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Research article

Association study of *5-HT1A, 5-HT2A* polymorphisms with schizophrenia and major depressive disorder in the Han Chinese population

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HIGHLIGHTS

- We investigated the association of *5-HT1A* and *5-HT2A* polymorphisms with both schizophrenia and major depressive disorder.
- The rs10042486 in *5-HT1A* demonstrated significant difference between schizophrenia patients and controls.
- The *5-HT1A* might be associated with schizophrenia in Chinese Han population.
- The rs1364043 and rs17289304 involved in our association study were explored for the first time.

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ABSTRACT

Schizophrenia (SZ) and major depressive disorder (MDD) are two common severe mental disorders that have arisen to public awareness in recent years. Serotonin (5-HT) receptors have been implicated in the pathophysiology of psychiatric disorders especially in MDD and SZ. The aim of this study is to explore whether the variants in the *5-HT1A* and *5-HT2A* gene are susceptible to SZ or MDD in the Chinese Han population. Five SNPs (Single Nucleotide Polymorphisms) (rs1364043, rs10042486, rs6313, rs6311, rs17289304) in these genes were genotyped from 752 SZ patients, 568 MDD patients, and 846 normal controls of Chinese Han origin. The results showed that the *5-HT1A* rs10042486 was significantly associated with SZ ($P_{allele} = 0.0369$, $P_{genotype} = 0.0098$). Moreover, the haplotype (C-T) composed of rs10042486 and rs1364043 showed significant difference between SZ cases and healthy controls ($P = 0.0302$) while another haplotype (T-G) was significant for MDD ($P = 0.0247$). Our study is the first to suggest a positive association of the *5-HT1A* gene with SZ in the Han Chinese population.

1. Introduction

With the advent of time and lifestyles to that of recent times, mental disorders have become more significant as diseases affecting human health and normalcy. Schizophrenia (SZ) and major depressive disorder (MDD) are two common severe psychiatric disorders and have relatively high morbidity and mortality. According to statistics so far, the prevalence of SZ has been estimated to be 0.34–0.85% [23] and 4–10% for MDD [13] in all populations. However, after one century's study, the etiology of these illnesses remains unclear [10]. Numerous family, twin and case-control studies have suggested that SZ and MDD were typically complex diseases involving both genetic and environmental factors [12,26] with substantial heritabilities of 60–85% [5] and 40–50% [20], respectively. Furthermore, GWAS (genomewide association studies) have shown evidence that various psychiatric disorders shared a common genetic risk background [14]. The genetic correlation evaluated via common SNPs (Single Nucleotide Polymorphisms) was 0.43 ± 0.06 s.e. [14] between SZ and MDD. Because genetic factor was considered to be the main factor of the etiology of the

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Table 1
The five SNPs in the *5-HT1A* and *5-HT2A* genes analyzed in this study.[a]

Gene	SNP ID	Chromosome	Chromosome Position[b]	Function	Allele
5-HT1A	rs1364043	5	63955024	Downstream	G/T
5-HT1A	rs10042486	5	63965502	Upstream	C/T
5-HT2A	rs6313	13	46895805	Intron variant, synonymous codon	C/T
5-HT2A	rs6311	13	46897343	Upstream	C/T
5-HT2A	rs17289304	13	46897583	Upstream	G/T

[a] Data comes from dbSNP database via NCBI website.
[b] The SNP Chromosome positions are based on the NCBI human genome build GRCh38.

Table 2
Allele and genotype distributions of *5-HT1A* and *5-HT2A* gene polymorphisms in the SZ and MDD case-control samples.

SNP	Allele Frequency		*P* value	Odds ratio (95% CI)	Genotype Frequency			*P* value	H-W *P* value
rs1364043	G	T			GG	GT	TT		
SZ	928(0.618)	574(0.382)	0.4105	0.9414(0.8154–1.0869)	281(0.374)	366(0.487)	104(0.138)	0.6428	0.3801
MDD	660(0.596)	448(0.404)	0.0534	0.8578(0.7342–1.0023)	195(0.352)	270(0.487)	89(0.161)	0.1522	0.7818
C	1063(0.632)	619(0.368)			334(0.397)	395(0.470)	112(0.133)		0.7781
rs10042486	C	T			CC	CT	TT		
SZ	310(0.209)	1170(0.791)	**0.0369**	1.2074(1.0114–1.4415)	25(0.034)	260(0.351)	455(0.615)	**0.0098**	0.0974
MDD	226(0.205)	878(0.795)	0.1042	1.1730(0.96755–1.4221)	29(0.053)	168(0.304)	355(0.643)	0.2826	0.125
C	298(0.180)	1358(0.820)			33(0.040)	232(0.280)	563(0.680)		0.1451
rs6313	C	T			CC	CT	TT		
SZ	638(0.425)	862(0.575)	0.1232	0.8955(0.7783–1.0304)	138(0.184)	362(0.483)	250(0.333)	0.2837	0.7291
MDD	474(0.425)	642(0.575)	0.1475	0.8933(0.7669–1.0407)	110(0.197)	254(0.455)	194(0.348)	0.1367	0.1057
C	762(0.452)	922(0.548)			171(0.203)	420(0.499)	251(0.298)		0.8456
rs6311	C	T			CC	CT	TT		
SZ	629(0.420)	867(0.580)	0.1005	0.8888(0.7722–1.0231)	132(0.176)	365(0.488)	251(0.336)	0.2432	0.9721
MDD	472(0.432)	620(0.568)	0.3738	0.9327(0.7999–1.0875)	109(0.200)	254(0.465)	183(0.335)	0.3011	0.2227
C	755(0.449)	925(0.551)			166(0.198)	423(0.504)	251(0.299)		0.6108
rs17289304	G	T			GG	GT	TT		
SZ	75(0.050)	1427(0.950)	0.2792	0.8436(0.6197–1.1484)	1(0.001)	73(0.097)	677(0.901)	0.4654	0.5022
MDD	56(0.051)	1044(0.949)	0.3833	0.8609(0.6147–1.2058)	2(0.004)	52(0.095)	496(0.902)	0.6458	0.6122
C	99(0.059)	1589(0.941)			3(0.004)	93(0.110)	748(0.886)		0.9518

P (<0.05) values are in bold.

two psychiatric disorders, numerous studies tried their best to find common susceptibility genes for SZ and MDD [6].

Notably, variation of serotonin (5-HT) receptors has been found to play an important role both in SZ and MDD [19]. Since the monoamine neurotransmitter was discovered by chance from antidepressant drugs in the 1950s, this big family of receptors has been increasingly focused on research of psychiatric disorders [1]. Belonging to this family, 5-HT1A and 5-HT2A receptors attracted the most attention with a number of encouraging results in epidemiological, clinical and molecular genetic studies. Characterized by its high affinity with 5-HT, 5-HT1A receptor is a representative of $G_{i/o}$-Coupled receptor distributed in both pre- and postsynaptically neurons within the brain and regulate inhibitory neurotransmission [18]. Researchers used 5-HT1A receptor knockout mice as genetic models of anxiety to show increased responsiveness to stress which suggested its potential capacity in the pathogenic processes of MDD [25]. Meanwhile, autopsy study has detected elevating density of 5-HT1A receptor in the prefrontal cortex in postmortem SZ patients [2]. This finding supported 5-HT1A receptor acting as a target for the treatment of SZ. As a $G_{q/11}$-Coupled Receptor, 5-HT2A receptor was known by being widely expressed in the brain and functionaling selectivity through alternative ligands [4]. PET (positron emission tomography) studies have shown that it is not only distributed most widely in cortical brain areas which known as highly correlative with cognition, but also exhibited various intracellular effects [15]. Rosier A et al. found that specific 5-HT2A receptors would decrease with age [21]. Using PET, Mintun MA et al. reported that 5-HT2A receptor binding in the hippocampus was reduced by 29% in MDD subjects compared to healthy controls [16]. Additionally, data from postmortem studies proved that 5-HT2A binding declined significantly (by 16.3%) in patients with SZ compared with healthy people [17]. Moreover, accumulating evidence from genetic studies suggested the substantial association between variation on their coding genes and both mental disorders [9,24].

Given the predictive potential of 5-HT1A and 5-HT2A receptors, we designed experiments to explore the association of *5-HT1A, 5-HT2A* with SZ and MDD in this study. We genotyped five SNPs (rs1364043, rs10042486, rs6313, rs6311, rs17289304) from 2166 individual DNA samples of the Han Chinese origin (752 SZ patients, 568 MDD patients, and 846 normal controls).

2. Materials and methods

2.1. Subjects

For this case-control study, we recruited a sample set consisting of 752 unrelated SZ cases (average age ± SD, 45.9 ± 13.13; 522 males and 230 females), 568 unrelated MDD cases (average age ± SD, 36.0 ± 12.90; 260 males and 308 females) and 846 healthy controls (average age ± SD, 33.9 ± 10.25; 485 males and 361 females). All subjects were interviewed by at least two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. None of the subjects included in this study presented more than one psychiatric pathology. All the control subjects were in good health and randomly selected from the general public with no psychiatric diseases, history of traumatic brain injury, or substance abuse. This study was reviewed and approved by the Ethics Committee of the Human Genetic Cen-

ter in Shanghai. Before data collection, all informed consent was obtained from every participant.

2.2. DNA extraction, SNP selection and genotyping

Genomic DNA was extracted from peripheral blood samples using the standard phenol-chloroform method. We totally selected five SNPs (rs1364043, rs10042486 from *5-HT1A*, rs6313, rs6311, rs17289304 from *5-HT2A*) according to the previous reports and works. These 5 SNPs' detail information is displayed in Table 1. All SNPs were genotyped via matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometer using MassARRAY® Analyzer 4 platform (Sequenom, San Diego, CA). Detailed information about the primers designing and PCR (polymerase chain reaction) conditions is available on request.

2.3. Statistical analysis

In this study, we used SHEsis (http://analysis.bio-x.cn/myAnalysis.php) to calculate single sample sets' allelic and genotypic frequencies as well as doing Hardy-Weinberg equilibrium (HWE) and association test between SZ and MDD cases and healthy controls respectively [22]. This online software compared the discrepancies between cases and controls using χ^2 test. We also assessed odds ratios and their 95% confidence intervals (CIs). Linkage disequilibrium (LD) of every two SNPs of the same gene and haplotype analysis was conducted on Haploview 4.2 [3] and further analyzed via SHEsis. We used Pearson's *P* value for all above analysis in this study, which was two tailed and the statistical significance was set at the threshold of 0.05.

3. Results

3.1. Single site associations

For all 5 SNPs, there is no significant deviation from HWE in either case or control groups. The allelic and genotypic distributions of these 5 SNPs of *5-HT1A* and *5-HT2A* in the healthy control sets and two patient sample sets are shown in Table 2. From this result, we observed a significant association between rs10042486 and SZ [P_{allele} = 0.0369 (Chi^2 = 4.3540, df = 1), $P_{genotype}$ = 0.0098 (Chi^2 = 9.2450, df = 2), OR (95% CI) = 1.2074 (1.0114–1.4415)]. Nevertheless, we did not find significant differences between SZ cases and healthy controls in both allele and genotype frequency distributions for the other SNPs. On the other hand, none of these 5 SNPs showed significant statistically association with MDD.

3.2. Haplotype analysis

Pairwise LD evaluation between SNPs in the same gene for SZ and MDD are shown in Table 3, which was displayed using D' standard measurement. We identified two haplotype blocks (rs10042486-rs1364043; rs6313-rs6311-rs17289304) according to the strong LD between every set of SNPs in pair. Interestingly, the pairwise LDs between investigated SNPs were highly similar in two case-control analysis sets. The additional haplotype analysis of these two identified haplotype blocks was conducted on SHEsis. The single haplotype of rs10042486 and rs1364043 (C-T) was nominally associated with SZ [*P* = 0.0302, OR (95% CI) = 1.218 (1.019–1.455)] and another haplotype (T-G) with MDD [*P* = 0.0247, OR (95% CI) = 0.835 (0.714–0.977)] as well. This analysis is shown in Table 4.

Table 3
Linkage disequilibrium between pairwise SNPs both in SZ and MDD case-control analysis.

Gene	Pairwise SNPs	D′in SZ	D′in MDD
5-HT1A	rs1364043-rs10042486	0.984	0.965
5-HT2A	rs6313-rs6311	0.996	0.984
	rs6311-rs17289304	0.982	0.980
	rs6313-rs17289304	1.000	0.999

4. Discussion

In the present study, we evaluated the role of the *5-HT1A* and *5-HT2A* genes both in SZ and MDD through genetic association analysis. The major finding was the significant association of rs10042486 within *5-HTR1A* promoter region with SZ in the Han Chinese population. Another consistent result has been reported in Korean patients by Crisafulli et al. in 2012 (*P* = 0.002) [7]. These findings might implicate the susceptibility of rs10042486 to SZ. The association was not observed between rs10042486 and MDD in our study, which to our knowledge was the first exploratory analysis. We suggest further studies in this subject that should be conducted in a larger population. As another candidate SNP in *5-HTR1A,* rs1364043 was not associated with SZ or MDD. The SNP is located downstream of *5-HTR1A* and there were fewer reports illustrating its function. A study carried out in Caucasian also showed that there was no significant difference of its genetic distribution between MDD patients and healthy controls (P_{allel} = 0.630) [9]. Notably, these two SNPs exhibit strong LD in our study and corresponds with the study by Kato et al. in 2007 [11].

Numerous studies comparing the genetic discrepancies of *5-HT2A* between patients and healthy persons, although the findings have often been inconsistent. Williams et al. firstly carried out a meta-analysis involving 15 studies (1533 cases and 1771 controls, most of the subjects from European samples) and found a significant association between rs6313 in *5-HT2A* and SZ [27]. However, Zhang et al. did not replicate the finding in southern Chinese populations (291 cases and 307 controls) in 2004 (P_{allele} = 0.748) [28]. More recently, Tan et al. conducted a meta-analysis in a larger sample including 56 studies (12,098 cases and 13,433 controls) to explore the relationship between rs6313 and SZ as well as MDD [24]. The results were similar to ours, that is, neither SZ nor MDD was related to rs6313 variations.

Conflicting results are reported for the association of *5-HT2A* rs6311 with psychiatric disorders. In 2013, a meta-analysis involving 10 studies in Caucasian population and 5 studies in Asian

Table 4
Association analysis of rs1364043-rs10042486 haplotype in the *5-HT1A* gene with SZ and MDD.

	Controls	SZ			MDD		
	Frequency	Frequency	*P* value	Odds Ratio (95% CI)	Frequency	*P* value	Odds Ratio (95% CI)
GC	3.67(0.002)	2.47(0.002)	–	–	7.60(0.007)	–	–
TC	292.33(0.177)	307.53(0.208)	**0.0302**	1.218(1.019–1.455)	218.40(0.200)	0.1216	1.166(0.960–1.417)
GT	1041.33(0.632)	909.53(0.615)	0.3308	0.931(0.805–1.076)	640.40(0.586)	**0.0247**	0.835(0.714–0.977)
TT	310.67(0.189)	258.47(0.175)	0.3205	0.912(0.760–1.094)	225.60(0.207)	0.2189	1.128(0.931–1.366)
Global	1648	1478	0.0838	–	1092	0.0782	–

P (<0.05) values are in bold.

population (4213 cases and 4670 controls in total) [8] discovered a significant association between rs6311 and SZ in samples of the general population but not in Asian population subgroup. Consistent with it, our study did not find a significant relationship between rs6311 and SZ in the Han Chinese population. Meanwhile, this article tested whether this SNP was susceptible to MDD but failed to obtain a significant finding [8]. However, another meta-analysis reported a significant relationship between rs6311 and MDD in both Asian and Caucasian population groups [29]. The discrepancy might lie in significant heterogeneity between association studies caused by various sources of controls, different sample size and genotyping methods [8].

To the best of our knowledge, no previous studies explored the association of rs17289304 with psychotic disorders. Our findings do not support that rs17289304 is a risk factor for SZ or MDD. Besides, the LD analysis showed there was a strong linkage between rs17289304 and the other two SNPs (rs6311 and rs6313) in *5-HT2A*, which might suggest there was indeed no association between the three SNPs with SZ or MDD.

5. Conclusion

In summary, our results highlight the role of the *5-HTR1A* especially rs10042486 to SZ in the Chinese Han population. There was no significant association between the *5-HT2A* gene and SZ or MDD. However, considering the limitation of incomplete SNP coverage, further genetic analysis need to be performed in larger size of samples with more saturated SNP coverage and in different ethnic groups. The study shows that it is necessary to continue to investigate more on the role of *5-HT1A* and further functional studies are suggested for the elucidation of its molecular mechanisms.

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