a gene shared by five major neuropsychiatric disorders.¹⁴ This gene encodes cytosolic 5'-nucleotidase II (cN-II), a ubiquitous nucleotide-hydrolyzing enzyme involved in purine metabolism.^{6,15} Page et al.¹⁶ demonstrated that purine dysmetabolisms were often related to various degrees of neuromotor dysfunctions, mental retardation, or both.

Table 2 Distribution of genotype and allele frequency and HWE test for rs11191580

SNP_ID	Group	Genotype					p_{HWE}	Allele			
		CC	TC	TT	χ^2	p1		C	T	χ^2	p2
rs11191580 (T/C)	Case	25	157	276	4.926	0.085	0.689	207	709	2.656	0.103
	Control	31	244	321				306	886		

HWE = Hardy-Weinberg equilibrium.

Table 3 Association between rs11191580 polymorphism and SCZ risk (adjusted for age and sex)

SNP_ID	Model	Crude		Adjusted	
		OR (95%CI)	p-value	OR (95%CI)	p_{adj}
rs11191580 (T/C)	Additive	0.840 (0.684-1.033)	0.098	0.837 (0.681-1.028)	0.090
	Dominant	0.770 (0.601-0.985)	0.038	0.769 (0.600-0.984)	0.037
	Recessive	1.052 (0.612-1.809)	0.854	1.026 (0.596-1.765)	0.927

95%CI = 95% confidence interval; OR = odds ratio; SCZ = schizophrenia.

Table 4 Linear regression results for genotypic association of rs11191580 with PANSS total and subscale scores

SNP_ID	Variables	Additive			Dominant			Recessive				
		Crude β (95%CI)	p-value	Adjusted β^{adj} (95%CI)	Crude β (95%CI)	p-value	Adjusted β^{adj} (95%CI)	Crude β (95%CI)	p-value	Adjusted β^{adj} (95%CI)		
rs11191580 (T/C)	Total score	3.760 (-0.121-7.640)	0.058	3.801 (-0.081-7.683)	3.186 (-1.534-7.907)	0.187	3.249 (-1.474-7.973)	0.178	11.290 (0.987-21.590)	0.032	11.280 (0.973-21.580)	0.032
	Positive	0.349 (-1.112-1.811)	0.640	0.372 (-1.079-1.823)	0.177 (-1.602-1.956)	0.846	0.214 (-1.553-1.980)	0.813	1.608 (-2.256-5.473)	0.415	1.593 (-2.241-5.428)	0.416
	Negative	1.736 (0.530-2.941)	0.005	1.763 (0.561-2.966)	1.773 (0.298-3.248)	0.019	1.821 (0.350-3.293)	0.016	3.776 (0.595-6.958)	0.020	3.747 (0.573-6.921)	0.021
	General psychopathology	1.158 (-0.690-3.007)	0.220	1.157 (-0.694-3.009)	0.731 (-1.517-2.979)	0.524	0.730 (-1.522-2.983)	0.525	4.650 (-0.236-9.535)	0.063	4.647 (-0.245-9.539)	0.063

95%CI = 95% confidence interval; PANSS = Positive and Negative Syndrome Scale; β = partial regression coefficient; β^{adj} = adjusted partial regression coefficient.

Table 5 Linear regression results for genotypic association between rs11191580 and PANSS syndrome scores

SNP_ID	Variables	Additive			Dominant			Recessive				
		Crude β (95%CI)	p-value	Adjusted β^{adj} (95%CI)	Crude β (95%CI)	p-value	Adjusted β^{adj} (95%CI)	Crude β (95%CI)	p-value	Adjusted β^{adj} (95%CI)		
rs11191580 (T/C)	Lack of response	0.523 (-0.056-1.101)	0.077	0.529 (-0.042-1.099)	0.392 (-0.313-1.098)	0.277	0.407 (-0.289-1.104)	0.252	1.788 (0.270-3.305)	0.021	1.759 (0.261-3.256)	0.022
	Thought disturbance	0.351 (-0.445-1.147)	0.388	0.362 (-0.432-1.155)	0.306 (-0.661-1.272)	0.536	0.319 (-0.645-1.283)	0.517	1.017 (-1.098-3.132)	0.347	1.027 (-1.083-3.137)	0.341
	Activation	0.042 (-1.397-0.481)	0.851	0.046 (-0.389-0.482)	0.051 (-0.485-0.586)	0.185	0.054 (-0.477-0.586)	0.841	0.057 (-1.099-1.212)	0.924	0.068 (-1.079-1.214)	0.908
	Paranoid	0.378 (-0.315-1.167)	0.260	0.446 (-0.288-1.180)	0.361 (-0.544-1.266)	0.435	0.396 (-0.501-1.293)	0.387	1.275 (-0.673-3.223)	0.200	1.248 (-0.682-3.178)	0.206
	Depression	0.363 (-0.169-0.895)	0.182	0.365 (-0.167-0.896)	0.421 (-0.229-1.071)	0.205	0.428 (-0.221-1.077)	0.197	0.552 (-0.843-1.947)	0.438	0.532 (-0.861-1.925)	0.455
	Aggressivity	0.688 (-0.287-1.663)	0.168	0.698 (-0.272-1.668)	0.687 (-0.507-1.880)	0.26	0.707 (-0.481-1.894)	0.244	1.570 (-0.987-4.127)	0.230	1.551 (-0.995-4.096)	0.233

95%CI = 95% confidence interval; PANSS = Positive and Negative Syndrome Scale; β = partial regression coefficient; β^{adj} = adjusted partial regression coefficient.

Low cN-II activity was also found to be present in the brain.¹⁷ Pesi et al.¹⁸ reported that fluctuations in cN-II activity were involved with the pathological mechanism of Lesch-Nyhan syndrome, a metabolic-neurological syndrome related to hypoxanthine phosphoribosyl transferase deficiency. Moreover, a knockdown study in human astrocytoma cells revealed that cN-II activity was essential for their survival.¹⁹ Thus, additional studies are necessary to identify the underlying molecular mechanism involved in the potential association of purine dysmetabolism with SCZ risk.

In the current study, we observed that GWAS-supported locus rs11191580 exerted significant impacts on PANSS total scale score, negative scale score, and lack of response scale score. Different clinical symptoms of SCZ have been defined as symptom dimensions, because SCZ is a clinically heterogeneous disorder.²⁰ A comprehensive global approach to capture the symptom dimensions of SCZ has not been developed. Heterogeneity at the etiological level of SCZ cannot be solved until the clinical heterogeneity of SCZ has been elucidated comprehensively. PANSS, as a tool for evaluating symptom dimensions of SCZ, may help reduce such heterogeneity in SCZ genetic association research. This scale may also facilitate determination of the genetic mechanism of SCZ.²¹ For example, the rs140700 polymorphism in the *SLC6A4* gene was proven to be strongly associated with SCZ risk and PANSS scores (negative score and depression/anxiety score) simultaneously.²² Li et al.²³ revealed that the A-T-C haplotype of rs6265-rs12273539-rs10835210 was significantly associated with susceptibility to SCZ, and the A-C-A haplotype, with negative symptoms. PANSS may also be beneficial in the diagnosis and prevention of SCZ. Traditional diagnosis of SCZ is mainly based on descriptive clinical characteristics. This process should be replaced with a new classification and diagnostic tool based on symptom dimensions, such as PANSS. Moreover, symptom control in SCZ patients could be evaluated by PANSS severity scores; this evaluation has proven to be conducive in reducing hospitalization and direct costs of care in SCZ.²⁴

This work is limited by several factors. First, the biological function of the GWAS-supported locus rs11191580 to SCZ risk remains unclear, although this locus was significantly associated with SCZ risk in this study. Therefore, further experiments should be conducted to better determine the biological mechanism underpinning the involvement of the rs11191580 polymorphism in SCZ risk. Second, selection bias was inevitable in the present case-control study, because the samples were mainly recruited from patients in hospital. Therefore, further research with more representative samples, especially population-based samples, is necessary to establish the relationship between the rs11191580 polymorphism and SCZ. Third, although this study did find the rs11191580 polymorphism to be significantly associated with SCZ risk, we cannot rule out the possibility of false positives. Samples had a power of 76.32% to detect a susceptibility locus, and this relative statistical weakness may have made misleading results possible. Finally, although genetic effects are crucial to elucidating the cause of SCZ, non-genetic factors

(such as prenatal stress, exposure to viruses during pregnancy, and social disorganization of neighborhoods) should not be ignored.²⁵⁻²⁷

In conclusion, this study validated the association of the rs11191580 polymorphism within *NT5C2* with SCZ susceptibility in a South Chinese Han population. Furthermore, this work is the first to report that GWAS-supported variant rs11191580 conferred negative and lack of response symptoms in SCZ. These results should be validated using a larger sample size.

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Disclosure

The authors report no conflicts of interest.

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