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Effect of *SOX10* gene polymorphism on early onset schizophrenia in Chinese Han population

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HIGHLIGHTS

- We determined rs139887 of sex-determining region Y-box 10 (*SOX10*) and early onset schizophrenia.
- A significant association in allele and genotype frequencies were found in schizophrenic patients, especially male patients.
- The C/C genotype of rs139887 was significantly associated with an earlier age of onset in male schizophrenics.
- *SOX10* rs139887 may be related to the development of schizophrenia in a gender-specific manner.

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ABSTRACT

Schizophrenia is one of highly heritable psychiatric disorders. Patients with early onset schizophrenia tend to have a greater genetic loading and may be an attractive subpopulation for genetics studies. A single nucleotide polymorphism (SNP) rs139887 in sex-determining region Y-box 10 (*SOX10*), a candidate gene for schizophrenia, was suggested to be associated with schizophrenia although inconsistent results had been reported. The aim of this study was to evaluate the association between *SOX10* rs139887 polymorphism and schizophrenia using an early onset sample in the Chinese Han population. A total of 321 schizophrenic patients with onset before age 18 and 400 healthy controls were recruited for association study. In addition, two populations involved in three studies were selected for meta-analysis to determine the effect of rs139887 on schizophrenia. Our association study results showed that the allele and genotype frequencies were significantly different between schizophrenic patients and controls ($P = 0.013$ and $P = 0.034$, respectively). Interestingly, a significant association in allele and genotype frequencies were found in male patients ($P = 0.017$ and $P = 0.045$, respectively), but not female patients. Moreover, the C/C genotype had a significant association with an earlier age of onset in male schizophrenic patients (Kaplan–Meier log-rank test $P = 0.029$), but not in female patients (Kaplan–Meier log-rank test $P = 0.876$). The meta-analysis result showed the same C allele was significantly associated with schizophrenia ($P = 0.007$). In conclusion, the *SOX10* rs139887 polymorphism was related to the development of schizophrenia in a gender-specific manner, and may be a significant genetic marker for managing subgroups and etiological clues in schizophrenia.

1. Introduction

Schizophrenia is a major debilitating neuropsychiatric disorder affecting approximately 1% of the population worldwide. It is characterized by delusions, hallucinations and deficits of cognition. Evidence from family, adoption and twins studies supported high heritability in the development of schizophrenia (≈80%). However, its exact etiology and genetic mechanism are still unknown. Genetic epidemiology data suggested that schizophrenic patients with early onset age (e.g. less than 18 years old) tended to have a more severe form of the disorder associated with a greater genetic predisposition than their adult counterparts [30,32]. Thus, early onset schizophrenia is believed to be an attractive subpopulation for genetic studies [14].

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Functional abnormalities of neuronal connectivity have been reported in patients with schizophrenia [35]. Histological and neuroimaging studies have led to the hypothesis that dysfunctional myelination may be involved in the pathogenesis of schizophrenia. Magnetic transfer imaging, which is considered to be a useful technique to measure myelin in vivo, demonstrated decreased myelin or axonal membrane integrity in the temporal lobes of patients with schizophrenia [11]. In addition, ultrastructural alterations of myelin sheath lamellae have been described in the frontal cortex in schizophrenia [2]. Therefore, it implied that there may be a pathological damage of myelin in schizophrenia.

Gene expression analyses using DNA microarray also supported the above hypothesis. Decreased expression of oligodendrocyte-related genes in schizophrenic patients has been identified [34]. Among these genes, the expression of sex-determining region Y-box 10 (*SOX10*), a major oligodendrocyte-specific transcription factor involved in neurogenesis and myelination in the central nervous systems [23], was significantly decreased in the brains of patients with schizophrenia. Interestingly, DNA methylation status of the *SOX10* correlated with its down regulation and other oligodendrocyte-related genes has been reported in schizophrenic patients [16]. Besides the epigenetic alteration, it is possible that genetic variations affecting expression of *SOX10* gene may also contribute to the susceptibility to schizophrenia. Iwamoto et al. [17] firstly reported no association between six single nucleotide polymorphisms in the *SOX10* gene and schizophrenia in two separate Japanese samples. However, another association study in Japanese populations showed three of these six SNPs were significantly associated with schizophrenia, especially, a significant association was found in male patients, but not in female patients [26]. Given the above controversial results on the association of rs139887 with schizophrenia, its contribution to the etiology of the disorder requires further clarification.

Therefore, in order to further evaluate the role of rs139887 polymorphism in *SOX10* in susceptibility to schizophrenia and to enhance the potential power for detecting the association, we conducted a case–control study using early onset schizophrenia samples from Chinese Han population. Also, we performed a meta-analysis to identify the effect of rs139887 on schizophrenia.

A total of 321 early onset schizophrenic patients were recruited from Shanghai Mental Health Center. Each patient was assessed and diagnosed by two independent senior psychiatrists according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). The age at onset of schizophrenia was defined as the age when positive symptoms (either delusions or hallucinations) firstly became apparent based on interview and supplemental clinical information obtained from medical records and family informants [12]. Early onset schizophrenia was defined as schizophrenia with onset before age 18 [20]. The patients with schizophrenia consisted of 218 males and 103 females (mean age: 31.5 ± 15.8 years; mean age of first episode: 14.6 ± 2.7 years, range from 6 to 18 years). Control group consisted of 400 healthy volunteers (270 males and 130 females; mean age: 32.6 ± 11.7 years) who were free from physical diseases, as well as individual and family history of mental illness. All subjects were of Chinese Han origin from the same geographical area and provided written informed consent. The study protocol and process were assessed and approved by the ethics committee at Shanghai Mental Health Center.

Genomic DNA was extracted from whole blood using Tiangen DNA isolation kits (Tiangen Biotech, Beijing, China). Rs139887 was genotyped using a TaqMan SNP Genotyping Assay according to manufacture's protocol (Applied Biosystems, Foster City, CA, USA). SNP detection was performed with ABI PRISM 7900 sequence detection system instrument and data were analyzed using SDS 2.0 software (Applied Biosystems). For quality control, all genotypes were determined without knowledge of case or control status in the genotyping process. All assays were repeated in 5% of the samples, and the results were 100% concordant.

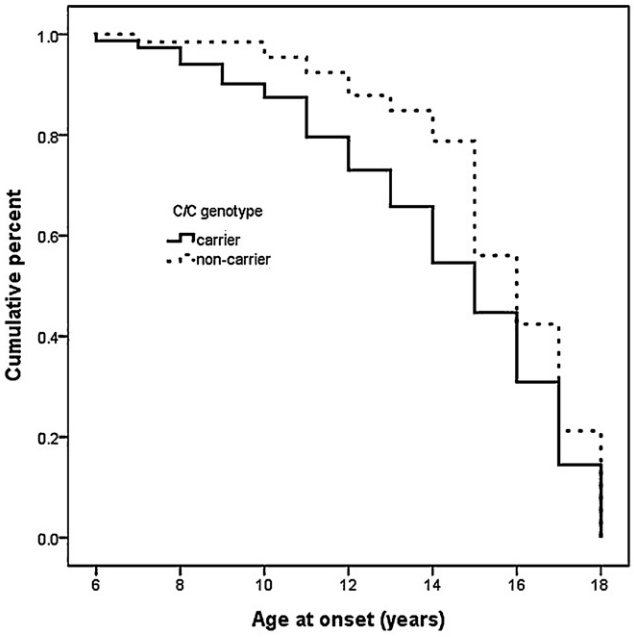

Fig. 1. Kaplan–Meier plot showing the earlier age at onset in male schizophrenic patients carrying the C/C genotype of rs139887 polymorphism (log rank statistic: 4.79, $P = 0.029$).

UNPHASED (v.3.10) (http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphase) was used to test Hardy–Weinberg equilibrium and to analyze the association of schizophrenia risk with rs139887 alleles and genotypes. Power calculations for our sample size were calculated using the G*Power program [10]. The association between age at onset and rs139887 polymorphism was evaluated using the Kaplan–Meier method and the log-rank test for analyses of survival [1]. All the *P* values in this study were two-tailed and the significance level was set at $P = 0.05$.

Studies included in the meta-analysis were identified using Medline database with the key words "*SOX10*" and "Schizophrenia". All the data analyzed were previously published. All statistical analyses were performed using the RewMan (v.5.0) program (http://www.cochrane.org/revman). The significance of the subtotal OR was determined by *Z* test, and the heterogeneity of the group of ORs was assessed using a chi-square test.

No deviation from Hardy–Weinberg equilibrium was found in genotype distribution of the polymorphism.

Significant difference was found in allele and genotype frequencies between the schizophrenic patients and controls ($P = 0.013$ and $P = 0.034$, respectively). Further analyses based on gender stratification revealed a significant association between the allele and genotype frequencies and male patients ($P = 0.017$ and $P = 0.045$, respectively), but not female patients with schizophrenia (Table 1). The Kaplan–Meier survival analysis showed the age at onset in total schizophrenic patients was not associated with the C/C genotype (log rank statistic: 3.39, $P = 0.070$). The mean ± standard deviation ages at onset of C/C genotype carriers and those not carrying C/C genotype were 14.4 ± 2.9 years and 15.2 ± 2.4 years, respectively. Interestingly, the age at onset in male patients was significantly associated with the C/C genotype (log rank statistic: 4.79, $P = 0.029$) (Fig. 1). The mean ± standard deviation ages at onset of C/C genotype carriers and those not carrying C/C genotype were 14.3 ± 3.0 years and 15.5 ± 2.3 years, respectively. In females, the significance seems lost (log rank statistic: 0.02, $P = 0.876$). The Kaplan–Meier survival