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LETTER TO THE EDITOR

# Association of *MSI2* Gene Polymorphism with Age-at-Onset of Schizophrenia in a Chinese Population

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**Dear Editor,**

Schizophrenia is one of the most complicated and challenging mental disorders psychiatrists and mental health caregivers confront. It is a heavy burden for the patients and usually occurs during adulthood. With a peak age-at-onset of 18–25 years, schizophrenia results in the loss of productivity, poses a considerable burden on the relatives, and causes high medical and social costs. In the general population worldwide, the life risk for schizophrenia is about 1% [1]. Schizophrenia has a strong genetic component, which has been consistently indicated by genetic epidemiological studies [2]. In spite of high genetic risk, genetic influence alone does not fully determine the etiology of schizophrenia. It has been estimated that the heritability of schizophrenia ranges from 66% to 85%, leaving space for the contribution of environmental factors. The inheritance pattern of schizophrenia suggests a non-Mendelian mode of transmission and makes simple major gene dependency impossible. Instead, a polygenic model seems to provide a better explanation [3].

The human *MSI2* gene is a member of the Musashi gene family which encodes an evolutionarily conserved group of neural RNA-binding proteins. *MSI2* is developmentally regulated, predominantly expressed in neural stem cells, and important for cell fate determination during embryonic neurodevelopment [4]. The human *MSI2* gene is located on chromosome 17q, a potential susceptibility region for schizophrenia [5]. Our previous genome-wide association study (GWAS) in a Han Chinese population revealed a moderate association of *MSI2* and schizophrenia [6]. A further replication and combined association study showed significant association of three *MSI2* tag SNPs (rs9892791, rs11657292, and rs1822381) with schizophrenia susceptibility [7]. Age-at-onset is considered as one of the most valuable clues to the etiology of schizophrenia. A genetic contribution to the age-at-onset of schizophrenia was confirmed by several genome-wide linkage studies [8]. A genome-wide linkage study conducted by Cardno *et al.* indicated a peak LOD score on chromosome 17q (D17S787) [9], close to the *MSI2* gene region. Here, we aimed to investigate the potential association between three *MSI2* tag SNPs and age-at-onset of schizophrenia in a Han Chinese sample of schizophrenia patients.

Six hundred and twelve schizophrenia patients were recruited from the Institute of Mental Health, Peking University, Beijing, China. All the patients were diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria by at least two experienced psychiatrists. None had severe medical complications. Prior to participation, the patients or their guardians gave written consent after ensuring they

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completely understood the research purpose and procedures. The age-at-onset for each patient was defined as the age at which he or she was first diagnosed with schizophrenia or experienced the first symptoms of schizophrenia. Three intronic SNPs (rs1822381, rs11657292, and rs9892791) of *MSI2* were investigated. These three tag SNPs were significantly associated with schizophrenia in our previous two-stage association analysis. Genomic DNA was extracted using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). PCR primers were designed by Oligo 6.0 (MBI Inc., Norwalk, CT) to amplify DNA fragments including the three selected SNPs (rs1822381: 5′-GCATTTCCTCCTCAA-3′ and 5′-CACCA TCCTCCGTTA -3′; rs11657292: 5′-AGATGTTTGCTC CTGA-3′ and 5′-AATAGAACCAACTCCC -3′; and rs9892791: 5′-GCTGACTGCTGAGGAT-3′ and 5′-ATTT GATTTGGGACAC-3′). The PCR products were verified by restriction fragment length polymorphism or direct sequencing. Genotype deviation analysis of Hardy–Weinberg equilibrium was tested for the three SNPs by a $\chi^2$ goodness-of-fit test in SHEsis software (http://analysis.bio-x.cn/SHEsisMain.htm). The Kaplan–Meier method and the log-rank test for analysis of survival were applied to investigate the association of age-at-onset with genotype.

Hardy–Weinberg analysis showed no significant results for the three SNPs in schizophrenia patients, indicating genotype and allele frequencies constant from generation to generation. We compared the age-at-onset in patients between different genotypes and alleles for the three SNPs (Table 1). No significant results showed for rs11657292 and rs9892971. However, we found significant differences in the mean age-at-onset for the rs1822381 genotypes ($F = 8.144$, $P = 0.0003$). Significant increases showed in the mean age-at-onset with the CC genotype compared to the CA genotype and the CC genotype compared to the AA genotype (CC-CA: $P = 0.0035$; CC-AA: $P = 0.0037$). However, there was no difference in the mean age-at-onset with the CA genotype compared to the AA genotype ($P = 0.964$), indicating no dose-dependent response of age-at-onset for rs1822381 alleles. The presence of the A allele showed a younger age-at-onset in schizophrenia patients ($P = 0.0005$). The mean age-at-onset in patients with one copy of the A allele was 22.67 years, while for patients without A allele it was 25.19 years. The association between the genotypes of the three SNPs and age-at-onset was also analyzed by survival analysis. The Kaplan-Meier plot and proportional hazards regression also indicated that rs1822381 but not rs11657292 and rs9892971 affected age-at-onset of schizophrenia (rs1822381, $P_{\text{log-rank}} = 0.001$; rs11657292, $P_{\text{log-rank}} = 0.850$; rs9892971, $P_{\text{log-rank}} = 0.483$, Fig. S1), suggesting that individuals carrying the rs1822381 risk allele A showed an accelerated rate of schizophrenia onset. In our sample, one copy of rs1822381

**Table 1** Mean age-at-onset and statistical analysis for genotype and allele frequency of three *MSI2* SNPs in schizophrenia.

| SNP | Sample MAF | HWE | Genotype | Age-at-onset (years) Mean ± SD | *F*/*t** | *P* value | *P*-value# | | | Allele frequencies | | Age-at-onset (years) Mean ± SD | *t* | *P*-value# |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | CC-CA | CC-AA | CA-AA | C | | | | |
| rs1822381 | 0.504 | 0.570 | CC | 25.19 ± 8.04 | | | | | | | Present | 23.55 ± 6.96 | 1.654 | 0.0986 |
| | | | | | | | | | | | Absent | 22.49 ± 6.18 | | |
| | | | CA | 22.75 ± 6.22 | 8.144 | **0.0003** | **0.0035** | **0.0037** | 0.964 | A | Present | 22.67 ± 6.20 | 3.534 | **0.0005** |
| | | | AA | 22.49 ± 6.18 | | | | | | | Absent | 25.19 ± 8.04 | | |
| rs11657292 | 0.241 | 0.315 | CC | 23.21 ± 6.77 | | | | | | C | Present | 23.26 ± 6.70 | 0.538 | 0.591 |
| | | | | | | | CC-CT | CC-TT | CT-TT | | Absent | 23.94 ± 8.29 | | |
| | | | CT | 23.34 ± 6.62 | 0.173 | 0.841 | 0.813 | 0.568 | 0.649 | T | Present | 23.41 ± 6.82 | 0.372 | 0.710 |
| | | | TT | 23.94 ± 8.29 | | | | | | | Absent | 23.21 ± 6.77 | | |
| | | | | | | | AA-AC | AA-CC | AC-CC | A | Present | 23.30 ± 6.75 | 1.716 | 0.087 |
| rs9892971 | 0.091 | 0.680 | AA | 23.37 ± 6.74 | | | | | | | Absent | 17.50 ± 4.44 | | |
| | | | AC | 22.97 ± 6.81 | 0.548 | 0.584 | – | – | – | C | Present | 22.77 ± 6.80 | 0.841 | 0.400 |
| | | | CC | 17.50 ± 4.44 | | | | | | | Absent | 23.37 ± 6.74 | | |

*ANOVA test or t-test

# Significant *P*-values (0.05) are in boldface

risk allele A accelerated the rate of onset to even before the age of 20. For rs9892971, the mean age-at-onset with the CC genotype was 17.50 years, about 5.5 years younger than the AA and AC genotypes. However, as the minor allele frequency for rs9892971 was low in our sample with only 4 cases of the CC genotype, the statistical analysis showed no significant results.

Schizophrenia occurs commonly in the late teens or early adulthood. As an important implication for its pathogenesis, the age-at-onset of schizophrenia is significantly determined by genetic variants, and associated with a worse outcome of symptom severity, suicide, cognitive impact, and prognosis [10]. Despite the severity and heavy social burden of schizophrenia, the interaction between genetic factors and age-at-onset of schizophrenia is still undefined. It has been considered that age-at-onset in schizophrenia may regulate disease penetrance, and better understanding of the genetic mechanisms in schizophrenia onset can improve early intervention, delay the onset of schizophrenia, and achieve a better prognosis.

It seems that age-at-onset in schizophrenia is strongly determined by genetic variants regulating prenatal neurodevelopment. We previously reported that the human *MSI2* gene may be a susceptibility gene for schizophrenia in a two-stage case-control association study [7]. MSI2 is a member of the RNA-binding protein Musashi family which is importantly involved in stem-cell maintenance, asymmetric division, and differentiation during prenatal neurodevelopment. MSI2 may play a role in neural precursors at the translational level. In mammals, MSI2 has a constant expression pattern in neural stem cells, and may have a unique role in regulating specific neuronal lineages. It has been shown that knockdown of *MSI2* interrupts the differentiation of embryonic stem cells and also decreases their self-renewal capacity. The human *MSI2* gene is located in 17q22 and close to D17S787, a genetic marker, with the highest LOD score in a genome-wide linkage study of age-at-onset in schizophrenia in a sample from the United Kingdom [9]. Even though rs1822381 achieved no significant genome-wide association with schizophrenia in our previous GWAS and showed no significance in the replication association study, the fact that both susceptibility genes for schizophrenia and loci acting independently for schizophrenia risk can contribute to age-at-onset may explain this result. The association result for rs9892971 showed no significance in our present sample, however, the mean age-at-onset decreased greatly for individuals carrying the CC allele, indicating that enlarging the sample may improve the result. Rs9892971 was associated with schizophrenia in our replication association study, and some of its linkage SNPs and itself have been reported with a significant *cis*-eQTL effect for *MSI2* genes.

Conclusively, our current results provide evidence that *MSI2* variants may contribute to the age-at-onset in schizophrenia. Additional studies are still required for further understanding of the involvement of *MSI2* in the pathology of schizophrenia.

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