Neurosci. Bull. June, 2016, 32(3):239–245
DOI 10.1007/s12264-016-0026-9

www.neurosci.cn
www.springer.com/12264

REPORT

The Human *MSI2* Gene is Associated with Schizophrenia in the Chinese Han Population

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Received: 29 November 2015 / Accepted: 25 January 2016 / Published online: 8 April 2016

Abstract It has been suggested that altered neurogenesis may be involved in the etiology of schizophrenia, so genes impacting on neurogenesis could be potential candidates for schizophrenia. A member of the *Musashi* family, the human *MSI2* gene plays a substantial role in stem-cell maintenance, asymmetric division, and differentiation during neurogenesis. Our previous genome-wide association study (GWAS) implied an association of *MSI2* with schizophrenia in a Han Chinese population. To further explore this association, three single-nucleotide polymorphisms (SNPs), rs9892791, rs11657292, and rs1822381, were selected for a replication study involving 921 schizophrenia cases and 1244 controls. After rigorous Bonferroni correction, two of the SNPs (rs9892791 and rs11657292) displayed significant differences in allele and genotype distribution frequencies between the case and control groups. When our GWAS and replication samples were combined, the three *MSI2* SNPs were all strongly associated with schizophrenia (rs9892791: allelic $P = 1.07\text{E}{-5}$; rs11657292: allelic $P = 1.95\text{E}{-12}$; rs1822381: allelic $P = 1.44\text{E}{-4}$). These results indicate that the human *MSI2* gene might be a susceptibility gene for schizophrenia and encourage future research on the functional relationship between this gene and schizophrenia.

Keywords Schizophrenia · Neurogenesis · Single-nucleotide polymorphism · Musashi · *MSI2*

Introduction

Abnormal neuronal development has been implicated in the etiopathogenesis of schizophrenia. The developmental disturbance, caused by genetic and environmental factors, leads to defective neuronal connectivity and biochemical functioning. Stress and maladaptation may trigger the pathological circuits later in life, resulting in the emergence of clinical symptoms [1, 2]. Neuronal development encompasses multiple processes including neurogenesis, the generation of new neurons, which is an intricate process responsible for populating the developing brain with functional neurons from neural stem cells. Aberrant neurogenesis is involved in the hippocampal volume reduction and cognitive impairment reported in schizophrenic patients [3, 4]. As a heterogeneous disorder, the risk for schizophrenia probably results from the mutual effects of many loci with small contributions [5]. Numerous identified schizophrenia susceptibility genes are indispensable in the regulation of neurogenesis [6–8]. A number of genes specifically or highly expressed in the central nervous system (CNS) have been reported to be associated with neurogenesis, and variants of these genes may participate in the onset of schizophrenia.

During the last decade, genome-wide association studies (GWAS) have become a powerful and efficient approach for investigating genetic variants associated with schizophrenia [9, 10]. In our earlier GWAS in a Han Chinese population [11],

Electronic supplementary material The online version of this article (doi:10.1007/s12264-016-0026-9) contains supplementary material, which is available to authorized users.

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several novel schizophrenia candidate genes were found, and among them, the *Musashi2* (*MSI2*) gene caught our attention. *MSI2* is a member of the *Musashi* gene family encoding an evolutionarily-conserved group of neural RNA-binding proteins [12]. Musashi was originally isolated in *Drosophila* as a molecule required for the asymmetric division of sensory organ precursor cells [13]. Since then, Musashi family genes have been identified and cloned in various species. In mammals, two family members, *MSI1* and *MSI2*, have been identified [14, 15]. The expression of human *Musashi* is developmentally regulated in neural precursor cells, including CNS stem cells in the subventricular zone and dentate gyrus of the hippocampus where neurogenesis occurs [16]. Some neurodevelopmental factors have been identified as the targets of Musashi proteins [17]. The human *MSI2* gene has been mapped to chromosome 17q, a potential susceptibility region for schizophrenia [18]. To verify the association between the human *MSI2* gene and schizophrenia in the Han Chinese population, a replication association study involving three SNPs of *MSI2* was performed in an independent sample of 921 schizophrenia cases and 1244 healthy controls.

Methods and Materials

Participants

In the present replication association study, 921 schizophrenia patients (449 males and 472 females; mean age, 29.3 ± 9.8 years) and 1244 healthy controls (597 males and 647 females; mean age, 29.6 ± 8.7 years) were included. All participants were Han Chinese from the same region of northern China and unrelated to the previous GWAS samples. The patients were all recruited from the Institute of Mental Health, Peking University, Beijing, China. Consensus diagnoses were made by at least two experienced psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. None of the patients had severe medical complications. Healthy controls were selected by a simple non-structured interview, excluding individuals with a history of mental health problems or neurological diseases. The healthy controls were matched with the patients for age, gender, and ethnicity. Approval for the current study was obtained from the Ethics Committee of the Institute of Mental Health, Peking University. After informing the participants or guardians of the objectives and procedures of the current study, written informed consent was obtained.

SNP Selection

The *MSI2* gene spans >400 kb in the human genome (Fig. 1A), and our previous GWAS included 229 SNPs in and around the human *MSI2* gene region (Fig. 1B). Information on these SNPs was downloaded from the International HapMap project database (http://hapmap.ncbi.nlm.nih.gov/). Linkage disequilibrium (LD) blocks were determined using Haploview version 4.1. Three SNPs (rs9892791, rs11657292, and rs1822381) with significant association with schizophrenia in our previous GWAS were selected for replication analysis. All three SNPs were in *MSI2* introns.

Sample Preparation and Genotyping

Peripheral blood samples were collected from all participants, and genomic DNA was extracted using a commercially-available QIAamp DNA Mini kit (Qiagen, Hilden, Germany). Three pairs of PCR primers (rs9892791: 5′-GC TGACTGCTGAGGAT-3′ and 5′-ATTTGATTTGGGAC AC-3′; rs11657292: 5′-AGATGTTTGCTCCTGA-3′ and 5′-AATAGAACCAACTCCC -3′; and rs1822381: 5′-GCA TTTCCTCCTCAA-3′ and 5′-CACCATCCTCCGT TA -3′) were designed to amplify the three DNA fragments containing the three selected MSI2 SNPs using Oligo6.0 software (MBI Inc., Norwalk, USA). The PCR amplification was performed as previously described [6]. Briefly, PCR was performed in a 25-mL volume containing 10 mmol/L Tris-HCL (pH 8.3), 50 mmol/L KCl, 1.5 mmol/L $MgCl_2$, 200 mmol/L of each dNTP, 0.25 mmol/L of each primer, 1 U of Taq DNA polymerase, and 40 ng genomic DNA. The conditions used for PCR amplification were initial denaturation at 94 °C for 5 min, followed by 36 cycles at 94 °C for 30 s, 58–62 °C for 30 s, and 72 °C for 40 s, and a final elongation at 72 °C for 7 min. PCR products were purified using a BigDye Terminator Cycle Sequencing Ready Reaction kit, and then either completely digested with 4 U of restriction enzyme overnight followed by agarose gel electrophoresis (2–3% gel) stained with ethidium bromide, or sequenced on an ABI PRISM 377-96 DNA Sequencer (Applied Biosystems, New York, USA).

Statistics

Deviation of the genotypes from Hardy–Weinberg equilibrium was tested using a χ^2 goodness-of-fit test. The distribution of gender and the difference of age between cases and controls were evaluated using Pearson's χ^2-test and Student's *t*-test with SPSS 16.0 (SPSS Inc., Chicago, IL). Statistical differences in allelic distribution between patients and controls were evaluated by Pearson's χ^2-test. Pairwise LD between any two alleles was evaluated using the D′ value. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were calculated to evaluate the effect of different alleles. These analyses were performed using

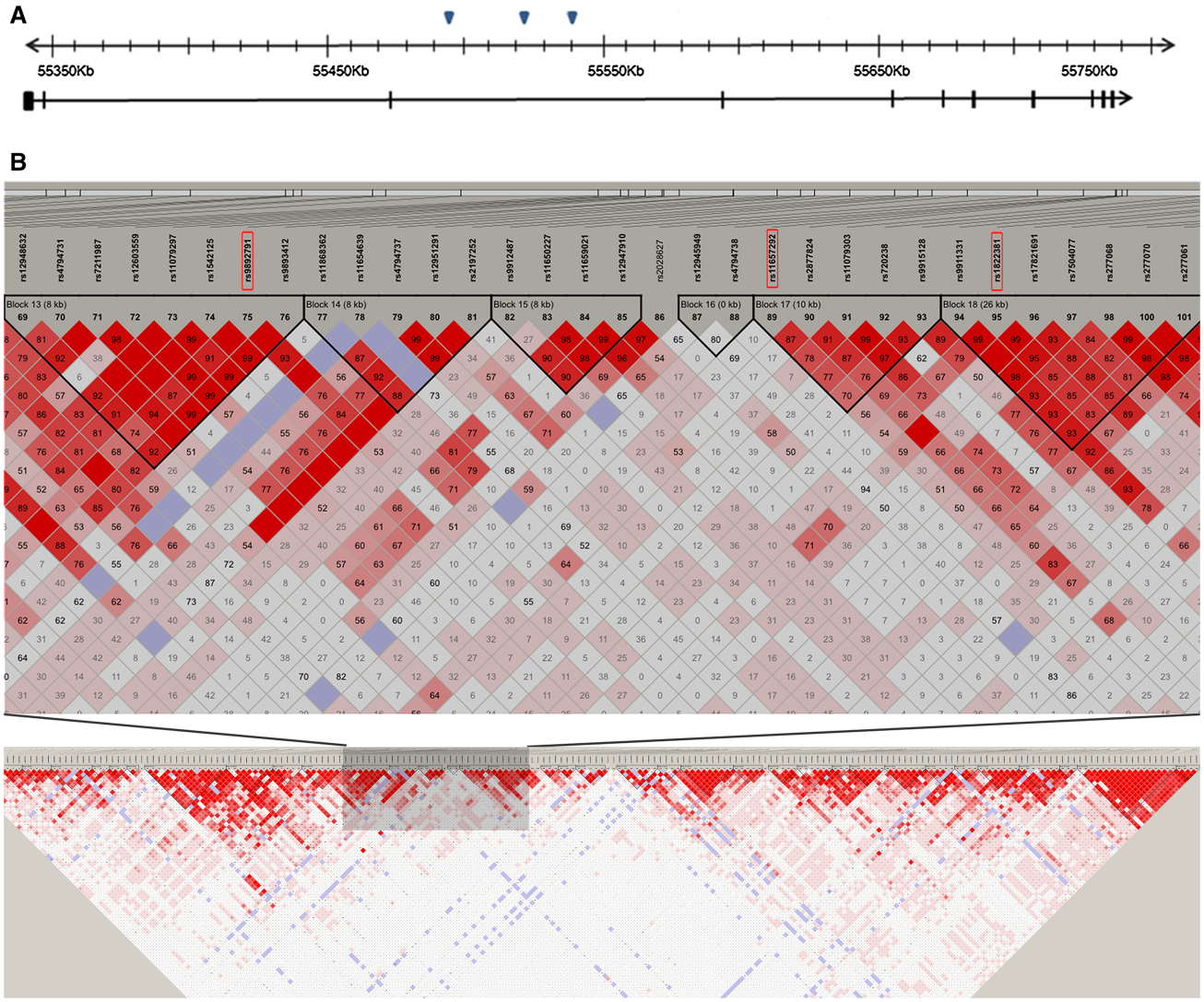

Fig. 1 Genomic structure and linkage disequilibrium (LD) of MSI2. **A** Genomic structure of the human MSI2 gene. The gene spans 423 kb, and the largest isoform is composed of 11 exons. The positions of the three SNPs selected for the replication study are indicated by *arrowheads*. **B** LD of the MSI2 gene in a previous GWAS. Pairwise LDs were computed for all possible combinations of the 229 SNPs using D′ values. The *number* in each *cell* represents the D′ value after the decimal point between SNPs. The three SNPs are in three different LD blocks shown in the *grey panel* and magnified in the *upper panel*.

Haploview version 4.1 (http://www.broad.mit.edu/mpg/haploview/) [19] and SHEsis [20] software (http://analysis.bio-x.cn/SHEsisMain.htm). The statistical power of our first sample size was calculated using the genetic power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/cc2.html) [21]. The joint analytical power of the combined sample was calculated using the Power Calculator for Two Stage Association Studies (http://www.sph.umich.edu/csg/abecasis/CaTS/) [22]. The Bonferroni correction was applied for multiple tests analyzing independent variables in order to control inflation of the type I error rate according to an effective number of independent marker loci. Results were considered significant at two-tailed $P < 0.05$.

Results and Discussion

GWAS Analysis

Two-hundred-twenty-nine *MSI2* SNPs were included in our previous GWAS. Pairwise LD was computed between each pair of SNPs in the control sample using the criterion $D' > 0.8$ (Fig. 1B). According to the GWAS results, only one SNP (rs11657292) reached genome-wide significance ($P = 2.31E{-}6$, $\chi^2 = 22.368$, OR 0.69, 95% CI 0.59–0.81), but we also considered four SNPs (rs9892791, rs11654639, rs1822381, and rs7504077) with $P < 0.05$ (Table 1).

Table 1 *MSI2* association results of GWAS[a].

SNP	Position[b]	Allele[c]	MAF			HWE (p)	χ^2	P	OR (95% CI)
			HCB[d]	Case	Control				
rs9892791	55495095	C/A	0.044	0.091	0.066	0.445	8.673	3.24E−3	0.71 (0.56–0.89)
rs11654639	55499909	A/G	0.000	0.003	0.000	1.000	8.786	3.00E−3	–
rs11657292	55522855	T/C	0.239	0.239	0.178	0.752	22.368	2.31E−6	0.69 (0.59–0.81)
rs1822381	55540246	A/C	0.422	0.482	0.420	0.715	15.011	1.08E−4	1.28 (1.13–1.45)
rs7504077	55543961	T/C	0.389	0.439	0.382	0.589	11.834	5.86E−4	0.79 (0.69–0.90)

HCB Han Chinese in Beijing, *MAF* minor allele frequency, *CI* confidence interval.

[a] 746 patients with schizophrenia and 1599 healthy controls included in the previous GWAS [11].

[b] Based on HapMap database release #27.

[c] Minor allele/major allele.

[d] MAF of HCB in the International HapMap project.

Replication Study

From these five SNPs, three (rs9892791, rs11657292, and rs1822381) from different LD blocks (Table 2) were selected based on the initial GWAS results and the HapMap information on the Han Chinese in Beijing population, and genotyped in 921 patients with schizophrenia and 1244 healthy controls for the replication association study. The independent case-control sample-set had ~80% power to detect allele frequency differences assuming an OR of 1.5 with a minor allele frequency of 0.1. None of the genotype distributions of the three SNPs in cases and controls deviated from Hardy-Weinberg equilibrium (Table S1). The genotype and allele distribution frequencies of all SNPs in the case and control groups are shown in Table 3. The significant differences in both genotype and allele distribution frequencies remained for rs9892791 (allelic $P = 0.00108$, $\chi^2 = 10.690$, OR 0.69, 95% CI 0.55–0.86; genotypic $P = 0.00436$, $\chi^2 = 10.879$) and rs11657292 (allelic $P = 6.84\text{E}{-5}$, $\chi^2 = 15.881$, OR 0.74, 95% CI 0.64–0.86; genotypic $P = 4.02\text{E}{-4}$, $\chi^2 = 15.664$). After rigorous Bonferroni correction, significance remained for both SNPs.

Combined Sample Analysis

We combined the data from the current replication study and the previous GWAS (Table 4). The joint analytical power of the combined sample reached 80%. After combination, the three SNPs all had a strong association with schizophrenia (rs9892791: $P = 1.07\text{E}{-5}$, $\chi^2 = 19.419$, OR 0.70, 95% CI 0.59–0.82; rs11657292: $P = 1.95\text{E}{-12}$, $\chi^2 = 49.786$, OR 0.68, 95% CI 0.61–0.76; rs1822381: $P = 1.44\text{E}{-4}$, $\chi^2 = 14.471$, OR 0.85, 95% CI 0.76–0.92).

Table 2 Pairwise linkage disequilibrium among the three tagged SNPs based on previous GWAS data.

r^2	D′		
	rs9892791	rs11657292	rs1822381
rs9892791		0.110	0.167
rs11657292	0.004		0.327
rs1822381	0.036	0.036	

For most biomedical diseases including schizophrenia, the results of association studies are inconsistent and unrepeatable. In this study, a replication association analysis was performed for the human *MSI2* gene, a novel candidate gene identified from our previous GWAS [11], in an independent sample of 921 cases and 1244 controls from the Han Chinese population. We chose three SNPs (rs9892791, rs11657292, and rs1822381) from different LD blocks and found a significant association between two SNPs and schizophrenia. Rs11657292, which the only SNP reaching genome-wide significance in our GWAS, showed the most significant association with schizophrenia. To obtain stronger statistical evidence, a combined analysis of the replication study and GWAS data was performed and indicated that the human *MSI2* gene is involved in the development of schizophrenia. We also downloaded genotyping data from the 1000 Genome Project [23]. Individuals from five East Asian populations (Han Chinese in Beijing, Japanese in Tokyo, Southern Han Chinese, Chinese Dai in Xishuangbanna, and Kinh in Ho Chi Minh City) were used to identify linkage SNPs for the three schizophrenia-associated SNPs (rs9892791, rs11657292, and rs1822381). A total of 12 SNPs were identified as linkage SNPs ($r^2 > 0.8$) (Table 5). Several of these SNPs have a significant cis-eQTL effect for the *MSI2* gene [24] (Table 6), indicating that different variants of the three schizophrenia-associated SNPs may affect the expression level of *MSI2*.

The human *MSI2* gene is located on chromosome 17q in a potential susceptibility region for schizophrenia [18]. A genome-wide linkage study of age-at-onset in

Table 3 Genotype and allele frequencies of three *MSI2* tagged SNPs in 921 patients with schizophrenia and 1244 healthy controls.

SNP	Participants	Genotype and frequency[a]			χ^2 P (Bonferroni corrected)	Allele and frequency[a]		χ^2 P^b (Bonferroni corrected)	OR (95% CI)
		AA	AC	CC		A	C		
rs9892791	Patients	758(0.823)	156(0.169)	7(0.008)	$\chi^2 = 10.879$	1672(0.908)	170(0.092)	$\chi^2 = 10.690$	0.69(0.55–0.86)
	Controls	1087(0.874)	151(0.121)	6(0.005)	P = **0.00436** (**0.0131**)	2325(0.934)	163(0.066)	P = **0.00108** (**0.00324**)	
		CC	CT	TT		C	T		
rs11657292	Patients	542(0.588)	327(0.355)	52(0.056)	$\chi^2 = 15.664$	1411(0.766)	431(0.234)	$\chi^2 = 15.881$	0.74(0.64–0.86)
	Controls	831(0.668)	367(0.295)	46(0.037)	P = **4.02E−4** (**0.00121**)	2029(0.816)	459(0.184)	P = **6.84E−5** (**2.05E−4**)	
		AA	AC	CC		A	C		
rs1822381	Patients	217(0.236)	446(0.484)	258(0.280)	$\chi^2 = 1.904$	880(0.478)	962(0.522)	$\chi^2 = 1.089$	1.09(0.96–1.23)
	Controls	272(0.219)	592(0.476)	380(0.305)	P = 0.386 (1.000)	1136(0.457)	1352(0.543)	P = 0.168 (0.504)	

CI confidence interval.

[a] Frequencies are shown in parenthesis.

[b] Significant P values (<0.05) are in boldface.

schizophrenia indicated a peak LOD score on marker D17S787, which is close to the *MSI2* locus [25]. As a conserved RNA-binding protein, MSI2 is strongly expressed in neural precursor cells residing in the subventricular zone [15] that are subjected to the refined process of cell-fate specification during neurogenesis, which requires the post-transcriptional spatiotemporal regulation of the proteome by RNA-binding proteins. RNA-binding proteins can package specific mRNAs within ribonucleoprotein granules and target specific fragments of mRNAs to adjust the expression of functionally-related genes [26]. Despite the unclear targets of MSI2, it has been hypothesized that MSI2 may bind uridine-rich RNA sequences similar to MSI1 *in vivo* [15]. Msi2-silencing experiments in mouse $Msi1^{-/-}$ neural stem cells revealed functional redundancy and cooperation of Msi1 and Msi2 in the regulation of proliferation and maintenance of a neural stem cell population [27]. However, the human *MSI1* gene displayed no significant association with schizophrenia (Table S2 and Fig. S1). The reason for this association difference is unknown, and further functional exploration of these two genes may provide an explanation.

The expression of the *MSI2* gene is rapidly down-regulated in newly-generated postmitotic neurons, with the exception of GABAergic parvalbumin (PV)-containing interneurons in the neocortex and hippocampus [27]. Alterations in cortical GABAergic interneurons are thought to be pivotal in the pathology of schizophrenia as concluded from a series of postmortem studies [28, 29]. GABAergic interneurons are core components of the corticolimbic circuitry. They provide both inhibitory and disinhibitory modulation of cortical and hippocampal circuits and contribute to the generation of oscillatory rhythms, to discriminative information processing, and to the gating of sensory information within the corticolimbic system. All of these functions are abnormal in schizophrenia [30]. PV-containing GABAergic interneurons comprise a GABAergic interneuron subclass that is essential for the synchronization of neuronal activity [31], and the activity of PV-containing GABAergic interneurons has been linked to the production of cortical network oscillations [32]. Activation of PV-containing GABAergic interneurons *via* the N-methyl D-aspartate receptor (NMDAR) has been suggested to be a crucial element in the NMDAR hypofunction hypothesis of schizophrenia [33]. The wiring of PV-containing GABAergic interneurons is strongly modulated by the neuregulin signaling pathway which numerous genetic linkage and association studies indicate is involved in a high risk of schizophrenia [34]. So, apart from its role in neural stem cells and neuronal development, MSI2 may be involved in the maintenance of proper functioning of PV-containing GABAergic interneurons by controlling the local translation or stability of mRNAs that encode essential neurotransmitters, receptors, and channels. MSI2 is also expressed in the stem-cell compartments of other tissues and in aggressive tumors as well as playing a broad role in stemness and the

Table 4 Combined study of GWAS[a] and replication samples.

SNP	Allele[b]	MAF		χ^2	*P* (Bonferroni corrected)	OR (95% CI)
		Case	Control			
rs9892791	C/A	0.092	0.066	19.419	1.07E−5 (3.21E−4)	0.70 (0.59–0.82)
rs11657292	T/C	0.236	0.174	49.786	1.95E−12 (5.85E−12)	0.68 (0.61–0.76)
rs1822381	A/C	0.480	0.438	14.471	1.44E−4 (4.32E−4)	0.85 (0.76–0.92)

MAF minor allele frequency, *CI* confidence interval.

[a] 746 patients with schizophrenia and 1599 healthy controls included in the previous GWAS [11].

[b] Minor allele/major allele.

Table 5 Identified linkage SNPs of the three schizophrenia-associated SNPs.

SNP	Chromosome	Position	Linked SNP	Chromosome	Position	r^2
rs9892791	17	55495095	rs75402227	17	55488648	1
rs9892791	17	55495095	rs7218689	17	55490732	1
rs9892791	17	55495095	rs11650999	17	55491751	0.855
rs9892791	17	55495095	rs8071635	17	55493152	1
rs9892791	17	55495095	rs17761485	17	55494160	1
rs9892791	17	55495095	rs9892791	17	55495095	1
rs9892791	17	55495095	rs17834199	17	55495759	1
rs9892791	17	55495095	rs7213277	17	55498077	0.951
rs11657292	17	55522855	rs11657292	17	55522855	1
rs1822381	17	55540246	rs1822381	17	55540246	1
rs1822381	17	55540246	rs4794740	17	55543391	0.95
rs1822381	17	55540246	rs7504077	17	55543961	0.859

Table 6 Identified SNPs with significant cis-eQTL effect for the *MSI2* gene.

rs ID	cis-eQTL	Affected gene	Tissue
rs7218689	1.60E−08	MSI2	Whole blood
rs8071635	8.68E−09	MSI2	Whole blood
rs17761485	2.15E−09	MSI2	Whole blood
rs9892791	3.35E−09	MSI2	Whole blood
rs17834199	8.76E−09	MSI2	Whole blood
rs7213277	9.91E−10	MSI2	Whole blood

determination of cell fate [35–39]. The detailed action of MSI2 on physiological and pathological processes requires further research.

In conclusion, although it is unclear if and how the SNPs influence transcription of the *MSI2* gene, our association study suggests that the *MSI2* gene may be considered to be a risk gene for schizophrenia. Additional studies are required to elucidate the involvement of these SNPs in the regulation of *MSI2* gene transcription before we can confirm the potential role of *MSI2* in the pathogenesis of schizophrenia; moreover, multiple prospective studies in other ethnic populations are needed to confirm the results of our analysis.

References

1. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry 2005, 10: 434–449.
2. Cannon TD, van Erp TG, Bearden CE, Loewy R, Thompson P, Toga AW, *et al.* Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions. Schizophr Bull 2003, 29: 653–669.
3. Reif A, Schmitt A, Fritzen S, Lesch KP. Neurogenesis and schizophrenia: dividing neurons in a divided mind? Eur Arch Psychiatry Clin Neurosci 2007, 257: 290–299.
4. Eisch AJ, Cameron HA, Encinas JM, Meltzer LA, Ming GL, Overstreet-Wadiche LS. Adult neurogenesis, mental health, and mental illness: hope or hype? J Neurosci 2008, 28: 11785–11791.
5. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, *et al.* Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 2009, 460: 748–752.
6. Qu M, Tang F, Yue W, Ruan Y, Lu T, Liu Z, *et al.* Positive association of the Disrupted-in-Schizophrenia-1 gene (DISC1) with schizophrenia in the Chinese Han population. Am J Med Genet B Neuropsychiatr Genet 2007, 144B: 266–270.

7. Pisante A, Bronstein M, Yakir B, Darvasi A. A variant in the reelin gene increases the risk of schizophrenia and schizoaffective disorder but not bipolar disorder. Psychiatr Genet 2009, 19: 212.
8. Yang JZ, Si TM, Ruan Y, Ling YS, Han YH, Wang XL, *et al.* Association study of neuregulin 1 gene with schizophrenia. Mol Psychiatry 2003, 8: 706–709.
9. Seng KC, Seng CK. The success of the genome-wide association approach: a brief story of a long struggle. Eur J Hum Genet 2008, 16: 554–564.
10. Mowry BJ, Gratten J. The emerging spectrum of allelic variation in schizophrenia: current evidence and strategies for the identification and functional characterization of common and rare variants. Mol Psychiatry 2013, 18: 38–52.
11. Yue WH, Wang HF, Sun LD, Tang FL, Liu ZH, Zhang HX, *et al.* Genome-wide association study identifies a susceptibility locus for schizophrenia in Han Chinese at 11p11.2. Nat Genet 2011, 43: 1228–1231.
12. Okano H, Imai T, Okabe M. Musashi: a translational regulator of cell fate. J Cell Sci 2002, 115: 1355–1359.
13. Nakamura M, Okano H, Blendy JA, Montell C. Musashi, a neural RNA-binding protein required for Drosophila adult external sensory organ development. Neuron 1994, 13: 67–81.
14. Sakakibara S, Imai T, Hamaguchi K, Okabe M, Aruga J, Nakajima K, *et al.* Mouse-Musashi-1, a neural RNA-binding protein highly enriched in the mammalian CNS stem cell. Dev Biol 1996, 176: 230–242.
15. Sakakibara S, Nakamura Y, Satoh H, Okano H. Rna-binding protein Musashi2: developmentally regulated expression in neural precursor cells and subpopulations of neurons in mammalian CNS. J Neurosci 2001, 21: 8091–8107.
16. Song HJ, Stevens CF, Gage FH. Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons. Nat Neurosci 2002, 5: 438–445.
17. Imai T, Tokunaga A, Yoshida T, Hashimoto M, Mikoshiba K, Weinmaster G, *et al.* The neural RNA-binding protein Musashi1 translationally regulates mammalian numb gene expression by interacting with its mRNA. Mol Cell Biol 2001, 21: 3888–3900.
18. Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, *et al.* Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. Am J Hum Genet 2003, 73: 34–48.
19. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005, 21: 263–265.
20. Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005, 15: 97–98.
21. Purcell S, Cherny SS, Sham PC. Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. Bioinformatics 2003, 19: 149–150.
22. Skol AD, Scott LJ, Abecasis GR, Boehnke M. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. Nat Genet 2006, 38: 209–213.
23. Genomes Project C, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, *et al.* An integrated map of genetic variation from 1,092 human genomes. Nature 2012, 491: 56–65.
24. Westra HJ, Peters MJ, Esko T, Yaghootkar H, Schurmann C, Kettunen J, *et al.* Systematic identification of trans eQTLs as putative drivers of known disease associations. Nat Genet 2013, 45: 1238–1243.
25. Cardno AG, Holmans PA, Rees MI, Jones LA, McCarthy GM, Hamshere ML, *et al.* A genomewide linkage study of age at onset in schizophrenia. Am J Med Genet 2001, 105: 439–445.
26. Loya CM, Van Vactor D, Fulga TA. Understanding neuronal connectivity through the post-transcriptional toolkit. Genes Dev 2010, 24: 625–635.
27. Sakakibara S, Nakamura Y, Yoshida T, Shibata S, Koike M, Takano H, *et al.* RNA-binding protein Musashi family: roles for CNS stem cells and a subpopulation of ependymal cells revealed by targeted disruption and antisense ablation. Proc Natl Acad Sci U S A 2002, 99: 15194–15199.
28. Berretta S, Munno DW, Benes FM. Amygdalar activation alters the hippocampal GABA system: "partial" modelling for postmortem changes in schizophrenia. J Comp Neurol 2001, 431: 129–138.
29. Reynolds GP, Abdul-Monim Z, Neill JC, Zhang ZJ. Calcium binding protein markers of GABA deficits in schizophrenia–postmortem studies and animal models. Neurotox Res 2004, 6: 57–61.
30. Benes FM, Berretta S. GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 2001, 25: 1–27.
31. Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci 2007, 8: 45–56.
32. Gonzalez-Burgos G, Hashimoto T, Lewis DA. Alterations of cortical GABA neurons and network oscillations in schizophrenia. Curr Psychiatry Rep 2010, 12: 335–344.
33. Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, *et al.* Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. Trends Neurosci 2008, 31: 234–242.
34. Fazzari P, Paternain AV, Valiente M, Pla R, Lujan R, Lloyd K, *et al.* Control of cortical GABA circuitry development by Nrg1 and ErbB4 signalling. Nature 2010, 464: 1376–1380.
35. Barbouti A, Johansson B, Hoglund M, Mauritzson N, Strombeck B, Nilsson PG, *et al.* Multicolor COBRA-FISH analysis of chronic myeloid leukemia reveals novel cryptic balanced translocations during disease progression. Genes Chromosomes Cancer 2002, 35: 127–137.
36. Barbouti A, Hoglund M, Johansson B, Lassen C, Nilsson PG, Hagemeijer A, *et al.* A novel gene, MSI2, encoding a putative RNA-binding protein is recurrently rearranged at disease progression of chronic myeloid leukemia and forms a fusion gene with HOXA9 as a result of the cryptic t(7;17)(p15;q23). Cancer Res 2003, 63: 1202–1206.
37. De Weer A, Speleman F, Cauwelier B, Van Roy N, Yigit N, Verhasselt B, *et al.* EVI1 overexpression in t(3;17) positive myeloid malignancies results from juxtaposition of EVI1 to the MSI2 locus at 17q22. Haematologica 2008, 93: 1903–1907.
38. Kharas MG, Lengner CJ, Al-Shahrour F, Bullinger L, Ball B, Zaidi S, *et al.* Musashi-2 regulates normal hematopoiesis and promotes aggressive myeloid leukemia. Nat Med 2010, 16: 903–908.
39. Ito T, Kwon HY, Zimdahl B, Congdon KL, Blum J, Lento WE, *et al.* Regulation of myeloid leukaemia by the cell-fate determinant Musashi. Nature 2010, 466: 765–768.