•Original research article•

Association of schizophrenia with the rs821633 polymorphism in the *DISC1* gene among Han Chinese

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Background: Previous studies report that various single nucleotide polymorphisms (SNP) in the Disrupted-in-Schizophrenia 1 (*DISC1*) gene are closely associated with schizophrenia, but there are no studies that assess the relationship of age of onset of schizophrenia with these SNPs.

Objective: Investigate the relationship between the rs821633 SNP in the *DISC1* gene and the occurrence and age of onset of schizophrenia in Han Chinese.

Methods: We used the TaqMan genotyping technology to examine the rs821633 SNP in the *DISC1* gene among 315 individuals who developed schizophrenia prior to 19 years of age ('early-onset'), 407 individuals who developed schizophrenia when 19 years of age or older ('late-onset'), and 482 healthy controls. We used survival analyses to investigate the relationship between the rs821633(C) risk allele and the age of onset of schizophrenia.

Results: Compared to the prevalence in healthy controls, the prevalence of the C/C genotype of rs821633 and of the C allele in rs821633 were significantly greater in individuals with early-onset schizophrenia (X^2=7.17, *df*=1, *p*=0.007; X^2=7.20, *df*=2, *p*=0.032) and significantly greater in individuals with late-onset schizophrenia (X^2=5.36, *df*=1, *p*=0.022; X^2=6.58, *df*=2, *p*=0.041). However, there were no significant differences in the prevalence of the C/C genotype or the C allele between individuals with early-onset and late-onset schizophrenia. Kaplan-Meier survival analyses found no significant association between the rs821633(C) risk allele and age of onset in schizophrenia.

Conclusion: We confirm the association of polymorphism in the rs821633 SNP in the *DISC1* gene with schizophrenia among Han Chinese, but we found no association between the rs821633(C) risk allele and the age of onset in individuals with schizophrenia.

Keywords: schizophrenia; *DISC1* gene; transmission disequilibrium test; single nucleotide polymorphism; age of onset; China

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1. Introduction

Schizophrenia is a common mental illness of unknown etiology that usually starts in young adulthood and includes various combinations of positive psychotic symptoms, negative symptoms, and cognitive impairment in attention and information processing.[1] In 2000 Millar and colleagues[2] first reported an association of the Disrupted-in-Schizophrenia 1 (*DISC1*) gene with

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schizophrenia in a large Scottish genealogy. Subsequent studies by Paunio,[3] Burdick,[4] and Cannon[5] showed that the *DISC1* gene is associated with brain structure and cognitive function. More recent studies confirmed that the *DISC1* gene is one of the genes most closely associated schizophrenia[6] and that the three primary risk alleles in the *DISC1* gene are rs1538979(T), rs821577(G), and rs821633(C).[7,8] Moreover, Tomppo and colleagues[7] reported that social anhedonia – a symptom that often occurs before the onset of the core psychotic symptoms of schizophrenia[9,10] – is more prominent in carriers of the risk allele for rs821633 than among carriers of the risk alleles for rs1538979 and rs821577.

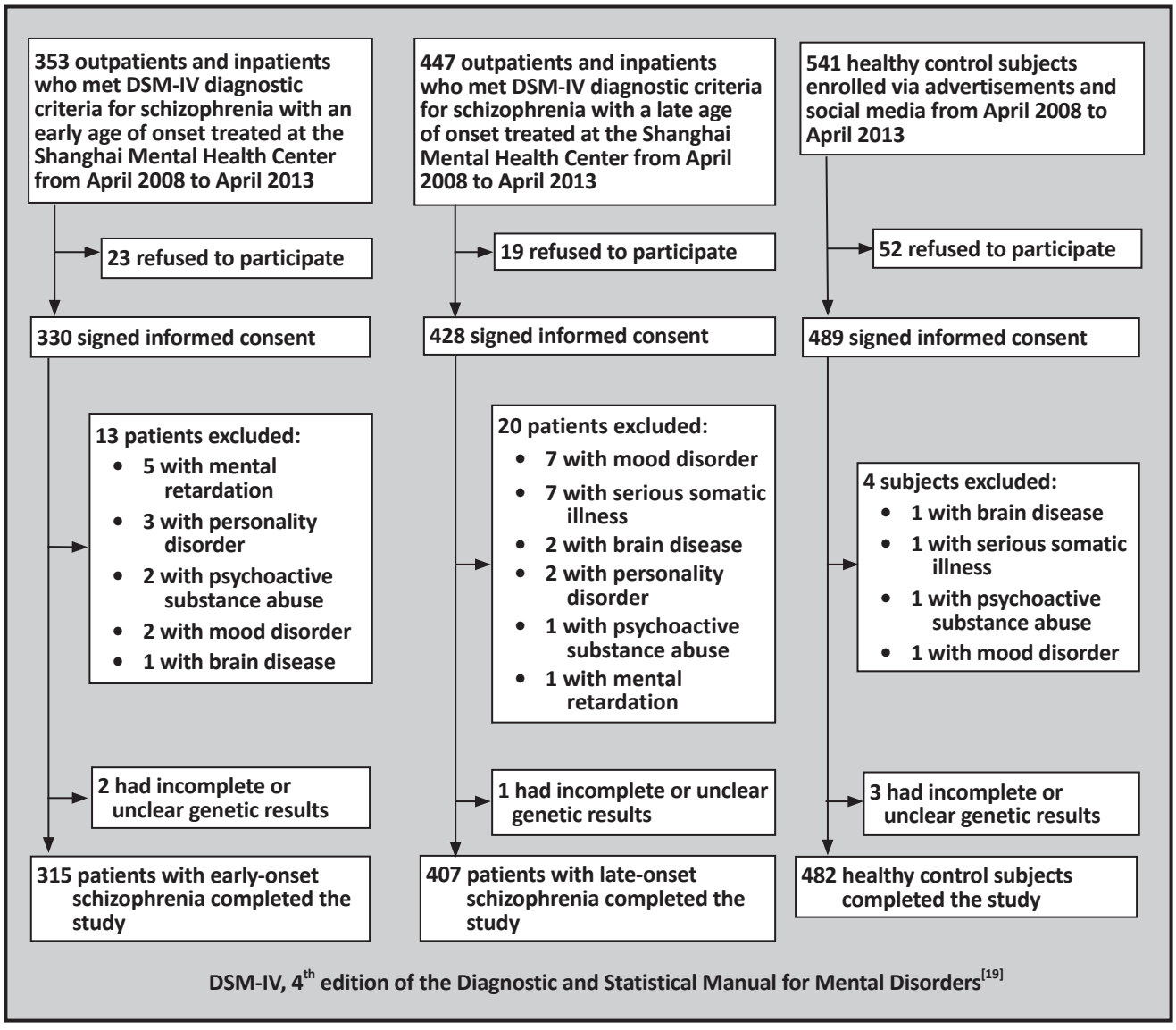
There have been several previous studies of *DISC1* gene polymorphisms among individuals with schizophrenia in China,[11-16] but none of them have considered the relationship of the polymorphisms to the age of onset of the illness. The current study assesses the relationship between the rs821633(C) risk allele in the *DISC1* gene and the occurrence and age of onset of schizophrenia in the main ethnic group of Chinese individuals (i.e., Han Chinese). The goals of the study are to (a) confirm the relationship between the rs821633 polymorphism and schizophrenia reported in other racial groups among Han Chinese, and (b) assess whether or not the relationship of this risk allele with schizophrenia is different in genetically more homogeneous early-onset schizophrenia (defined as those who developed the illness prior to 19 years of age[17-18]) than in genetically more heterogeneous late-onset schizophrenia (those who develop the illness at 19 years of age or older).

2. Methods

2.1 Sample

The recruitment process is shown in Figure 1. Participants with schizophrenia were recruited from among outpatients and inpatients treated at the

Figure 1.Enrollment of participants in the study



Shanghai Mental Health Center from April 2008 to April 2013. All recruited patients met the following criteria: (a) belonged to the Han Chinese ethnic group; (b) met the diagnostic criteria for schizophrenia of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[19] as determined by two senior clinicians who independently evaluated the patient using the Chinese version of the Structured Clinical Interview for DSM-IV Axis I Disorders[20] (the two clinicians' inter-rater reliability was excellent: Kappa=0.87); (c) were not in the first episode of illness (i.e., had one or more prior episodes of illness); (d) had been taking antipsychotic medication and been clinically stable for at least 6 months prior to recruitment; (e) did not have any other co-morbid mental disorder, a history of suicidal behavior, or a serious somatic illness; and (f) were not pregnant.

The age of onset was defined as the age when obvious positive symptoms (i.e., hallucinations or delusions) first appeared, based on information obtained during the clinical exam or as provided by family members. Individuals with an age of onset prior to becoming 19 were classified as 'early-onset' (n=315); those whose age of onset was after they turned 19 were classified as 'late-onset' (n=407).

During the same period we recruited 482 adult participants (i.e., 18 years of age or older) for the healthy control group via advertisements and social media. They were all from the Han Chinese ethnic group, had no mental illness (as assessed by the research psychiatrists), had no family history of mental illness, had no serious medical illnesses, and were not pregnant.

All subjects signed an informed consent form at the time of recruitment. The ethics committee of the Shanghai Mental Health Center approved the study (approval number: 2012-26R).

2.2 Genetic assessment

We considered single nucleotide polymorphism (SNP) markers smaller than +/- 500 bp with a minor allele frequency (MAF) equal to or above 20% in the Han Chinese ethnic group using data contained in the National Center for Biotechnology Information (NCBI) Database of Short Genetic Variation (dbSNP).[21] Based on previous findings in non-Han populations about the association of the rs821633 marker with schizophrenia,[7] we decided to make this the target SNP for the current study.

We obtained 2 ml of venous blood from all participants using 2% ethylenediamine tetraacetic acid (EDTA) anticoagulants. The Tiangen DNA extraction technique (Tiangen Biotech Co., Ltd, Beijing) was used to isolate leukocytes and extract DNA which was then stored at -80 °C. TaqMan probes were used to examine polymorphism in the rs821633 SNP of the *DISC1* gene. The polymerase chain reaction (PCR) steps were conducted using Applied Biosystems 17900 (ABI7900) real-time quantitative PCR equipment. All reagents were provided by Life Technologies Corporation, USA. The PCR buffer used on the 384 pore plate was a total of 5 ul, including 20 ng of DNA primer, 2.0 ul of 2 × TaqMan PCR Master Mix, and 0.05 ul of 40 × SNP Assay (including primers and FAM/VIC probes [a 6-carboxyfluorescein reporter dye probe specific for allele "T" and a fluorescent reporter dye probe specific for allele "C"]). The PCR amplification started with 10 min denaturation at 95℃, followed by 50 cycles of 15 s at 92℃ and 90 s at 60℃, and subsequent storage at 25℃. After the PCR amplification, we examined the distribution of alleles on the 384 pore plate using the Allele Discrimination program which assesses the signal strength of the FAM/VIC reporter dye probes. The sequence detection system (SDS) graphic analysis software was then used to genotype and save the results.

The two probes used in the TaqMan method used two different reporter dyes, FAM and VIC. In the process of the PCR, the probes combined with matched DNA templates and were decomposed by Ampli Taq Gold DNA Polymerase which strengthened the fluorescence of the affected probe. Analysis of the different signal strengths of the two types of fluorescence in the 384 pores determined the pattern of SNP alleles: if there were only samples of enhanced fluorescence of FAM or VIC, the SNP was classified as homozygote; if the fluorescence of both FAM and VIC were strengthened, the SNP was classified as heterozygote. We rechecked the samples in which the fluorescence signal strength showed no significant increase to confirm the result. We randomly chose 10 samples with increased fluorescence and re-tested the sample; the good test-retest concordance (0.99) indicated that the use of TaqMan methods for SNP genotyping produced reliable results.

2.3 Statistical analysis

We used SPSS 13.0 software to compare the gender and age distribution in the three groups of subjects. A Tukey-type multiple comparison method based on an arcsin transformation of the original proportions[22] was used to conduct a multiple comparison test of the gender distribution between the three groups. To confirm the homogeneity of the genetic backgrounds of the subjects, we used SHEsisPlus software (http://analysis.bio-x.cn/myAnalysis.php) to conduct Hardy-Weinberg equilibrium goodness-of-fit tests among the allele frequencies in each of the three groups of subjects. SHEsisPlus software was also used to assess the association of age and gender with the risk allele of interest (rs821633(C)) and to calculate the odds ratios (OR) and the associated 95% confidence intervals of this risk allele for the early-onset group versus the control group, for the late-onset group versus the control group, and for the early-onset group versus the late-onset group. The power of the association analysis to detect significant differences was assessed using the Quanto 1.2.4 statistical package.[23] We conducted three separate survival analyses using the Kaplan-Meier statistical test

in the SPSS statistical package to assess the relationship between the presence of the rs821633(C) risk allele (i.e., individuals with the C/C genotype or the C/T genotype versus individuals with the T/T genotype) and the age of onset of schizophrenia in individuals with early-onset schizophrenia, in individuals with late-onset schizophrenia, and in all individuals with schizophrenia (combining early-onset and late-onset patients). All statistical analyses used two-tailed tests with the level of statistical significance set at $p<0.05$.

3. Results

The age of onset among the 315 individuals in the early-onset group ranged from 7 to 18 years of age; their mean age of onset was 16.4 (2.1) years of age. The age of onset among the 407 individuals in the late-onset group ranged from 19 to 71 years of age; their mean age of onset was 37.5 (8.8) years of age.

Among the early-onset patients, late-onset patients, and normal control subjects, 53.0%, 53.6%, and 40.5% were females, respectively (X^2=21.91, df=2, $p<0.001$); multiple comparison assessment showed that individuals in the early-onset and late-onset groups were significantly ($p<0.01$) more likely to be female than those in the control group. The mean (sd) age at the time of enrollment in the three groups was 46.2 (16.6), 61.4 (15.7) and 32.6 (9.0) years of age, respectively (F=3960.59, df_1=2, df_2=1201, $p<0.001$); post-hoc Tukey multiple comparison tests found that early-onset patients were significantly younger than late-onset patients ($p<0.05$) and that both early-onset and late-onset patients were significantly older than healthy controls ($p<0.05$). Despite these significant differences in age and gender between the three groups, analyses using the SHEsisPlus software package found no significant correlation between age at the time of recruitment or gender and the prevalence of the risk allele of interest (rs821633(C)), so it is unlikely that these differences between groups confounded the main results.

The genotype frequencies of rs821633 for all three groups satisfied the Hardy-Weinberg equilibrium goodness-of-fit test: in the early-onset group X^2=0.00, df=1, p=0.980; in the late-onset group X^2=2.08, df=1, p=0.150; and in the control group X^2=0.03, df=1, p=0.860.

As shown in Table 1, the C/C genotype and the C allele of rs821633 were significantly more prevalent in the early-onset group and in the late-onset group than in the control group, but there were no significant differences in the prevalence of the genotypes or of the alleles between the early-onset group and the late-onset group.

The results of the Kaplan–Meier survival analyses are shown in Figures 2-4. There was no statistically significant relationship between the presence of the rs821633(C) risk allele and the age of onset of schizophrenia in the 315 early-onset patients (X^2=1.81, p=0.183), in the 407 late-onset patients (X^2=0.11, p=0.740), or in the combined group of 722 patients (X^2=0.18, p=0.672).

Table 1. Comparisons of allele and genotype frequencies for the rs821633 single nucleotide polymorphism in the *DISC1* gene between individuals with early-onset schizophrenia, individuals with late-onset schizophrenia, and healthy controls

group	genotype frequencies			allele frequencies	
	C/C	C/T	T/T	C	T
early-onset schizophrenia (N=315), n (%)	72 (22.9%)	157 (49.8%)	86 (27.3%)	301 (47.8%)	329 (52.2%)
late-onset schizophrenia (N=407), n (%)	95 (23.3%)	188 (46.2%)	124 (30.5%)	378 (46.4%)	436 (53.6%)
healthy controls (N=482), n (%)	80 (16.6%)	235 (48.8%)	167 (34.6%)	395 (41.0%)	569 (59.0%)
compare early-onset v. control	**X^2=7.20 (p=0.032)**			**OR=1.32 (95% CI,1.08-1.61)[a]**	
compare late-onset v. control	**X^2=6.58 (p=0.041)**			**OR=1.25 (95% CI, 1.03-1.51)[b]**	
compare early-onset v. late-onset	X^2=0.11 (p=0.947)			OR=1.02 (95% CI, 0.83-1.26)[c]	

OR, odds ratio CI, confidence interval
[a] X^2=7.17, df=1,p=0.007
[b] X^2=5.36, df=1, p=0.022
[c] X^2=0.03, df=1, p=0.851

Figure 2. Relationship between the rs821633(C) risk allele and age of onset among 315 individuals with early-age-of-onset schizophrenia

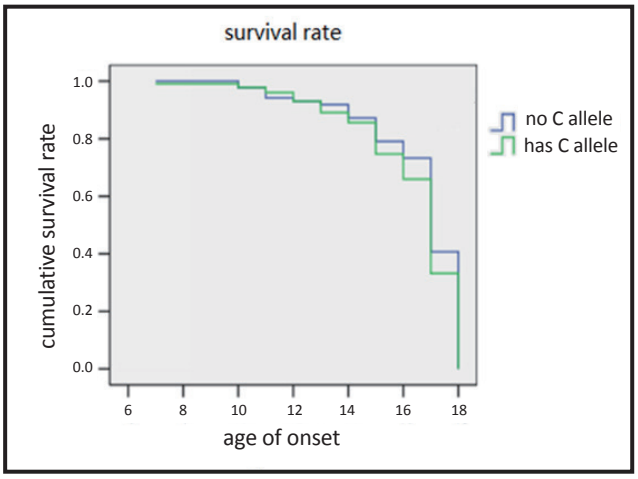


Figure 3. Relationship between the rs821633(C) risk allele and age of onset among 407 individuals with late-age-of-onset schizophrenia

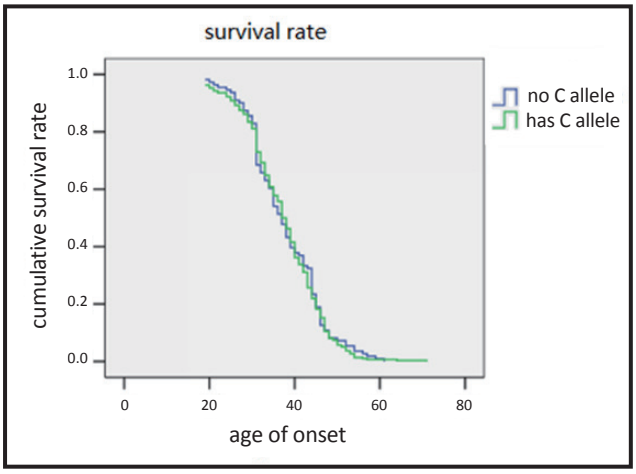
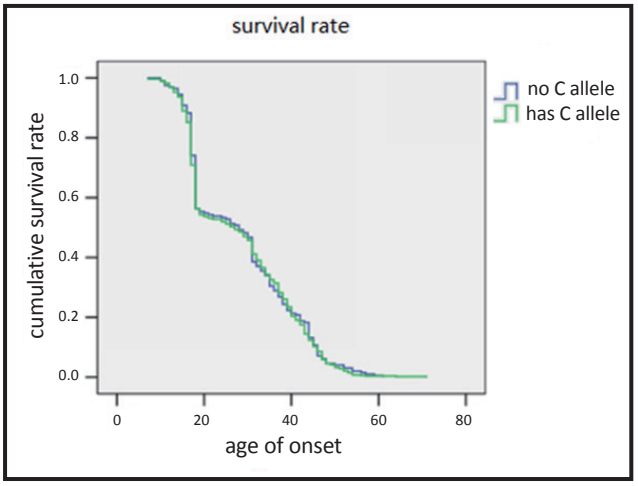


Figure 4. Relationship between the rs821633(C) risk allele and age of onset among 722 individuals with schizophrenia



4. Discussion

4.1 Main findings

We found significant differences between the genotype frequencies and allele frequencies of the rs821633 SNP of the *DISC1* gene in Han Chinese individuals with schizophrenia compared to those in healthy control subjects. This result confirms findings in other racial groups which indicate that polymorphism in the *DISC1* gene is associated with schizophrenia. Tomppo and colleagues[7] assessed the relationship between different psychotic symptoms and 41 markers in the *DISC1* gene among 4651 individuals in Finland and found significant correlations between the rs821633 marker and social anhedonia. Chakirova and colleagues[24] used functional magnetic resonance imaging (fMRI) to compare the association between three markers of the *DISC1* gene (rs1538979, rs821577, and rs821633) and brain activation when completing the Hayling Sentence Completion Task (HSCT) in 33 healthy controls, 20 individuals with schizophrenia, and 36 individuals with bipolar disorders; they found that presence of the risk alleles was associated with significant differences in location-specific brain activation when completing the task in both healthy controls and in the patient groups, confirming the relationship between *DISC1* polymorphism and the neurocognitive pathology in schizophrenia and bipolar disorder. We know of no studies that have failed to identify an association between schizophrenia and polymorphism of the rs821633 SNP of the *DISC1* gene.

The present study is the first to investigate the relationships between the rs821633 marker of the *DISC1* gene and the age-of-onset of schizophrenia. Using both a dichotomous classification of age of onset (early-onset versus late-onset schizophrenia) in a standard association analysis and a continuous measure of age of onset in Kaplan Meier survival analyses, we did not find a significant association between age of onset in schizophrenia and the prevalence of the different genotypes and alleles of rs821633. Failure to identify a relationship of *DISC1* polymorphism and age of onset in schizophrenia may be due to several reasons; two likely reasons are that multiple genes may affect age of onset[25] and that age of onset may be strongly influenced by both genetic and environmental factors.[26]

4.2 Limitations

There are several limitations in the present study. (a) The statistical power for comparing patients to healthy controls was sufficient (>80%), but the power for comparing early-onset versus late-onset patients was low (<80%), so failure to identify differences between the two groups of individuals with schizophrenia may have been due to Type II errors (i.e., small sample size). (b) All the patients included in this study were treated in a single hospital in Shanghai, so they may not be representative of all Han Chinese individuals with schizophrenia. (c) We did not consider the many environmental factors that could confound the relationship between age of onset and *DISC1*

polymorphism, including parents' reproductive age, a history of stress and infection during the maternal gestational period, and a positive family history of schizophrenia.[27] (d) We did not investigate the functions of the rs821633 SNP of the *DISC1* gene, so we were unable to assess the mechanism via which the rs821633(C) risk allele is associated with the onset of schizophrenia.

4.3 Significance

These results provide further evidence about the association of the *DISC1* gene with schizophrenia. Previous studies have shown that the *DISC1* gene is a candidate gene for mental illness that plays several roles in brain development. In a large Scottish family study, Blackwood and colleagues[28] found that the P300 amplitude of event-related potentials (ERP) was significantly decreased among family members with a specific genetic variant of the *DISC1* gene, which suggests that variations in *DISC1* can influence the core processing ability of the brain. Millar and colleagues[29] found that the *DISC1* protein interacts with other proteins (such as ataxin-1 and phosphodiesterase 4B [PDE4B]) which participate in neurite extension and arborization, and in neuronal proliferation, transport, and signal transmission. The *DISC1* protein is present in several parts of the brain, including the hippocampus, cerebellum, cerebral cortex, hypothalamus, and thalamic nuclei.[30] The specific mechanism(s) via which polymorphism in *DISC1* is associated with schizophrenia remains unknown, but several studies[24,31] suggest that different expressions of the *DISC1* protein in specific brain regions can influence perceptual and motor function – functions that are often abnormal in individuals with schizophrenia. Further work is needed to clarify these mechanisms, but our study has shown that the reported associations in other racial groups are probably equally evident in Han Chinese.

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Conflict of interest statement

The authors declare no conflicts of interest.

Informed consent

Every participant in this study signed a consent form at the beginning of the study.

Ethics approval

The ethics committee of the Shanghai Mental Health Center approved the study (approval number: 2012-26R).

Authors' contributions

GH participated in the design and data collection for the study and drafted the manuscript. CY performed the statistical analysis and critically reviewed the manuscript. JZ, YF, and CZ carried out the clinical diagnosis and critically reviewed the manuscript. MZ, XG, CB, SJ, AX, YJ, ZW, and CZ helped enroll the subjects. All authors read and approved the final manuscript.

DISC1 基因 rs821633 位点多态性与中国汉族人群精神分裂症的相关性研究

胡国芹，杨程青，赵静，朱明环，郭向晴，鲍晨曦，贾思，徐阿红，介勇，汪作为，张晨，何永光，吕钦谕，禹顺英，易正辉

背景：既往研究报告显示精神分裂症断裂基因 1 (Disrupted-in-Schizophrenia 1 gene, *DISC1*) 中不同的单核苷酸多态性 (single nucleotide polymorphisms, SNP) 与精神分裂症密切相关，但目前尚无研究评估了 SNP 与精神分裂症发病年龄之间的关系。

目的：探讨 *DISC1* 基因中 rs821633 位点的 SNP 和中国汉族精神分裂症患者的发病及首发年龄的相关性。

方法：我们采用 TaqMan 基因分型技术对 315 例 19 岁之前发病的精神分裂症患者（即“早发性”）、407 例 19 岁后发病的精神分裂症患者（即“非早发性”）和 482 名健康对照进行 *DISC1* 基因 rs821633 位点的 SNP 检测。我们使用生存分析研究 rs821633(C) 位点的危险等位基因与精神分裂症患者首发年龄之间的关系。

结果：相比健康对照组，rs821633 位点 C/C 基因型和 C 等位基因型频率分布在早发性 (X^2=7.17, *df*=1, *p*=0.007; X^2=7.20, *df*=2, *p*=0.032) 和晚发性 (X^2=5.36, *df*=1, *p*=0.022; X^2=6.58, *df*=2, *p*=0.041) 精神分裂症患者中显著较高。然而，C/C 基因型或 C 等位基因型的携带率在早发和晚发性精神分裂症患者中没有显著差异。Kaplan-Meier 生存分析发现 rs821633(C) 危险等位基因与精神分裂症首发年龄之间没有显著相关性。

结论：我们证实了 *DISC1* 基因 rs821633 位点多态性的 SNP 与中国汉族人群精神分裂症之间存在相关性，但未发现 rs821633(C) 危险等位基因与精神分裂症首发年龄之间的相关性。

关键词：精神分裂症；*DISC1* 基因；传递不平衡检验；单核苷酸多态性；首发年龄；中国

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