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rs11098403 polymorphism near *NDST3* is associated with a reduced risk of schizophrenia in a Han Chinese population

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HIGHLIGHTS

- This is the first study testing the relation of rs11098403 with schizophrenia in Chinese.
- The minor allele of rs11098403 was associated with a reduced risk of schizophrenia.
- This finding confirmed the data that previously obtained from Caucasians.

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ABSTRACT

A recent genome-wide association study indicated that rs11098403, a single nucleotide polymorphism in the vicinity of *NDST3*, was strongly associated with the risk of schizophrenia in Caucasians. However, this relation has not been validated in other populations or ethnic groups. Herein, we conducted a case-control study to investigate the association of rs11098403 polymorphism with the schizophrenia risk in a Han Chinese population comprising 440 schizophrenia patients and 450 control subjects. For the first time, we showed that the minor allele (G) of rs11098403 is closely associated with a reduced risk of schizophrenia (OR = 0.614; 95% CI: 0.453–0.833; $P = 0.002$; Power = 0.832). Meanwhile, the G allele of rs11098403 seemed to reduce the schizophrenia risk via a dominant manner (GG + AG vs. AA, OR = 0.526; 95% CI: 0.374–0.74; $P < 0.001$). Furthermore, this association was further confirmed using an independent replication sample containing 267 schizophrenia patients and 400 control subjects with a Han Chinese descent (OR = 0.652; 95% CI: 0.469–0.907; $P = 0.011$; Power = 0.772). Taken together, these findings demonstrate a significant association between rs11098403 and schizophrenia risk in Han Chinese, confirming the data that previously obtained from Caucasians.

1. Introduction

Schizophrenia is a severe and complex psychiatric disorder with the lifetime prevalence of 1% in general populations worldwide, which is characterized by positive symptoms (e.g., hallucination, delusions and disorganized behavior), negative symptoms (e.g., affective blunting, apathy and social withdrawal) as well as cognitive dysfunctions (e.g., attention, learning and memory impairments) [1,2]. Although the precise etiology of this disease remains largely unknown, several family-based and twin studies have revealed a strong genetic component in the pathogenesis of schizophrenia, with estimations of heritability about 80% [3,4]. In order to identify susceptibility loci of schizophrenia, several genome-wide association studies (GWASs) have been performed in Caucasian populations in recent year [5]. Among them, a large scale GWAS indicated that rs11098403, a single nucleotide polymorphism (SNP) in the vicinity of *NDST3*, was strongly associated with the risk of schizophrenia in Caucasians [6].

However, this association needs to be validated in other ethnic groups and population in addition to Caucasians. Herein, we conducted a case-control study to investigate the relation between rs11098403 and schizophrenia susceptibility in Han Chinese. We found that the minor allele of rs11098403 is closely associated with a reduced risk of schizophrenia in an exploratory sample

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Table 1
Characteristics of the exploratory and replication samples.

Characteristic	Exploratory sample			Replication sample		
	Schizophrenia patients (n = 440)	Schizophrenia patients (n = 440)	P-value	Schizophrenia patients (n = 267)	Schizophrenia patients (n = 400)	P-value
Age, years (mean ± SD)	41.75 ± 9	42.61 ± 9.64	0.171	42.26 ± 9.45	43.07 ± 9.84	0.291
Age range, years	22–63	23–66		21–69	23–68	
Age at onset, years (mean ± SD)	27.52 ± 4.56			27.26 ± 4.79		
Gender, n (%)						
Male	252 (57%)	275 (61%)	0.244	162 (61%)	237 (59%)	0.713
Female	188 (43%)	175 (39%)		105 (39%)	163 (41%)	

comprising 440 schizophrenia patients and 450 control subjects with a Han Chinese descent. Meanwhile, this association was further confirmed using an independent replication sample containing 267 schizophrenia patients and 400 control subjects. These findings demonstrate a significant association between rs11098403 and schizophrenia risk in Han Chinese, confirming the data that previously obtained from Caucasians.

2. Materials and methods

2.1. Samples

The procedures for this study were reviewed and approved by the Institutional Review Boards of the Wuxi Mental Health Center. This study was performed in accordance with the Declaration of Helsinki, and written informed consents were obtained from participants or their guardians.

Our exploratory sample contained 440 schizophrenia patients and 450 control subjects. All the subjects were unrelated Han Chinese residents from Jiangsu Province. The schizophrenia patients were recruited from Wuxi Mental Health Center as described [7]: (a) patients met the criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and the diagnoses were made based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders; (b) first-episode patients were not involved since exploratory diagnoses are often unreliable; and (c) patients had no physical disease, neurological disease or other psychiatric disorder aside from schizophrenia. Diagnosis and review of psychiatric case records were performed by two or more senior psychiatrists. The control subjects were enrolled among the staffs from Wuxi Mental Health Center and Nanjing Medical University who had been interviewed by two senior psychiatrists. Subjects with chronic physical diseases or psychiatric disorders were excluded from this study.

Our independent replication sample included 267 schizophrenia patients and 400 control subjects with a Han Chinese descent. The schizophrenia patients were recruited from the Encephalopathy Center of Qingdao Municipal Hospital using the criteria described above. The control subjects were enrolled among the staffs from Qingdao Municipal Hospital and Qingdao University.

2.2. DNA extraction and SNP genotyping

Genomic DNA was extracted from peripheral blood leukocytes of schizophrenia patients and control subjects using the Wizard genomic DNA purification kit (#A1125, Promega, USA) as described [8–11]. Genotyping of rs11098403 polymorphism was performed by polymerase chain reaction-ligase detection reaction on ABI Prism 377 sequence detection system as described. Data analysis was achieved using GeneMapper Software version 4.0. Randomly selected DNA samples from each genotype were analyzed in duplicate using ligation detection reaction and sequence analysis. Consistent results were obtained by these two methods, and the genotype call rates in cases and controls are >99%.

2.3. Statistical analysis

The statistical power of this study was estimated using the STPLAN version 4.3 software under a given sample size and significance level ($\alpha = 0.05$). Hardy–Weinberg equilibrium analysis was carried out in control subjects using Hardy–Weinberg equilibrium (HWE) version 1.20. The genotype and allele distributions in schizophrenia patients and control subjects were compared by the χ^2 test or Fisher's exact test, and the P-value, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using Stata software version 12.0. $P < 0.05$ was considered significant.

3. Results

The characteristics of the exploratory and replication samples were shown by Table 1. No statistically significant differences were observed in age and gender between schizophrenia patients and control subjects in both samples. In control groups from both samples, the distribution of rs11098403 was in HWE (for the controls from our exploratory sample: $P = 0.415$; for the controls from our replication sample: $P = 0.512$), and the genotype and allele frequencies of rs11098403 were consistent with CHB genotype data in HapMap database (see Table 2).

In our exploratory sample comprising 440 schizophrenia patients and 450 control subjects, there were significant differences in genotype frequency of rs11098403 between schizophrenia patients and control subjects (shown by Table 3, $P < 0.001$). The

Table 2
Comparison of genotypes and allele frequencies of rs11098403 between control subjects from the exploratory and replication samples and those obtained from the HapMap database.

Samples	n	Genotypes n (%)				Alleles n (%)		
		G/G	A/G	A/A	P-value	G	A	P-value
HapMap data	137	4 (2.9)	37 (27)	96 (70.1)	0.434	45 (16.4)	229 (83.6)	0.198
Control subjects from the exploratory sample	450	10 (2.2)	100 (22.2)	340 (75.6)		120 (13.3)	780 (86.7)	
HapMap data	137	4 (2.9)	37 (27)	96 (70.1)	0.973	45 (16.4)	229 (83.6)	0.869
Control subjects from the replication sample	400	12 (3)	104 (26)	284 (71)		128 (16)	672 (84)	