



No association of *SLC6A3* and *SLC6A4* gene polymorphisms with schizophrenia in the Han Chinese population



Beimeng Yang^{a,b}, Xiaoye Huang^{a,c}, Liemin Ruan^d, Tao Yu^{a,c}, Xin Li^{a,c}, Forrest Fabian Jesse^e, Yanfei Cao^{a,c}, Xingwang Li^{a,c}, Baocheng Liu^{a,c}, Fengping Yang^{a,c}, Yong-Seok Lee^f, Lin He^{a,b,c}, Weidong Li^{a,b,**}, Guang He^{a,*}

^a Bio-X Institutes, Key Laboratory for the Genetics of Development and Neuropsychiatric Disorders (Ministry of Education), Shanghai Jiao Tong University, 1954 Huashan Road, Shanghai 200030, China

^b Wuxi Mental Health Center, 156 Qian Rong Road, Wuxi 214151, China

^c Institute for Nutritional Sciences, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, 320 Yueyang Road, Shanghai 200031, China

^d Ningbo First Hospital, Liu Ting Street 59, Ningbo City, Zhejiang 315010, China

^e School of Computer and Information Technology, Beijing Jiao Tong University, Beijing 100044, China

^f Department of Life Science, Chung-Ang University, 221 Heuksuk-dong, Dongjak-gu, Seoul 156-756, Republic of Korea

H I G H L I G H T S

- No difference in allelic/genotypic frequency in the examined SNPs was found.
- No positive linkage disequilibrium (LD) was detected.
- No positive haplotype analysis were found within each gene.
- These 10 SNPs of the *SLC6A3* and *SLC6A4* do not play a major role in schizophrenia.

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The *SLC6A3* and *SLC6A4* genes are members of a class of neurotransmitter transporters for the release, re-uptake and recycling of neurotransmitters in synapses. *SLC6A3* and *SLC6A4* encode a dopamine transporter and serotonin transporter, respectively. Abnormal expression and genetic polymorphism of *SLC6A3* and *SLC6A4* genes may increase the risk of developing mental illness, such as schizophrenia, bipolar disorder, ADHD, and aggressive behavior in Alzheimer disease, etc. Nevertheless, association between *SLC6A3*, *SLC6A4* genes polymorphism and schizophrenia patients have not been well studied in Han Chinese people. In this study, we examined whether single nucleotide polymorphisms (SNPs) in *SLC6A3*, *SLC6A4* were associated with schizophrenia in Han Chinese people (893 schizophrenia patients and 611 healthy controls). No significant difference in allelic or genotypic frequency was found between schizophrenia patients and healthy controls. No positive linkage disequilibrium (LD) was detected either. No haplotypic distributions were positive. Accordingly, our study suggests that the 10 SNPs within both genes we examined do not play a major role in schizophrenia in the Han Chinese population.

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1. Introduction

Mental disorders (psychiatric disorders) are a widespread health problem, which are often associated with inadequate

treatment. Almost one third of people can be diagnosed one or more of the common types of mental disorders in different stages of their life [1]. Schizophrenia is one of the most mysterious and costliest mental disorders both in terms of individual suffering and societal burden [38]. Worldwide, schizophrenia affects 1% of the world's population and is characterized by delusions, emotional deterioration, withdrawal from reality, and other unusual behaviors [15,32]. Epidemiological genetic investigations have suggested that genetic factors contribute significantly to the etiology of schizophrenia and its estimated heritability ranges from 40% to 85% [7,27]. There are many genes which confer risk of schizophrenia,

* Corresponding author. Tel.: +86 021 62822491; fax: +86 021 62822491.

** Corresponding author at: Bio-X Institutes, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China. Tel.: +86 021 34205687; fax: +86 021 34205687.

E-mail addresses: liwd@sjtu.edu.cn (W. Li), heguang@sjtu.edu.cn (G. He).

including dopamine and serotonin transporter dysfunction caused by polymorphisms of genes leading to schizophrenia pathogenesis [23].

The solute carrier 6 (SLC6) family plays a significant role in neurotransmission, cellular, and whole body homeostasis. Abnormal and altered expression of these transporters may be associated with a variety of diseases including schizophrenia [5]. Each SLC6A transporters has a specific biological and physiological function, which is linked to various psychiatric disorders and physical diseases [4]. Previous reports have suggested the association of SLC6A3 and SLC6A4 with schizophrenia [12,23]. The SLC6A3 gene is located on human chromosome 5q15, which consists of 15 coding exons over 64 kb long [21]. The dopamine transporter (DAT) can act to reuptake the neurotransmitter dopamine out of the synapse back into cytosol of neuron [6]. There are two variable number tandem repeats (VNTR), one in the 3'-untranslated region (3'-UTR), another within intron 8 region of *SLC6A3* gene [11,33]. Polymorphisms of VNTR affect the expression of the transporter, which has been widely screened as risk factors for etiology of schizophrenia [14,20,31,42]. Results of association studies on the relationship between polymorphisms in dopamine receptors genes and schizophrenia risk have been inconclusive [10].

SLC6A4 is a serotonin transporter gene in chromosome 17q11.1-q12, which has 14 exons encoding a protein of 630 amino acids [30]. This transporter terminates the action of serotonin, and transports serotonin from the synaptic cleft back into the synaptic vesicles in a sodium-dependent manner [35]. Irregularity of serotonin transporter metabolism seems to be associated with many different diseases, including clinical depression, schizophrenia, obsessive-compulsive disorder [9], hypertension and generalized social phobia [37]. Although this gene had not usually been examined as a schizophrenia risk gene, recently a number of studies have investigated the association of *SLC6A4* polymorphisms with schizophrenia [3,8,39]. However, these studies have not concluded the consistent results.

Considering the discrepancies in the results of previous studies, we investigated 6 SNPs in *SLC6A3* and 4 SNPs in *SLC6A4* in 893 schizophrenia patients and 611 healthy controls, to explore whether *SLC6A3* and *SLC6A4* were associated with schizophrenia in the Han Chinese population. Linkage disequilibrium (LD) was calculated within each gene and haplotype analysis was conducted between the schizophrenia patients and controls.

2. Materials and methods

2.1. Subjects

In this case-control study, 1504 unrelated Chinese individuals were analyzed, consisting of 611 controls (278 women and 333 men; age: 42.0 ± 9.9 years) and 893 schizophrenic patients (389 women and 504 men; age: 50.4 ± 13.4 years). More patients' information can be found in our previous papers [24,34]. Clinical examinations were conducted by at least two research psychiatrists and were diagnosed via the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Furthermore, patients who had physical illness, history of traumatic brain injury, alcohol abuse, or substance abuse were excluded. Control volunteers had no psychiatric disorders, no individual and family history of psychiatric illness, traumatic brain injury, or substance abuse. A standard informed consent in the protocol, which was reviewed and approved by the Shanghai Ethical Committee of Human Genetic Resources, was given by the participating subjects after the nature of the study had been fully explained. Written informed consent was obtained from either participants or patient's legal representatives.

2.2. SNP selection and genotyping

We selected SNPs from the NCBI dbSNP database (<http://www.ncbi.nlm.nih.gov/SNP/>) to cover a [52] kb region of the *SLC6A3*, a [36] kb region within *SLC6A4* and all of the SNPs should have a MAF of above 5% according to the requirements of the statistical analysis. Some of the SNPs selected in our study were reported to be associated with schizophrenia in published papers including genome-wide association studies. Others were functional SNPs and those in regulatory regions. Details of selected SNPs are presented in Table 1.

Genomic DNA was collected from venous blood samples obtained from each participant using the standard phenol-chloroform method. Genotyping of all SNPs were successfully assayed using the TaqMan technology method on the ABI 7900 DNA detection system (Applied Biosystems, Foster City, CA, USA). All probes and primers were designed by Applied Biosystems. The standard PCR reaction was carried out in a total volume of 5 μ l, the cycling conditions following the protocols provided by the Taqman[®] Universal PCR Master Mix (Applied Biosystems) reagent.

2.3. Statistical analysis

The genotypes tested in the present study were obtained blind to the individuals' clinical status. Genepop 3.4 software [43] was selected to check for deviations from Hardy-Weinberg equilibrium for each polymorphism between the patient and the controls. Genotypic, allelic frequencies and pairwise linkage disequilibrium (LD) were analyzed by SHEsis (<http://202.120.31.177/myanalysis.php>) [41]. This online software integrates association analysis tools for case-control studies and implements a Monte Carlo simulation strategy. To substantiate the genotype frequencies, SPSS for windows (version 19.0; IBM, Armonk, NY, USA) was used. The differences of allelic and genotypic frequency between schizophrenia patients and healthy controls were compared using a χ^2 test. LD of all pairs of SNPs within each gene was confirmed by Haploview software (Haploview 4.1) using D' as the standardized measurement [2]. Odds ratios (ORs) and their 95% confidence intervals (CIs) were also calculated. Haplotype block was firstly conducted on HaploView and further analysis was substantiated on SHEsis. For all analyses, $p < 0.05$ indicates significant difference between groups.

3. Results

The calculated allelic and genotypic distributions did not show any significant deviations from Hardy-Weinberg equilibrium in the control population. The distribution of the genotypes and the allelic frequencies for the *SLC6A3*, and *SLC6A4* SNPs polymorphisms in schizophrenic patients and controls is summarized in Table 2. There were no significant differences in the frequencies of the genotypes or alleles for all ten SNPs between control subjects and patients with schizophrenia. No significant ($p = 0.071$) difference in the rs2020933 genotype frequency was detected between cases and controls. In other words, there were no significant associations for any of the other genetic polymorphisms.

For all pairs of SNPs within both genes, we calculated D' and r^2 in all the subjects as the metric of LD (data not shown). LD within the SNPs of each gene were not in linkage disequilibrium with $r < 0.1$, so there is no positive LD between SNPs. We then conducted haplotype analysis. In the *SLC6A3* gene, no 2-phase positive associations with schizophrenia were found (the smallest $p = 0.075$). No positive association with schizophrenia was found for either 3-phase, 4-phase, or 5-phase haplotypes in this gene. There is no positive association of haplotypic analysis in the *SLC6A4* gene.

Table 1
The ten SNPs in the *SLC6A3*, *SLC6A4* gene analyzed in this study.

Gene	SNP ID ^a	Chromosome ^b	Allele ^c	Function	HW test <i>p</i> -value
SLC6A3	rs12516948	1391369	A/G(0.668)	Downstream gene variant	1.0
	rs40184	1395077	C/T(0.595)	Intron	1.0
	rs2963253	1414773	A/G(0.035)	Intron	1.0
	rs6345	1422073	T/C(0.001)	Missense	1.0
	rs403636	1438354	A/C(0.247)	Intron	0.715
	rs6350	1443199	A/G(0.049)	Synonymous	0.644
SLC6A4	rs4325622	28526475	C/T(0.475)	Intron	0.577
	rs6354	28549898	G/T(0.213)	UTR-5	0.921
	rs2066713	28551665	A/G(0.261)	Intron	0.645
	rs2020933	28561755	A/T(0.129)	Intron	0.507

HW, Hardy–Weinberg; UTR, untranslated region.

^a As according to the dbSNP database.

^b The SNP locations are based on the NCBI Human Genome Build 37.3.

^c The allele under the slash is the minor allele.

Table 2
The distribution of alleles and genotypes for the 10 SNPs in *SLC6A3*, *SLC6A4*.

Gene	SNP ID	Genotype frequency			<i>p</i> value*	Allele frequency		χ^2	<i>p</i> value*	Odds ratio [95%CI]	H–W <i>p</i> value*	
SLC6A3	rs12516948	AA	AG	GG	0.667	A	G	0.806	0.369	0.922[0.771–1.101]	0.943	
		NZ	375(0.620)	203(0.336)		27(0.045)	953(0.788)					257(0.212)
		SZ	513(0.599)	300(0.350)		44(0.051)	1326(0.774)					388(0.226)
	rs40184	CC	CT	TT	0.752	C	T	0.270	0.603	1.047[0.882–1.242]	0.681	
		NZ	333(0.561)	226(0.380)		35(0.059)	892(0.751)					296(0.249)
		SZ	500(0.579)	312(0.361)		52(0.060)	1312(0.759)					416(0.241)
	rs2963253	AA	AG	GG	0.967	A	G	0.002	0.967	1.039[0.173–6.237]	0.967	
		NZ	0(0)	2(0.003)		595(0.997)	2(0.002)					1192(0.998)
		SZ	0(0)	3(0.003)		859(0.997)	3(0.002)					1721(0.998)
	rs6345	CC	CT	TT	0.410	C	T	0.678	0.410	1.862[0.415–8.355]	0.930	
		NZ	522(0.992)	4(0.008)		0(0)	1048(0.996)					4(0.004)
		SZ	729(0.996)	3(0.004)		0(0)	1461(0.998)					3(0.002)
	rs403636	AA	AC	CC	0.305	A	C	1.434	0.231	1.101[0.941–1.287]	0.256	
		NZ	62(0.102)	257(0.423)		289(0.475)	381(0.313)					835(0.687)
		SZ	91(0.104)	401(0.460)		380(0.436)	583(0.334)					1161(0.666)
	rs6350	AA	AG	GG	0.673	A	G	0.287	0.592	1.170[0.660–2.073]	0.694	
		NZ	0(0.000)	19(0.032)		582(0.968)	19(0.016)					1183(0.984)
		SZ	1(0.001)	30(0.035)		837(0.964)	32(0.018)					1704(0.982)
SLC6A4	rs4325622	CC	CT	TT	0.849	C	T	0.084	0.771	1.028[0.852–1.241]	0.434	
		NZ	24(0.040)	176(0.296)		395(0.664)	224(0.188)					966(0.812)
		SZ	33(0.038)	269(0.309)		568(0.653)	335(0.193)					1405(0.807)
	rs6354	GG	GT	TT	0.801	G	T	0.030	0.863	0.980[0.784–1.227]	0.746	
		NZ	10(0.017)	128(0.214)		461(0.770)	148(0.124)					1050(0.876)
		SZ	11(0.013)	190(0.218)		672(0.770)	212(0.121)					1534(0.879)
	rs2066713	AA	AG	GG	0.893	A	G	0.001	0.977	0.996[0.751–1.321]	0.906	
		NZ	3(0.005)	82(0.135)		521(0.860)	88(0.073)					1124(0.927)
		SZ	3(0.003)	121(0.138)		754(0.859)	127(0.072)					1629(0.928)
	rs2020933	AA	AT	TT	0.071	A	T	1.287	0.257	0.850[0.641–1.126]	0.305	
		NZ	2(0.003)	91(0.155)		493(0.841)	95(0.081)					1077(0.919)
		SZ	8(0.010)	101(0.120)		730(0.870)	117(0.070)					1561(0.930)

CI, confidence interval, NZ, control, SZ, schizophrenia.

* Pearson's *p* value.

4. Discussion

In this case–control study, we examined 1504 volunteers consisting of 893 schizophrenic patients and 611 controls. A total of 10 SNPs were evenly distributed across both genes. Six of the SNPs (rs12516948, rs40184, rs2963253, rs6345, rs403636 and rs6350) in *SLC6A3*, four (rs4325622, rs6354 and rs2066713) in *SLC6A4* were all in Hardy–Weinberg equilibrium. According to observed results, there was no positive association between both genes and schizophrenia.

SLC6A3 and *SLC6A4* are a subfamily of the *SLC6* family which plays a critical function in neurotransmission, cellular and whole body homeostasis [5,9]. The *SLC6A3* gene that translates dopamine transporter (DAT) can clear dopamine from synapses, which has a critical effect on the CNS [21]. Lack of protein expression from *SLA6A3* causes severe cognitive deficits, motor abnormalities, and hyperactivity in mice [16]. There are two variable number tandem

repeats (VNTR) in the human dopamine transporter gene, that may cause several neuropsychiatric diseases [8,17,22,33,40]. Polymorphisms of VNTR within *SLA6A3* have been widely screened as risk factors for etiology of schizophrenia, though the results were inconsistent [14,20,31,42]. The above studies suggest that *SLC6A3* may play a role in the etiology of these psychiatric diseases. This study intended to examine whether *SLC6A3* and *SLC6A4* are associated with schizophrenia by screened genetic polymorphisms in 1504 unrelated Chinese Han samples. There was no positive association between selected SNPs (rs12516948, rs40184, rs2963253, rs6345, rs403636 and rs6350) in *SLC6A3*, and selected SNPs (rs4325622, rs6354, rs2066713 and rs2020933) in *SLC6A4* and schizophrenia. In addition, no significant difference in the genotype or allele frequencies of the examined SNPs was found between patients with schizophrenia and control subjects. Haplotype analysis of *SLC6A3* (the smallest *p*=0.075) might be correlated with schizophrenia. Although our result does not support the association of *SLA6A3*

with schizophrenia, it does not exclude the possibility that this gene confers genetic susceptibility to schizophrenia in Chinese and in other populations.

Previous studies have suggested that the *SLC6A4* gene has long been involved in the pathogenesis of psychiatric disorders, including schizophrenia. Due to its critical role in terminating the action of serotonin and that it is implicated in the pathophysiology, *SLC6A4* is a candidate gene for schizophrenia [13]. Altered gene/protein expression of *SLC6A4* appears to be associated with many different disorders, schizophrenia [39], alcoholism [29], depression [28], obsessive-compulsive disorder [26] and autism [36]. Ikeda et al. reported no association of *SLC6A4* with schizophrenia in Japanese patients [19]. Vijayan et al. pointed to the *SLC6A4* gene as an indicator of potential susceptibility for schizophrenia in Indian samples [39]. Several association studies have found association between the *SLC6A4* polymorphisms and schizophrenia in the Han Chinese [18,25]. The above controversial findings could be explained by the following reasons: ethnicity, life style, environmental stress, individual differences and sample size may account for differences in genotype and allele frequencies of the *SLC6A4* gene. To show that the *SLC6A4* gene might confer schizophrenia risk in our Chinese participants, we explored 4 SNPs within *SLC6A4*. Though no positive association was detected, studies based on more SNPs of *SLC6A4* and combination with other genes within the *SLC6A* family would be worthwhile.

In this study, the first limitation is that our sample size was relatively small. Larger studies with participants of different races and meta-analyses are needed to further test the association. Another limitation is the SNP coverage in the present study. Genetic analyses with functional SNPs and more saturated SNP coverage of the gene region are necessary.

5. Conclusion

In conclusion, both transporters play roles in the human central nervous system. The results of this study found no association of *SLC6A3* and *SLC6A4* genetic polymorphisms with schizophrenia, indicating that these variants might not be used as susceptible genes for schizophrenia in the Chinese Han population. The data we obtained may provide a reference for future studies on the role of *SLC6A3* in the etiology of schizophrenia. To further elucidate whether *SLC6A3* and *SLC6A4* variants are related to schizophrenia, genetic analyses with more saturated SNPs coverage are necessary. Our data may provide a reference for further studies on the role of these two genes in schizophrenia in other populations.

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