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TPH2 gene polymorphisms in the regulatory region are associated with paranoid schizophrenia in Northern Han Chinese

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ABSTRACT. In the last years, serotonin (5-HT) has been related with the pathophysiology of several psychiatric disorders, including schizophrenia. Thus, genes related to the serotonergic (5-HTergic) system are good candidate genes for schizophrenia. The rate-limiting enzyme of 5-HT synthesis is tryptophan hydroxylase 2 (TPH2). Single nucleotide polymorphisms (SNPs) in the regulatory regions of TPH2 gene may affect gene expression and biosynthesis of 5-HT triggering to various neuropsychiatric disorders related to 5-HT dysfunction. The present study explored the association of SNPs within the TPH2 gene with paranoid schizophrenia in Han Chinese. A total of 164 patients with schizophrenia and 244 healthy controls were genotyped for six TPH2 SNPs (rs4570625, rs11178997, rs11178998, rs41317118, rs17110747, and rs41317114). Significant group differences were observed in the allele and genotype frequencies of rs4570625 and in the frequencies of GTA and TTA haplotypes corresponding to rs4570625-rs11178997-rs11178998. Our findings suggest that common genetic variations of TPH2 are likely to contribute to genetic susceptibility to paranoid schizophrenia in Han Chinese. Further studies in larger samples are

needed to replicate this association.

Key words: TPH2; 5-HT; Paranoid schizophrenia; Haplotype; Serotonin; SNP

INTRODUCTION

Schizophrenia is a complex disorder affecting approximately 1% of the population worldwide (Schwab and Wildenauer, 2008) with the paranoid type being more common. The etiology of schizophrenia remains unclear. A genetic basis of schizophrenia has been observed in family (Tsuang et al., 1985), twin (Sullivan et al., 2003), and adoption studies (Heston, 1966), and its heritability is estimated at approximately 80 to 85% (Cardno and Gottesman, 2000). Recent advances in human genome information and molecular biology techniques have facilitated significant progress in genetic studies of schizophrenia. A number of important candidate genes have been cloned and their preliminary positions identified. These genes are closely related to function, and thus have revealed broad contours of disease-related signaling pathways.

Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter synthesized in the raphe nuclei of the brain stem and involved in the control of a wide range of physiological events within the central nervous system. Accordingly, disruption of serotonergic (5-HTergic) function has been implicated in the pathogenesis of many psychiatric disorders, including schizophrenia (Abi-Dargham et al., 1997), and drugs targeting the 5-HTergic system are widely used for the treatment of various psychiatric diseases. Tryptophan hydroxylase (TPH), the rate-limiting enzyme in 5-HT biosynthesis, converts the amino acid tryptophan to 5-hydroxytrytophan, which is then decarboxylated into 5-HT. Thus, TPH has received a great attention in genetic studies of schizophrenia. To date, two TPH genes have been identified. The TPH1 gene is located on chromosome 11p15 and has been studied as a candidate gene for schizophrenia (Paik et al., 2000), but TPH1 is mainly expressed in the peripheral tissues. The TPH2 gene was recently described as a fairly large gene of 93.5 kb with 11 exons located on chromosome 12q21.1. TPH2 is expressed at high levels in the human brain but only at very low levels in other tissues (Zill et al., 2004a) and shows 72% sequence homology to TPH1. Moreover, total RNA samples from wild type mice (TPH+/+) revealed about 150 fold more TPH2 than TPH1 mRNA in the brain stem, suggesting that TPH2 may play a more important role in 5-HT synthesis in the brain (Walther et al., 2003). Therefore, TPH2 may also be a candidate gene for schizophrenia.

Genetic variation of TPH1 has previously been associated with schizophrenia risk (Zaboli et al., 2006; Anttila et al., 2007). A meta-analysis showed a significant association between TPH1 218A/C and schizophrenia (Li and He, 2006b). The newly updated schizophrenia gene meta-analysis revealed that TPH1 is one of the four genes positively associated with schizophrenia, showing strong epidemiological credibility (Allen et al., 2008). In contrast to TPH1, genetic studies have shown an association between TPH2 and suicidal behavior (Zill et al., 2004b; Li and He, 2006a), major depression (Zill et al., 2004c), panic disorder (Maron et al., 2007), chronic fatigue syndrome (Goertzelet et al., 2006; Smith et al., 2006) and Tourette syndrome (Mössner et al., 2007). However, no evidence has been found for a role of TPH2 in schizophrenia, despite several studies in this area (De Luca et al., 2005a; Higashi et al., 2007; Shiroiwa et al., 2010; Tee et al., 2010; Kim and Yoon, 2011; Zhang et al., 2011). It is noteworthy that a certain number of these studies focused mainly on the rs4570625 (-703G/T), a common polymorphic SNP in the putative promoter (Kennedy et al., 2003) that has

been reported to be associated with the attention deficit hyperactivity disorder (ADHD) (Walitza et al., 2005), emotional processing (Herrmann et al., 2007), personality traits, and disorders related to emotional dysregulation (Gutknecht et al., 2007; Reuter et al., 2007). The promoter polymorphism rs4570625 of TPH2 has been also found to affect the responsiveness of the amygdala, a structure critically involved in the regulation of emotional behaviors (Brown et al., 2005; Canli et al., 2005). Moreover, neuroimaging studies have shown that abnormal amygdala activity during emotional stimuli processing appears to be associated with augmentation of positive symptoms, especially paranoia (Goghari et al., 2010). However, a recent study suggested that rs4570625 might also play an important role in the development of positive symptoms of schizophrenia in Han Chinese (Zhang et al., 2011). These findings prompted us to further investigate whether TPH2 is a susceptibility gene for paranoid schizophrenia in the Han Chinese.

In particular, the aim of the present study was to investigate the association between paranoid schizophrenia in the Han Chinese and specific SNPs within TPH2, including rs4570625, and five additional SNPs that have received little or no attention to date (rs11178997, rs11178998, rs41317118, rs17110747, and rs41317114).

MATERIAL AND METHODS

Subjects

All subjects were ethnically Han Chinese. This case-control study involved 164 unrelated in-patients with paranoid schizophrenia (87 males; 77 females; mean age 45.0 ± 12.8 years) recruited from the Kaiyuan mental hospital in Liaoning Province, China. Patients were diagnosed by at least two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria and the Chinese Classification of Mental Disorders (CCMD3) for schizophrenia. The control group consisted of 244 unrelated healthy volunteers (126 males; 118 females; mean age 38.5 ± 16.2 years) free from present, past and family history of psychiatric illness. This study was approved by the Medical Research Ethics Committee at China Medical University, and informed consent was obtained from all subjects.

Genotyping

A 5-mL peripheral blood sample was obtained from each subject for extraction of genomic DNA. In particular, genomic DNA was extracted from leukocytes using a standard phenol-chloroform method. Two fragments that included the six SNPs of interest were amplified from the extracted DNA by PCR. SNPs were genotyped by DNA sequencing analysis using primers shown in Table 1.

Statistical analysis

Hardy-Weinberg equilibrium, linkage disequilibrium (LD) and allele-based association analyses of single markers, as well as haplotype analyses, were calculated using Haploview version 4.2. The chi-square test was performed in order to compare genotypic frequencies between schizophrenic patients and controls using the Statistical Analysis System (SAS) V.12.0 statistical package. All tests were two-tailed, and significance was set at 0.05.

Table 1. Primers used for amplification of the TPH2 gene.

Region	Fragment length	Primer
Promoter/exon 1	905 bp	Forward (-792): 5'-tgcatagaggcatcacagga-3' Reverse (113): 5'-agcaggggtactagaggg-3'
exon 11/3'flanking	1104 bp	Forward (92692): 5'-attacccgtcccttctca-3' Reverse (93795): 5'-caagcactgggacgaat-3'

RESULTS

Identification of TPH2 sequence variants

In this study a 905-bp 5' flanking region and a 1104-bp 3' flanking region of the TPH2 gene has been sequenced. In addition to the six reported SNPs [rs4570625 (-703G/T), rs11178997 (-473T/A), rs11178998 (90A/G), rs41317118 (92999A/G), rs17110747 (93329A/G), and rs41317114 (93724C/G)], the following variants were found: T/A in -454 site, G/A in -279 site, C/T in 92922 site and G/C in 93581 site, as shown in Table 2. These variants were observed only once in a heterozygotic individual (minor allele frequency <1%), and thus could represent mutations. Remarkably, the AA genotype at the rs41317118 locus was not detected, indicating that this genotype is rare in Han Chinese.

Table 2. Sequence variants of the human TPH2 gene identified in this current study.

Position	dbSNP ID	Region	Allele 1/2
-703	rs4570625	5' flanking region	G/T
-473	rs11178997	5' flanking region	T/A
-454	N	5' flanking region	T/A
-279	N	5' flanking region	G/A
90	rs11178998	exon1(5'- UTR)	A/G
92922	N	exon11(3'- UTR)	C/T
92999	rs41317118	exon11(3'- UTR)	G/A
93329	rs17110747	exon11(3'- UTR)	G/A
93581	N	3' flanking region	G/C
93724	rs41317114	3' flanking region	G/C

Single site association analysis

Distributions of genotype and allele frequencies of the six SNPs in schizophrenic patients and controls are summarized in Table 3. The genotype distributions of the six loci were in Hardy-Weinberg equilibrium for both patients and controls. Chi-square analysis showed significant group differences for distributions of allele ($P = 0.002$, OR = 1.574, 95%CI = 1.185-2.089) and genotype ($P = 0.004$) frequencies for rs4570625. These significant differences were due to a higher G allele frequency in patients (48.0%) than controls (37.7%). The OR and 95%CI were both greater than 1, suggesting that an increased frequency of allele G conferred an increased risk of schizophrenia. Moreover, when males and females were analyzed separately, there were significant differences in distributions of allele ($P = 0.009$, OR = 1.726, 95%CI = 1.144-2.605) and genotype ($P = 0.039$) frequencies for females but not for males ($P > 0.05$), suggesting that females carrying the G allele were more susceptible to schizophrenia than males. There were no statistical differences in allele ($P > 0.05$) and genotype ($P > 0.05$) frequencies between patients and controls for rs11178997, rs11178998, rs41317118, rs17110747 and rs41317117, even when males and females were analyzed separately.

Table 3. Genotype and allele frequencies for SNPs of *TPH2* gene and associations between schizophrenia and control groups.

SNP ID	Schizophrenia (N = 164)	Control (N = 244)	P	OR	95%CI
rs4570625					
All subjects					
TT	40 (24.4)	97 (39.7)	0.004		
TG	88 (53.6)	110 (45.1)			
GG	36 (22.0)	37 (15.2)			
T	168 (51.2)	304 (62.3)			
G	160 (48.8)	184 (37.7)	0.002	1.574	1.185-2.089
Male					
TT	21 (24.1)	49 (39.9)	0.079		
TG	50 (57.3)	58 (46.0)			
GG	16 (18.4)	19 (15.1)			
T	92 (52.3)	156 (61.9)			
G	82 (47.1)	96 (38.1)	0.063	1.448	0.979-2.142
Female					
TT	19 (24.7)	48 (40.7)	0.039		
TG	38 (49.3)	52 (44.1)			
GG	20 (26.0)	18 (15.2)			
T	76 (49.4)	148 (62.7)			
G	78 (50.6)	88 (37.3)	0.009	1.726	1.144-2.605
rs11178997					
All subjects					
TT	121 (73.8)	169 (69.3)	0.611		
TA	37 (22.6)	64 (26.2)			
AA	6 (3.6)	11 (4.5)			
T	279 (85.1)	402 (82.4)			
A	49 (14.9)	86 (17.6)	0.312	0.821	0.560-1.204
Male					
TT	65 (74.7)	84 (66.7)	0.385		
TA	17 (19.5)	35 (27.8)			
AA	5 (5.8)	7 (5.5)			
T	147 (84.5)	203 (80.6)			
A	27 (15.5)	49 (19.4)	0.298	0.761	0.454-1.274
Female					
TT	56 (72.7)	85 (72.0)	0.659		
TA	20 (26.0)	29 (24.6)			
AA	1 (1.3)	4 (3.4)			
T	132 (85.7)	199 (84.3)			
A	22 (14.3)	37 (15.7)	0.708	0.896	0.506-1.588
rs11178998					
All subjects					
AA	121 (73.8)	169 (69.3)	0.554		
AG	38 (23.2)	64 (26.2)			
GG	5 (3.0)	11 (4.5)			
A	280 (85.4)	402 (82.4)			
G	48 (14.6)	86 (17.6)	0.259	1.248	0.849-1.833
Male					
AA	65 (74.7)	84 (66.7)	0.385		
AG	17 (19.5)	35 (27.8)			
GG	5 (5.8)	7 (5.5)			
A	147 (84.5)	203 (80.6)			
G	27 (15.5)	49 (19.4)	0.298	1.314	0.785-2.201
Female					
AA	56 (72.7)	85 (72.0)	0.254		
AG	21 (27.3)	29 (24.6)			
GG	0 (0)	4 (3.4)			
A	133 (86.4)	199 (84.3)			
G	21 (13.6)	37 (15.7)	0.580	1.178	0.660-2.101

Continued on next page

Table 3. Continued.

SNP ID	Schizophrenia (N = 164)	Control (N = 244)	P	OR	95%CI
rs41317118					
All subjects					
AA	0 (0)	0 (0)	0.996		
AG	17 (10.4)	26 (10.7)			
GG	147 (89.6)	218 (89.3)			
A	17 (5.2)	26 (5.3)			
G	311 (94.8)	462 (94.7)	0.928	0.971	0.518-1.820
Male					
AA	0 (0)	0 (0)	0.812		
AG	13 (14.9)	15 (11.9)			
GG	74 (85.1)	111 (88.1)			
A	13 (7.5)	15 (6.0)			
G	161 (92.5)	237 (94.0)	0.534	1.276	0.591-2.753
Female					
AA	0 (0)	0 (0)	0.572		
AG	4 (5.2)	11 (9.3)			
GG	73 (94.8)	107 (90.7)			
A	4 (2.6)	11 (4.7)			
G	150 (97.4)	225 (95.3)	0.300	0.546	0.171-1.745
rs17110747					
All subjects					
GG	93 (56.7)	129 (52.9)	0.641		
AG	62 (37.8)	97 (39.7)			
AA	9 (5.5)	18 (7.4)			
G	248 (75.6)	355 (72.7)			
A	80 (27.4)	133 (27.3)	0.361	0.861	0.624-1.187
Male					
GG	48 (55.2)	65 (51.6)	0.873		
AG	33 (37.9)	52 (41.3)			
AA	6 (6.9)	9 (7.1)			
G	129 (74.1)	182 (2.7)			
A	45 (25.9)	70 (27.8)	0.662	0.907	0.586-1.404
Female					
GG	45 (58.4)	64 (54.2)	0.548		
AG	29 (37.7)	45 (38.1)			
AA	3 (3.9)	9 (7.6)			
G	119 (77.3)	173 (73.3)			
A	35 (22.7)	63 (26.7)	0.377	0.808	0.503-1.298
rs41317114					
All subjects					
GG	121 (73.8)	196 (80.3)	0.230		
CG	41 (25.0)	44 (18.0)			
CC	2 (1.2)	4 (1.6)			
G	283 (86.3)	436 (89.3)			
C	45 (13.7)	52 (10.7)	0.185	1.333	0.871-2.042
Male					
GG	66 (75.9)	100 (9.4)	0.586		
CG	20 (23.0)	23 (18.2)			
CC	1 (1.1)	3 (2.4)			
G	152 (87.4)	223 (88.5)			
C	22 (12.6)	29 (11.5)	0.723	1.113	0.616-2.010
Female					
GG	55 (71.4)	96 (81.4)	0.269		
CG	21 (27.3)	21 (17.8)			
CC	1 (1.3)	1 (0.8)			
G	131 (85.1)	213 (90.2)			
C	23 (14.9)	23 (9.8)	0.121	1.626	0.877-3.015

Data represent N (%).

LD mapping

Figure 1 shows the data from pairwise LD analyses between schizophrenia and control groups across six SNPs, as represented by the LD coefficient (D'). Strong LD was observed between rs4570625, rs11178997 and rs11178998 in both groups, while strong LD between rs41317118, rs17110747 and rs41317114 was present only in controls but not in schizophrenia patients, suggesting a possible disease association. Accordingly, we identified two haplotype blocks for further investigation via haplotype association analysis.

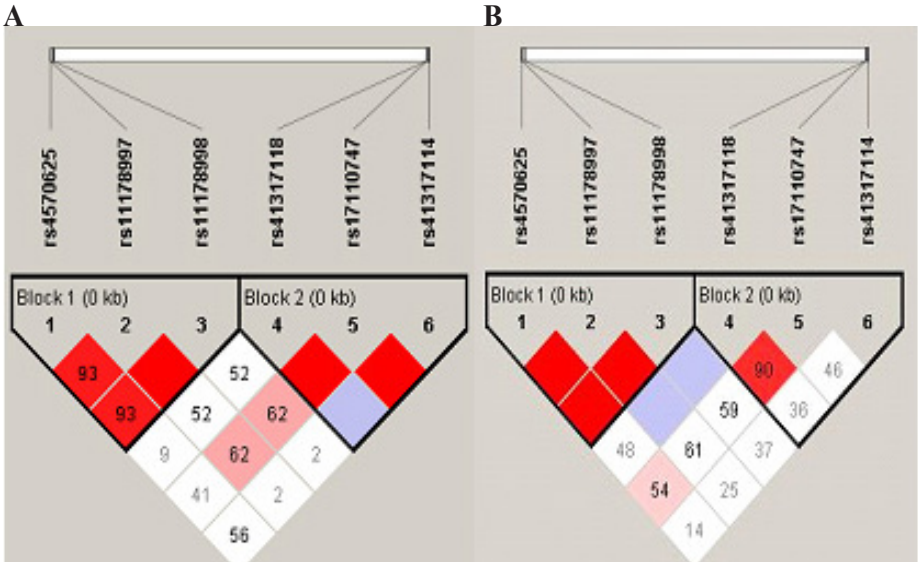

Figure 1. Linkage disequilibrium and D' for six SNPs in TPH2 in control subjects (**A**) and patients with schizophrenia (**B**). Empty squares indicate D' = 1.

Haplotype association analysis

Table 4 shows the results of the haplotype analysis. Significant group differences were observed for haplotypes GTA (P = 0.001, OR = 1.591, 95%CI = 1.198-2.114) and TTA (P = 0.014, OR = 0.700, 95%CI = 0.525-0.933) in block 1. The frequency of haplotype GTA was greater in schizophrenic patients (0.487) than in controls (0.374), and the OR and 95%CI were both greater than 1, suggesting that an increased frequency of haplotype GTA conferred an increased risk of paranoid schizophrenia. Furthermore, significant group differences in distribution were detected in females ($P < 0.05$) but not in males ($P > 0.05$), suggesting that females with haplotype GTA were more susceptible to paranoid schizophrenia than males. There were no significant group differences for haplotype TAG in block 1 or for any haplotypes in block 2, even when males and females were analyzed separately.

Table 4. Haplotype block analyses in schizophrenia and control cases.

Haplotype block	Haplotype[a]	Schizophrenia	Control	P	OR	95%CI
Block1: SNPs 1-3	GTA					
	All subjects	0.487	0.374	0.001	1.591	1.198-2.114
	Male	0.471	0.381	0.063	1.448	0.979-2.142
	Female	0.505	0.367	0.007	1.769	1.171-2.674
	TTA					
	All subjects	0.364	0.450	0.014	0.700	0.525-0.933
	Male	0.374	0.425	0.291	0.808	0.544-1.201
	Female	0.352	0.476	0.015	0.599	0.394-0.911
	TAG					
	All subjects	0.146	0.173	0.294	0.814	0.553-1.196
	Male	0.155	0.194	0.293	0.761	0.454-1.274
	Female	0.135	0.151	0.667	0.879	0.492-1.573
Block 1: SNPs 4-6	GGG					
	All subjects	0.625	0.622	0.945	1.078	0.806-1.442
	Male	0.624	0.607	0.731	1.118	0.750-1.667
	Female	0.626	0.640	0.782	1.111	0.723-1.709
	GAG					
	All subjects	0.186	0.218	0.273	0.793	0.557-1.130
	Male	0.175	0.218	0.276	0.697	0.423-1.151
	Female	0.198	0.216	0.679	0.918	0.555-1.517
	GGC					
	All subjects	0.128	0.105	0.305	1.143	0.735-1.776
	Male	0.118	0.115	0.933	0.920	0.495-1.711
	Female	0.140	0.092	0.142	1.383	0.727-2.629
	AAG					
	All subjects	0.048	0.053	0.779	0.841	0.437-1.620
	Male	0.075	0.060	0.534	1.306	0.603-2.830
	Female	0.018	0.046	0.167	0.091	0.008-1.100

[a]Haplotypes with frequency <0.01 were not included in analysis.

DISCUSSION

To our knowledge, this is the first study to investigate an association between paranoid schizophrenia in Han Chinese and specific SNPs in the TPH2 gene, including rs4570625, rs11178997, rs11178998, rs41317118, rs17110747 and rs41317114. These six SNPs were located in the regulatory region, including the promoter region, 5' UTR and 3' flanking region, which do not alter the protein sequence, but might be involved in regulation of gene expression. We identified three different haplotypes of the human TPH2 promoter: GTA, TTA and TAG, supporting previous findings (Scheuch et al., 2007). TTA was the most prevalent TPH2 promoter haplotype in Han Chinese.

In the present study, we successfully identified significant associations in the genotype distributions and allele frequencies of rs4570625 with paranoid schizophrenia in Han Chinese. Schizophrenic patients had an increased frequency of the G allele, suggesting that this allele confers an increased risk of schizophrenia. A previous study by Yoon and Kim (2009) showed that the homozygous G allele frequency was significantly higher in suicidal depressed patients than in controls, and increased frequency of this allele conferred an increased risk of suicide. The reason maybe that rs450625 is situated in the promoter region of the TPH2 gene, which impacts expression of TPH2 by modifying binding sites for transcription factors (e.g., POU3F2, a crucial regulator of TPH2 expression) (Lin et al., 2007; Sacco et al., 2007; Chen et al., 2008). A postmortem study revealed a trend toward higher TPH2 expression in the dorsolateral prefrontal cortex (Brodmann Area 46) in schizophrenic patients relative to controls (De Luca et al., 2005b).

Moreover, an association was also observed between paranoid schizophrenia in Han Chinese and haplotype frequencies of GTA and TTA combined with rs4570625-rs11178997-rs1178998. Such haplotypes include rs4570625, which was discussed earlier. The SNP in the rs11178997 site is also in the POU3F2 binding site, and an electrophoretic mobility shift assay revealed reduced binding of the transcription factor POU3F2 to the A allele, suggesting that the human TPH2 promoter polymorphism rs11178997 impacts gene expression (Lin et al., 2007; Scheuch et al., 2007). A recent study showed that SNP rs1178998 might affect expression of the TPH2 gene at the post transcriptional level, and the three SNPs mentioned above differentially regulated gene expression via haplotype-specific effects on transcriptional activity of the TPH2 gene (Chen et al., 2008).

It is noteworthy that we observed an association with paranoid schizophrenia in females only in the genotype distributions and allele frequency of rs4570625 and in the haplotype frequencies of GTA and TTA corresponding to rs4570625- rs11178997-rs11178998, suggesting that females with G alleles or haplotype GTA were more susceptible to paranoid schizophrenia than males. The epidemiological survey showed a significantly higher incidence of mental illness in females. The reasons underlying this sex difference are unclear and require further study, but may be related to estrogen levels.

In the present study, we found no significant differences in genotypic distributions or allelic frequencies of rs11178997, rs11178998, rs41317118, rs17110747 and rs41317114. Furthermore, frequencies of haplotypes constructed with rs41317118-rs17110747-rs41317114 were not associated with schizophrenia, consistent with other findings (De Luca et al., 2005a; Shiroiwa et al., 2010; Serretti et al., 2011).

Prior to our study, no studies had reported an association between genetic variations in the TPH2 gene and schizophrenia (De Luca et al., 2005a; Higashi et al., 2007; Shiroiwa et al., 2010; Tee et al., 2010, Kim and Yoon, 2011; Zhang et al., 2011). There are several possible explanations for our novel results. First, unlike in previous studies, SNPs in the current study were in the regulatory region of the TPH2 gene and therefore could affect gene expression. Second, schizophrenia is a heterozygous disease, and clinical heterogeneity of disease phenotypes may prevent a more detailed understanding of genetic structure (Cherlyn et al., 2010). We indeed specifically studied the paranoid subtype of schizophrenia. The relatively small sample size of the current study limits the possibility to generalize our results, and these data should be replicated in an independent study.

In conclusion, we found associations between paranoid schizophrenia in Han Chinese and the genotype distributions and allele frequency of rs4570625 and haplotype frequencies of GTA and TTA combined with rs4570625-rs11178997-rs1178998. This is the first report to show that specific SNPs in TPH2 are associated with paranoid schizophrenia.

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