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

Aihua Yuan[a], Zhenghui Yi[a], Jinhua Sun[a], Yasong Du[a], Tao Yu[b], Chen Zhang[a], Yi Liu[a], Ying Zhou[b], Dengtang Liu[a], Huafang Li[a], Yifeng Xu[a], Zaohuo Cheng[c], Weidong Li[b,c,**], Shunying Yu[a,*]

[a] *Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, 600 Wan Ping Nan Road, Shanghai 200030, PR China*
[b] *Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Ministry of Education, Shanghai Jiao Tong University, 800 Dong Chuan Road, Shanghai 200240, PR China*
[c] *Wuxi Mental Health Center, 156 Qian Rong Road, Wuxi 214151, PR China*

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].

* Corresponding author. Tel.: +86 21 6438 7250; fax: +86 21 6438 7986.
** Corresponding author. Tel.: +86 21 3420 5687; fax: +86 21 3420 5687.
E-mail addresses: weidongbiox@gmail.com (W. Li), yushuny@yahoo.com (S. Yu).

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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.

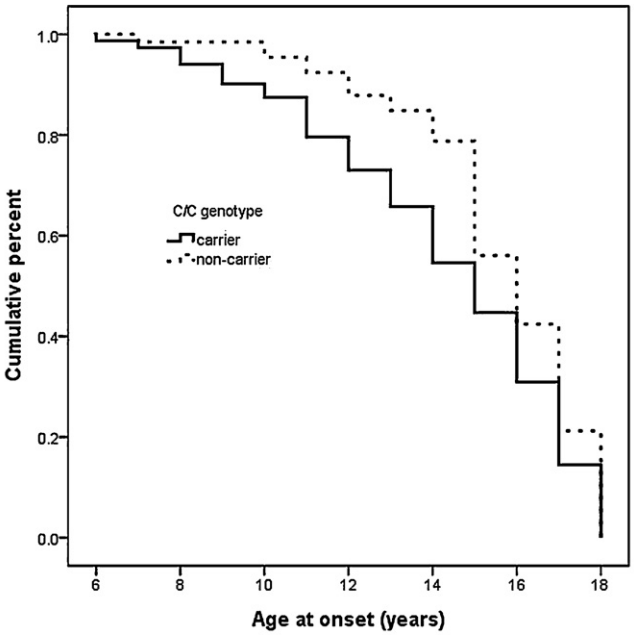

Fig. 1. Kaplan–Meier plot showing the earlier age at onset in male schizophrenic patients carrying the C/C genotype of rs139887 polymorphism (log rank statistic: 4.79, $P = 0.029$).

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

Table 1
Distribution of rs139887 genotype and allele in schizophrenia patients (cases) and controls.

Cases	*N*	Genotype distribution (%)			Odds ratio[a] (95%CI)	*P* value	Allele (%)		Odds ratio[b] (95%CI)	*P* value
		C/C	C/G	G/G			C	G		
Total										
Schizophrenia	321	223 (69.5)	92 (28.7)	6 (1.9)	1.50 (1.10–2.04)	0.034	538 (83.8)	104 (16.2)	1.40 (1.07–1.84)	0.013
Control	400	241 (60.3)	147 (36.7)	12 (3.0)			629 (78.6)	171 (21.4)		
Female										
Schizophrenia	103	71 (68.9)	29 (28.2)	3 (2.9)	1.39 (0.80–2.39)	0.428	171 (83.0)	35 (17.0)	1.48 (1.07–2.06)	0.352
Control	130	80 (61.5)	47 (36.2)	3 (2.3)			207 (79.6)	53 (20.4)		
Male										
Schizophrenia	218	152 (69.7)	63 (28.9)	3 (1.4)	1.55 (1.07–2.27)	0.045	367 (84.2)	69 (15.8)	1.25 (0.78–2.00)	0.017
Control	270	161 (59.6)	100 (37.0)	9 (3.3)			422 (78.1)	118 (21.9)		

The odds ratio was calculated for cases homozygous for C allele [a](C/C vs C/G + G/G), and with respect to the C-allele[b].

analysis also showed that the age at onset was not significantly associated with the C allele in total patients (log rank statistic: 1.82, $P = 0.178$), male patients (log rank statistic: 3.03, $P = 0.082$) and female patients (log rank statistic: 0.04, $P = 0.845$).

In the power calculations using the G*Power program based on Cohen's method, our sample size had >85% power in the case–control samples to detect a significant association ($\alpha < 0.05$) for genotypes and alleles when an effect size index of 0.1 (corresponding to a "weak" gene effect) was used.

For the meta-analysis, we combined and analyzed the data from two populations (including the samples in the current study). We identified two independent case–control studies that tested for association between rs139887 of *SOX10* and schizophrenia [17,26]. We combined rs139887 data from the two studies with the current study, and investigated the polymorphism in the *SOX10* gene locus. Statistic summary of the meta-analysis for rs139887 was shown in Fig. 2.

The heterogeneity for rs139887 of the combined samples was tested. The result showed that it was not significant ($\chi^2 = 5.69$, df = 2, $P = 0.06$), which enabled us to test for association of the polymorphism by using a fixed-effect meta analysis. Finally, a significant difference was found between patients and controls for the C-allele of rs139887 (subtotal OR = 1.15, 95%CI = 1.04–1.27, $Z = 2.71$, $P = 0.007$).

In this study, we investigated the *SOX10* rs139887 polymorphism in an early onset schizophrenia sample from the Chinese Han population, the sample size of which was sufficient to detect an association. There was a significant association between rs139887 and early onset schizophrenia. Even after the stratification for gender, the polymorphism still had a direct contribution to the susceptibility of male patients, but not to that of female patients. Subsequent meta-analysis also showed the same C allele was significantly associated with schizophrenia. Rs139887 is located within intron three of *SOX10*. As some introns contain enhancer elements or alternative promoters, it is likely for them to influence gene function directly and there is evidence for intronic contribution to gene expression. Eom et al. reported rs951660 in intron two of *PHLDB2* delayed the expression of this gene in vivo [9]. An intron one polymorphism rs10748842 was significantly associated with *NRG3* gene expression in the brains of schizophrenics as a potential underlying mechanism for its disease association [18]. Reduced expression of *SOX10* has been observed in schizophrenic patients [6]. Therefore, it will be important to further determine the potential role of rs139887 in *SOX10* gene expression and the pathogenesis of schizophrenia.

Genetic variations in *SOX10* may interact with the formation and maintenance of myelin sheath and may lead to dysfunctional synaptic connectivity. These variations may be responsible for an individual patient's vulnerability for the development of schizophrenia. Oligodendrocytes, major glial cells involved in producing a multilayered myelin sheath wrapping neighboring axons in CNS, provide nerve insulation and facilitate salutatory conduction of nerve impulse by invoking the myelin-dependent ion channels distribution [22], and changes in *SOX10* activity may cause alterations in ion channels-triggered signal transduction and subsequent neuronal activity. In addition to genetic variants, interaction between *SOX10* and other genes may also contribute to the alteration of myelination in schizophrenia. Evidence from research using postmortem tissue showed the expression of *Olig2*, a transcription factor essential to the initial specification of oligodendrocyte lineage [25], was reduced in the brains of patients with schizophrenia compared with those of controls [34]. Data on epigenetic mechanisms and transcriptome regulation suggest that at least some changes in gene expression may be due to changes in levels of gene promoter methylation or microRNA in the central nervous system of patients with schizophrenia [4]. Convergent evidence from genetic linkage, genetic association and biological studies support *DISC1*, another differentiation regulation factor of oligodendrocytes [19], affects susceptibility to schizophrenia [8,15,24]. Interestingly, both *Olig2* and *DISC1* have recently been reported to regulate the expression of *SOX10* in vivo [7,21]. Therefore, there might be a schizophrenia-specific pathway into which several myelin-related genes converge. Moreover, stratified by sex, only male patients demonstrated the significant association. This

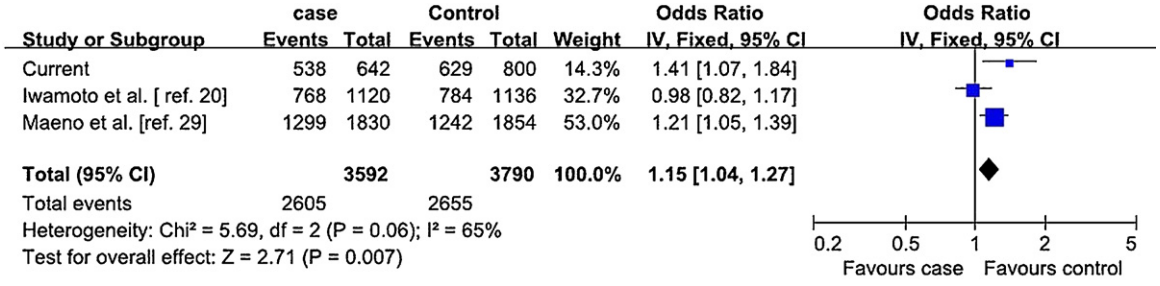

Fig. 2. Forest plots of pooled OR with 95%CI for association between rs139887C allele and schizophrenia risk. The size of each box is proportional to the weight of each study.

result may support there may be different mechanisms of myelination between sexes [27]. This speculation, however, needs further clarification.

Furthermore, our results showed the rs139887 was significantly associated with age at onset in male patients, but not in total or female patients. The male patients carrying the C/C genotype had a lower age at onset than those not carrying the C/C genotype, which is in agreement with previous studies that proposed early age at onset of schizophrenia was associated to greater genetic vulnerability [31]. The correlation between the age at onset and the distribution of the C allele of rs139887 was also analyzed. However, there was no association between them. The C allele might thus be related to an early pathogenesis of schizophrenia by interacting with other factors but not lower age at onset.

The age at onset has been considered as an important characteristic of schizophrenia [3], and there is strong evidence for a genetic contribution to age at onset of schizophrenia. Decoster et al. [5] reported Val66Met of *BDNF* was associated with an onset at an age 1.2 years earlier in schizophrenia. *NRG1* variants were associated with early age of onset and high positive symptom of schizophrenia when the frequency was compared with control [28]. Therefore, we used the Kaplan–Meier method to determine whether a significant association exists between the rs139887 polymorphism and age at onset of schizophrenia in our sample. Our findings showed C/C genotype of rs139887 played an important role in the age at onset of schizophrenia in a gender-specific manner. One neuroimaging study demonstrated the slower growth rates of white matter in the left hemisphere might be more pronounced in schizophrenic patients with earlier age at onset [13]. *SOX10* gene was critical to the differentiation of oligodendrocytes and formation of myelin sheath [29]. Thus, C/C genotype may induce early age at onset via altering brain morphology in schizophrenia. In addition, there are evidence demonstrated the brains of men showed later maturation of neuronal connexions and axonal myelination than those of the women [33]. This slower rate of development might make male subjects more vulnerable to early brain insults including genetic variants that predispose to schizophrenia, which may contribute to their early age at onset of the disorder. Therefore, we speculate that sex steroids were involved in the effect of rs139887 on the age of onset of schizophrenia. Further studies, however, are required for confirmation.

There are two limitations in the present study that should be mentioned. First, the most suspicious patients did not want to participate in the study. This is probably a real problem for many studies of schizophrenia. Second, the control subjects were not psychiatrically screened and potential selection bias of the case–control study could not be ruled out.

The present finding suggests that a genetic factor may play a major role in the development of schizophrenia by interacting with a factor related to the male and lower age at onset. The *SOX10* rs139887 polymorphism has an important effect on age of onset in schizophrenia and might thus be related to an early pathogenesis of schizophrenia in young male patients. Alternatively, these findings may represent a significant genetic marker for managing subgroups and etiological clues in schizophrenia.

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