LETTER TO THE EDITOR

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An Association Analysis between 5-HTTLPR Polymorphism and Obsessive–Compulsive Disorder, Tourette Syndrome in a Chinese Han Population

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Obsessive–compulsive disorder (OCD) is a chronic and severe anxiety disorder presented with obsession and/or compulsion. With a lifetime prevalence of 1.9–3.3% [1], OCD negatively impacts many aspects of life. Tourette syndrome (TS) is a neurodevelopmental disorder with an estimated prevalence of 1–10 persons per 1000 in school age children [2]. TS is a characterized by chronic involuntary motor tics, vocal tics in particular (DSM-IV, American Psychiatric Association, 1994). OCD and TS are distinct entities, but share common features of repetitive behaviors with a juvenile onset. A number of candidate genes of dopamine and serotonin system have been studied in OCD and in TS [3,4]. Particular emphasis has been placed on functional variants in the serotonin transporter gene in the past few years. The serotonin transporter (5-HTT) gene, located on chromosome 17q11.1-q12, is in charge of encoding 5-HTT binding sites in cell lines. However, it's expression is differential due to functional polymorphism of serotonin-transporter-linked polymorphic region (5-HTTLPR) including the long (L) and short (S) variants which consists of a 44-bp insertion or deletion involving repeat elements 6–8 respectively [5]. Because the initial description of the function of this allele in a study of OCD by Lesch et al., two family-based association studies [6,7] and two case–control-based meta-analyses [3,8] have supported the relevance of this polymorphism to OCD. A study of Italian population by Cavallini et al. failed to associate serotonin-transporter-linked polymorphic region (5-HTTLPR) with TS [4].

This study included 207 OCD patients (101 male and 106 female; mean age: 35.9 ± 15.7 years) and 275 healthy control subjects (150 male and 125 female; mean age: 32.7 ± 13.9 years). All subjects are Chinese from the same geographic region and of the same ethnic origin. A total of 108 trios with TS (25 female and 83 male outpatients; age: 5–18 years) were also recruited from the Affiliated Hospital of Medical College of Qingdao University and Linyi People's Hospital.

Genotyping for the 5-HTTLPR polymorphism was carried out using a PCR method. Statistical analysis was performed using SPSS (Version 12.0 for Windows; SPSS, Inc., Chicago, IL, USA). The Hardy–Weinberg equilibrium of the genotype distribution was tested using the homogeneity χ^2-test. A case–control study was performed using the homogeneity χ^2-test. For all data of 108 TS trios, a family-based study was performed to assess genetic association by means of haplotype relative risk (HRR) and transmission disequilibrium test (TDT) statistics.

Table 1 shows the distribution of alleles and genotypes of the 5-HTTLPR marker in OCD patients and controls. Genotype frequencies of the sample distributed according to the Hardy–Weinberg equilibrium ($\chi^2 = 2.461$, df = 1, $P = 0.117$). There was no difference of allele frequencies ($\chi^2 = 1.826$, df = 1,

Table 1 Genotype and allele frequency of the 5-HTTLPR polymorphism in OCD patients and controls

Group	N	Genotype					Allele					
		LL	LS	SS	χ^2	*P* value	L	S	χ^2	*P* value	OR	95%(CI)
Male OCD	106	14(13%)	39(37%)	53(50%)	2.22	0.33	67(32%)	145(68%)	0.21	0.65	0.91	0.62–1.35
Male control	125	13(10%)	58(46%)	54(43%)			84(34%)	166(67%)				
Female OCD	101	14(14%)	37(37%)	50(49%)	5.43	0.07	65(32%)	137(68%)	6.04	0.01	1.65	1.10–2.46
Female control	150	10(7%)	47(31%)	93(62%)			67(22%)	233(78%)				
Onset OCD(<18)	113	12(13%)	37(39%)	45(48%)	1.02	0.60	61(32%)	127(68%)	0.83	0.36	1.22	0.79–1.85
Onset OCD(≥18)	94	13(12%)	38(34%)	62(55%)			64(28%)	162(72%)				
OCD with tic	11	3(27%)	5(46%)	3(27%)	3.83	0.15	11(50%)	11(50%)	4.32	0.038	2.44	1.03–5.78
OCD without tic	196	22(11%)	70(36%)	104(53%)			114(29%)	278(71%)				
OCD patients	207	25(12%)	75(36%)	107(52%)	1.83	0.40	125(32%)	289(68%)	0.87	0.35	1.14	0.86–1.51
OCD controls	275	23(8%)	105(38%)	147(54%)			151(28%)	399(73%)				

Table 2 The results of HRR analysis and TDT analysis of TS study

Transmitted allele	Untransmitted allele		Total	TDT χ^2	*P* value
	L	S			
L	a = 22	b = 40	W = 62		
S	c = 46	d = 108	X = 154		
Total	Y = 68	Z = 148	2N = 432	0.412	0.518

Genotype of case	Genotype of control			Total	χ^2	*P* value	HRR	95%(CI)
	LL	LS	SS					
LL, LS	A = 49		B = 59	W = 108				
SS	C = 57		D = 51	X = 108				
Total	Y = 106		Z = 110	N = 216	0.025	0.87	1.25	0.57–1.95

$P = 0.401$) or genotypic frequencies ($\chi^2 = 0.876$, df = 2, $P = 0.352$, OR = 1.143, CI = 0.863–1.514) between OCD patients and controls. An increased frequency of the L allele was noticed in female OCD patients versus female controls ($\chi^2 = 6.04$, df = 1, $P = 0.01$). Allelic frequencies analysis between OCD patients with tic versus those without tic also showed a statistically significant difference ($\chi^2 = 4.32$, df = 1, $P = 0.038$; Table 1). The genotypic distribution of 5-HTTLPR polymorphism was not significantly different from the predicted distribution based on Hardy–Weinberg equilibrium in TS patients ($\chi^2 = 3.72$, df =1, $P = 0.065$) and their parents ($\chi^2 = 0.75$, df =1, $P = 0.36$). TDT and HRR tests did not detect biased transmission of alleles from parents to affected offsprings (TDT = 0.412, df = 1, $P = 0.518$; HRR = 1.05, $\chi^2 = 0.025$, $P = 0.87$, 95% CI: 0.57–1.95; Table 2).

The findings from this study do not support an association of 5-HTTLPR polymorphism with either OCD or TS. A previous study found higher frequency of the S/S genotype in OCD and association of the S allele with OCD but only in female subjects [9]. A study by Baca-Garcia et al. [10] also reported a linear association between 5-HTTLPR genotypes (L/L, L/S, and S/S) in three female samples (OCD, nonimpulsive controls, and impulsive suicide attempters): OCD patients had the highest L/L genotype frequency; impulsive suicide attempters the lowest L/L genotype frequency. Similar to a previous case–control association study [4], we did not find evidence that supports the hypothesis of linkage disequilibrium between the 5-HTTLPR and TS.

The case–control design in this study is vulnerable to population stratification. However, we did attempt to minimize this problem by matching ethnicities between cases and controls. The negative finding can also be attributed to clinical heterogeneity of OCD and TS. Finally, population-based differences, particularly in the extent of linkage disequilibrium between the tested polymorphism and other potential variants in the gene, may have contributed the discrepant finding.

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