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Sex determines which section of the *SLC6A4* gene is linked to obsessive–compulsive symptoms in normal Chinese college students

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ABSTRACT

Previous case–control and family-based association studies have implicated the *SLC6A4* gene in obsessive–compulsive disorder (OCD). Little research, however, has examined this gene's role in obsessive–compulsive symptoms (OCS) in community samples. The present study genotyped seven tag SNPs and two common functional tandem repeat polymorphisms (*5-HTTLPR* and *STin2*), which together cover the whole *SLC6A4* gene, and investigated their associations with OCS in normal Chinese college students ($N = 572$). The results revealed a significant gender main effect and gender-specific genetic effects of the *SLC6A4* gene on OCS. Males scored significantly higher on total OCS and its three dimensions than did females ($ps < .01$). The *5-HTTLPR* in the promoter region showed a female-specific genetic effect, with the *l/l* and *l/s* genotypes linked to higher OCS scores than the s/s genotype ($ps < .05$). In contrast, a conserved haplotype polymorphism (*rs1042173| rs4325622| rs3794808| rs140701| rs4583306| rs2020942*) covering from intron 3 to the 3′ UTR of the *SLC6A4* gene showed male-specific genetic effects, with the *CGAAGG/CGAAGG* genotype associated with lower OCS scores than the other genotypes ($ps < .05$). These effects remained significant after controlling for OCS-related factors including participants' depressive and anxiety symptoms as well as stressful life events, and correction for multiple tests. These results are discussed in terms of their implications for our understanding of the sex-specific role of the different sections of the *SLC6A4* gene in OCD.

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1. Background

Obsessive–compulsive disorder (OCD) is a psychiatric disorder characterized by clinically significant recurrent, intrusive and disturbing thoughts and images and/or repetitive ritualistic physical or mental acts (APA, 2007; Mathews et al., 2004). Approximately 2–3% of people in the world are suffering from OCD (Kessler et al., 2005a, 2005b). As a prevalent psychiatric disorder, OCD has a median onset age of around 20 years old (Brynska and Wolanczyk, 2005; Mathews et al., 2004), which suggests that college students between 18 and 25 years old are at higher risk than other age groups to develop OCD. OCD patients usually display one or more common clusters of obsessive–compulsive symptoms (OCS), such as cleanliness and contamination, obsessions, compulsions, symmetry, and ordering (Bloch et al., 2008a; Mathews et al., 2004; Moore et al., 2010). Moreover, continuous distributions of these OCS in the general population exist with few obsessive–compulsive behaviors and minimal severity at one end and many obsessive–compulsive behaviors and severe impairment at the other (Apter et al., 1996; Brynska and Wolanczyk, 2005).

OCD has a substantial genetic basis (Walitza et al., 2010), which implies that OCS in normal population would also likely have some genetic influence. A better understanding of the genetic basis of OCS in normal populations, especially in the highly susceptible college students, could provide insights into the pathology of OCD and thereby, promote more effective methods of prevention, diagnosis, and treatment of OCD. The estimated heritability for OCD ranges from 0.45 to 0.65 for children and adolescents and from 0.27

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to 0.47 for adults in twin and family studies (van Grootheest et al., 2005), indicating that early-onset OCD may have a different etiology (including genetic factors) from late-onset OCD. Molecular genetic association studies have specifically provided further evidence for the genetic contributions of *SLC6A4* to OCD (Bloch et al., 2008b; Hu et al., 2006; Lin, 2007; Voyiaziakis et al., 2011). SLC6A4 transports serotonin from the synaptic cleft to presynaptic neurons, thereby attenuating current serotonin neurotransmission while also maintaining the pool of available serotonin for subsequent release (Lesch and Gutknecht, 2005). SLC6A4 is also the molecular target of selective serotonin reuptake inhibitors (SSRIs), the most clinically effective medications for OCD treatment (APA, 2007; Geller et al., 2003; Goddard et al., 2008). Brain imaging studies have also suggested that late-onset OCD, but not the early-onset OCD, is associated with abnormally low serotonin transporter availability in the brain (Hasselbalch et al., 2007; Hesse et al., 2011). Therefore, the *SLC6A4* gene is an ideal candidate gene for research on OCD/OCS. When examining OCS gender is an important variable, not only because of gender differences in OCD/OCS but also because of potential interactions between gender and genes. Growing literature shows that sex differences are prevalent in the neural and genetic bases of behaviors (Cahill, 2006). Such differences have been linked to not only sex chromosomes (X- and Y-linked genes and proteins) and gonadal hormone secretions (Ngun et al., 2011), but also autosomal chromosomes and general neurochemical mechanisms (Bocklandt and Vilain, 2007; Sanchez and Vilain, 2010). For example, recent studies found that gender modulated the associations of catechol-o-methyltransferase (*COMT*) genetic variants with brain function (Harrison and Tunbridge, 2008) and personality traits (Chen et al., 2011), and the associations of monoamine oxidase A (*MAOA*) genetic variants with brain circuitry underling aggression and personality traits (Buckholtz et al., 2008; Buckholtz and Meyer-Lindenberg, 2008). More specifically, gender × gene interactions involving the *SLC6A4* gene have been frequently reported for behaviors such as depression (Baune et al., 2008; Brummett et al., 2008) and anxiety (Mizuno et al., 2006). Of most relevance to our study, three previous association studies directly reported gender-specific genetic effects of *SLC6A4* variants on OCS (Dickel et al., 2007; Voyiaziakis et al., 2011) and obsessive–compulsive personality disorder (OCPD) (Blom et al., 2011), although the specific interaction effects were not consistent across studies (a point to which we will return in the discussion). Therefore, the current study specifically examined gender and gender-by-gene (*SLC6A4*) interaction effects on OCS.

The *SLC6A4* gene has two well-known common functional polymorphisms: one in the upstream regulatory region (*5-HTTLPR*) and the other (the 17 bp tandem repeat, *STin2*) in intron 2 (Fiskerstrand et al., 1999; Heils et al., 1996). The *s* allele of *5-HTTLPR* has been linked to reduced *SLC6A4* expression and low serotonin reuptake compared to the *l* allele (Heils et al., 1996). The *10R* allele of *STin2* has been associated with lower transcriptional activity than the *12R* allele (Fiskerstrand et al., 1999). Earlier studies (Bengel et al., 1999; Hu et al., 2006; Kim et al., 2005; McDougle et al., 1998) and a recent review (Bloch et al., 2008b) reported that the *l* allele of *5-HTTLPR* was a risk factor for OCD while some other studies reported that the *s* allele was a risk factor (Lin, 2007; Perez et al., 2006). As mentioned early, interactions of *SLCA64* by gender on OCD (Dickel et al., 2007; Voyiaziakis et al., 2011) and OCPD (Blom et al., 2011), were also reported. Two studies reported no association (Camarena et al., 2001; Chabane et al., 2004).

There are three limitations in previous studies. First, they were either case–control or family-based studies, with clinical OCD samples of heterogeneous age of onset and medication treatments (e.g., SSRIs). These patients were also comorbid with various psychiatric disorders, such as major depression, panic disorder and anxiety disorder (Perez et al., 2006; Voyiaziakis et al., 2011), which would not allow for a separation of the *SLC6A4* effects on OCS from related psychiatric symptoms. Only one recent association study examined *5-HTTLPR* and obsessive–compulsive personality disorder (OCPD) trait in a community sample of European ancestry, with the finding that the *s* allele was linked to lower obsessive–compulsive personality trait scores in males and to higher obsessive–compulsive trait scores in females (Blom et al., 2011). The second limitation of previous research is that most studies were done with European ancestry populations (Bloch et al., 2008b; Blom et al., 2011; Lin, 2007; Voyiaziakis et al., 2011). Considering that allele frequencies of *SLC6A4* polymorphisms have substantial differences between Asian and European ancestry individuals (Gelernter et al., 1997; Zhong et al., 2009), these allele frequency diversities may reflect different behavioral adaptive functions in different cultures and living environments (Chiao and Blizinsky, 2010) or differential physiological functions of the *SLC6A4* gene in different populations (Smits et al., 2004). The third limitation of previous research is that much attention was focused on *5-HTTLPR* without examining polymorphisms in other sections of the *SLC6A4* gene. Only a few studies have included *STin2* and several other single nucleotide polymorphisms (Voyiaziakis et al., 2011; Wendland et al., 2008), and none included normal community samples.

The current study was designed to investigate the role of the *SLC6A4* gene in OCS in normal Chinese college students. To cover the whole gene, we included the often-studied *5-HTTLPR*, *STin2*, and seven tag single nucleotide polymorphisms (SNPs) (see Fig. 1 and Table 1). Finally, to untangle the role of the *SLC6A4* gene in OCS versus related affective disorder symptoms such as depression and anxiety, we further analyzed our results by taking into account these symptoms as well as a major environmental factor—stressful life events (Carter et al., 2004; Middeldorp et al., 2007; Ogilvie et al., 1996; Quarantini et al., 2011).

2. Method and participants

2.1. Participants

Five hundred and seventy-two (312 females) undergraduate students (all Han Chinese, 20.47 ± 1.01 years old) were recruited from Beijing Normal University (Beijing, China) (He et al., 2010). All participants had normal or corrected-to-normal vision, no neurological and psychiatric problems based on self-reports. Informed written consent was obtained from each participant. The current study was approved by the Beijing Normal University Institutional Review Board.

2.2. Behavioral measures

Participants were asked to complete the 20-item Leyton Obsessional Inventory-Child Version (LOI-CV) on a 4-point scale of symptom frequency (always = 3, mostly = 2, sometimes = 1, and never = 0) (Berg et al., 1988), which has been widely used to measure obsessive–compulsive symptoms in epidemiological studies (Maggini et al., 2001; Mather and Cartwright-Hatton, 2004; Roussos et al., 2003). The Chinese translation of LOI-CV was done by a team of several bilingual psychologists and had high internal consistency (Cronbach $\alpha = 0.829$). In addition, participants were also asked to completed the 21-item Beck Depression and Anxiety Inventory (BDI and BAI) (Beck, 1990; Beck et al., 1996), and a scale of stressful life events (Beam et al., 2002; Wills et al., 1992). The Cronbach α's were 0.809 for BDI, 0.89 for BAI, and 0.746 for stressful life events.

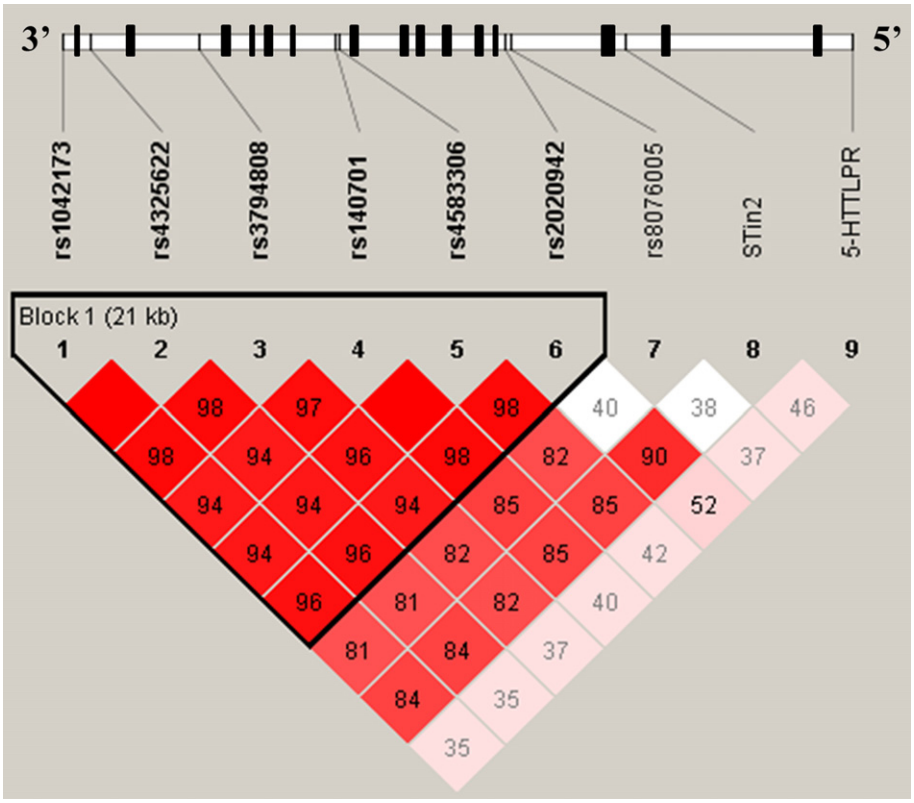

Fig. 1. Position and linkage disequilibrium (LD) map of the selected polymorphisms on the *SLC6A4* gene.

2.3. Genotyping

A 4 ml venous blood sample was collected from each participant. Genomic DNA was extracted according to the standard method within 2 weeks. *5-HTTLPR* and *STin2* were genotyped by using the standard polymerase chain reaction technique (PCR). Detailed PCR protocols for *5-HTTLPR* (He et al., 2010) and *STin2* (Li et al., 2007) were described in previous studies. Finally, PCR products of both *5-HTTLPR* (the *l* allele of 528 bp and the *s* allele of 484 bp), and *STin2* (*10R* of 267 bp and *12R* of 300 bp) were separated by 2% agarose gels stained with ethidium bromide and then analyzed with a Gel Doc 2000 imaging system (Bio-Rad Laboratories Ltd, UK).

Ambiguous and unidentifiable amplification were eliminated from the study, yielding 569 participants (310 females, 54.48%) with clear genotypes for *5-HTTLPR* and 536 participants (286 females, 53.36%) for *STin2* (See Table 1). Distributions of both *5-HTTLPR* ($\chi^2 = 1.615$, $p = .204$) and *STin2* ($\chi^2 = 0.11$, $p = .914$) were in Hardy–Weinberger equilibrium and were also consistent with frequency reported in previous studies of Asian samples (Gelernter et al., 1997; Zhong et al., 2009).

The seven tag SNPs of the *SLC6A4* gene (see Table 1 and Fig. 1) were genotyped using the standard Illumina GoldenGate Genotyping protocol (www.southgene.com.cn) in 480 participants selected randomly out of the total sample. They all passed the criteria of a call rate of >95%, Minor Allele Frequency (MAF) of >0.05, and Hardy–Weinberger equilibrium of $ps > .05$.

Table 1
Information on the candidate polymorphisms of the *SLC6A4* gene.

SNP	Position (base-pair)	Location	*N*	Alleles Major/minor	MAF
rs1042173	25,549,137	3′ UTR	480	*C/A*	0.21
rs4325622	25,550,601	Intron 14	480	*G/A*	0.21
rs3794808	25,555,919	Intron 13	480	*A/G*	0.21
rs140701	25,562,658	Intron 9	480	*A/G*	0.21
rs4583306	25,562,841	Intron 9	480	*G/A*	0.20
rs2020942	25,571,040	Intron 3	479	*G/A*	0.08
rs8076005	25,571,336	Intron 3	479	*A/G*	0.14
STin2[a]	–	Intron 2	536	*10R/12R*	0.07
5-HTTLPR	–	5′ UTR	569	*s/l*	0.28
Haplotype[b]	–	–	479	*AAGGAA/ AAGGAG/CGAAGG*	0.08/0.12/0.78

SNP: Single nucleotide polymorphism; MAF: minor allele frequency.

[a] In the current population, in addition to the common *10R* and *12R*, there were two *13R*, two *14R* and two *15R*.

[b] This haplotype block consists of *rs1042173| rs4325622| rs3794808| rs140701| rs4583306| rs2020942*. There are three main haplotypes: *AAGGAA* (0.08), *AAGGAG* (0.12) and *CGAAGG* (0.78). There were 301 individuals with the *CGAAGG/CGAAGG* one as a group. The remaining 179 individuals with minor genotypes were merged to a non-*CGAAGG/CGAAGG* group.

2.4. Analysis

Analyses were conducted using Plink v1.07 (Purcell et al., 2007), Haploview 4.0 (Barrett et al., 2005), and SPSS for Windows (release 16.0).

The OCS score was normally distributed in the current population (Skewness = 0.54, Kurtosis = 0.48) and all participants were located within Mean ± 3SD. An exploratory factor analysis of the current data showed similar three-factor structure as reported in previous studies: Compulsions, Obsessions, and Cleanliness (Bamber et al., 2002; Moore et al., 2010). Thus, in the current study, three dimension scores were also calculated for each participant. Age range of the current sample was narrow (18–26 years) and showed no significant effect on OCS, thus was excluded in subsequent analysis.

Table 2
Effects of *STin2*, *5-HTTLPR*, and the haplotype block on OCS scores.

	Male				Female			
	G1	G2	*F*	Adj. *F*	G1	G2	*F*	Adj. *F*
5-HTTLPR (G1 = s/s; G2 = l/s and l/l)								
N	143	116			155	155		
Total OCS	22.52 ± 7.38	21.46 ± 7.73	1.393	0.148	18.79 ± 7.24	20.99 ± 7.31	7.198*** (**0.008**)	8.489*** (**0.004**)
Compulsions	8.00 ± 3.37	7.56 ± 3.58	1.060	0.056	6.80 ± 3.37	7.31 ± 3.39	1.724	1.853
Obsessions	7.03 ± 2.84	6.48 ± 2.94	2.486	0.721	5.64 ± 2.44	6.28 ± 2.87	4.213* (**0.041**)	4.777* (**0.029**)
Cleanliness	7.50 ± 3.49	7.41 ± 3.20	0.043	0.013	6.35 ± 2.90	7.40 ± 3.15	8.454*** (**0.004**)	8.154*** (**0.004**)
STin2 (G1 = 10R; G2 = non-10R)								
N	32	218			39	246		
Total OCS	23.06 ± 8.91	22.01 ± 7.4	0.595	2.605	20.23 ± 5.94	19.72 ± 6.99	0.166	0.530
Compulsions	7.88 ± 3.73	7.86 ± 3.45	0.001	0.349	6.79 ± 3.25	7.05 ± 3.32	0.194	0.072
Obsessions	6.59 ± 3.32	6.79 ± 2.85	0.137	0.073	6.26 ± 2.71	5.91 ± 2.66	0.506	1.166
Cleanliness	8.59 ± 3.53	7.36 ± 3.32	4.246* (**0.040**)	6.122* (**0.014**)	7.18 ± 2.54	6.76 ± 3.07	0.601	0.794
Haplotype (G1 = *CGAAGG/CGAAGG*; G2 = non-*CGAAGG/CGAAGG*)								
N	123	84			178	95		
Total OCS	21.71 ± 7.55	23.49 ± 7.36	2.989† (**0.085**)	5.140* (**0.024**)	19.70 ± 7.53	19.87 ± 6.29	0.034	0.006
Compulsions	7.81 ± 3.61	8.24 ± 3.45	0.763	1.499	7.06 ± 3.47	6.92 ± 3.13	0.112	0.352
Obsessions	6.86 ± 2.77	6.89 ± 3.09	0.006	0.088	5.96 ± 2.82	5.97 ± 2.54	0.006	0.071
Cleanliness	7.03 ± 3.28	8.36 ± 3.24	8.558*** (**0.004**)	9.691*** (**0.002**)	6.68 ± 3.26	6.99 ± 2.94	0.581	0.414

†$p < .10$; *$p < .05$; **$p < .01$; ***$p < .05$, corrected for multiple comparisons *F* is without controlling for depression, anxiety and stressful life events. Adj. *F* is after controlling for depression, anxiety and stressful life events. Significant *p* values are shown in parentheses.

As shown in Fig. 1, six SNPs (*rs1042173*, *rs4325622*, *rs3794808*, *rs140701*, *rs4583306* and *rs2020942*) were in strong linkage and constructed a conserved haplotype block ($D' > 0.95$) covering from intron 3 to 3′ UTR of the *SLC6A4* gene. Three main haplotypes, *CGAAGG*, *AAGGAG* and *AAGGAA* (*rs1042173*| *rs4325622*| *rs3794808*| *rs140701*| *rs4583306*| *rs2020942*) showed respective frequencies of 0.78, 0.12 and 0.08. The homozygotes of the *CGAAGG* haplotype ($n = 301$) were assigned the label *CGAAGG/CGAAGG*, whereas the homozygotes and heterozygotes of the minor and other rare haplotypes were merged to a combined non-*CGAAGG/CGAAGG* group.[1] In terms of *5-HTTLPR*, individuals with *l/l* ($n = 52$) and *l/s* ($n = 219$) genotypes were merged together as in previous research (Kim et al., 2005). For *Stin2*, there were few participants with *10R/10R* ($n = 3$), *12R/13R* ($n = 2$), *12R/14R* ($n = 2$) and *12R/15R* ($n = 2$). Thus, *10R/10R* ($n = 3$) and *10R/12R* ($n = 68$) were merged together as the *10R* carriers while *12R/12R* ($n = 458$) and others were merged as the non-*10R* carriers.

General linear models (GLM) in SPSS for Windows (version 16) were used to examine the main and interactive effects of genetic variations and gender on OCS. To further investigate whether potential covariates could have accounted for such effects, we added depression, anxiety, stressful lift events into the above models as covariates. Finally, in order to examine whether genetic effects were specific for particular dimensions or all dimensions of OCS, we repeated the above analyses for each of the three dimensions of OCS.

Due to the linkage disequilibrium in the *SLC6A4* gene, we used the Bonferroni correction procedure proposed by Nyholt (2004). The effective number (Meff) of independent marker loci in the three genetic variants (the haplotype, *STin2* and *5-HTTLPR*) was calculated using the SNPSpD method (Nyholt, 2004), yielding an Meff of 2.49. Thus, for the general linear models of OCS, the significant threshold was adjusted by dividing the conventional alpha 0.05 by 2.49, resulting in 0.02. For the general linear models of three dimensions of OCS, the significant threshold was adjusted by dividing the conventional alpha 0.05 by the effective number of tests ($N = 3 \times 2.49$), resulting in 0.007.

3. Results

Significant gender main effects were found in OCS scores, *p*s < .01. Males scored higher than females in total OCS score as well as three dimensions. As shown in Table 2 and the left panel of Fig. 2, different polymorphisms of the *SLC6A4* gene were associated with OCS for the two genders. *5-HTTLPR* showed female-specific genetic effects on OCS, with the female minor allele carriers (*l/l and l/s)* displaying higher scores on total OCS than the female major allele homozygotes (*s/s*), $p = .008$. This result remained significant after taking into account OCS-related factors including depression, anxiety, and stressful life events, $p = .004$. Furthermore, these results survived correction for multiple tests. For males, however, *5-HTTLPR* was not significantly associated with OCS. This gender specificity was supported by a significant interaction between *5-HTTLPR* and gender, $F = 7.171$, $p < .01$. These results were consistent for the dimensions of Cleanliness ($F = 4.450$, $p < .05$) and Obsessions ($F = 6.49$, $p < .05$).

In contrast to the female-specific effect of *5-HTTLPR*, the haplotype block (*rs1042173*| *rs4325622*| *rs3794808*| *rs140701*| *rs4583306*| *rs2020942*) and *STin2* showed male-specific genetic effects (see Supplementary Table S1 for the same pattern of data for each SNP). As shown in Table 2 and the right panel of Fig. 2, male *CGAAGG/CGAAGG* carriers showed lower scores in total OCS (marginally at $p = .085$ without covariates and significantly at $p = .024$ with covariates of depression, anxiety, and stressful life events), and especially in the Cleanliness dimension ($p = .004$ without covariates and .002 with covariates), than did the male non-*CGAAGG/CGAAGG* carriers. The male-specific genetic effect of the haplotype on Cleanliness dimension also remained significant after correction for multiple tests. The interaction between the haplotype and gender on Cleanliness was marginally significant, $F = 2.782$, $p < .10$. Male *10R* carriers of *STin2* scored significantly higher in Cleanliness dimension than non-*10R* carriers, $p = .04$ without covariates and $p = .014$ with covariates. However, the male-specific effect of the *STin2* on Cleanliness did not survive

[1] The non-CGAAGG/CGAAGG group included AAGGAG/CGAAGG (n = 82), AAGGAA/CGAAGG (n = 54), AAAAGA/CGAAGG (n = 1), AAAAGG/CGAAGG (n = 3), AAGAGG/CGAAGG (n = 4), AAGGAA/AAAAGG (n = 1), AAGGAA/AAGGAA (n = 3), AAGGAA/CGAGAG (n = 1), AAGGAG/AAAAGA (n = 1), AAGGAG/AAGGAA (n = 13), AAGGAG/AAGGAG (n = 8), AAGGAG/CGAGAA (n = 1), AAGGAG/CGGGAA (n = 2), AAGGGG/AAGGAG (n = 1), AAGGGG/CGAAGG (n = 1), CGAGAA/CGAAGG (n = 2), CGAGAG/CGAAGG (n = 3), CGGGGG/CGAAGG (n = 1).

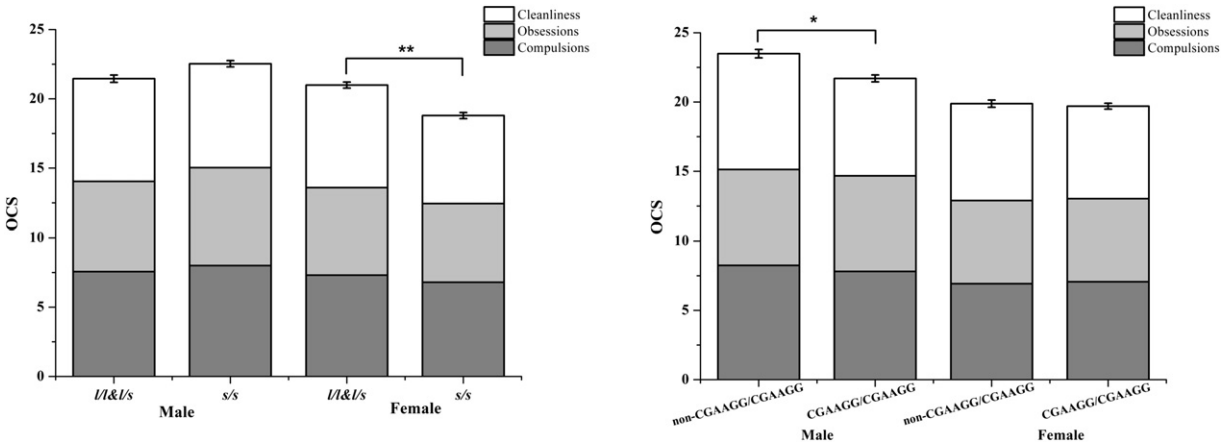

Fig. 2. Male-specific and female-specific genetic effects of the haplotype block and *5-HTTLPR* on OCS. Error bars represents standard error (SE) in the figure.

correction of multiple tests. There were no significant associations between the *SLC6A4* genetic variants and depression, anxiety and stress life events.

4. Discussion

The current study was the first to investigate gender-specific effects of the whole *SLC6A4* gene on OCS in a large sample of normal Chinese college students. It was also the first to consider the confounding effects of depression, anxiety and stressful life events when examining genetic effects on OCS. We found significant gender differences in OCS, with males scoring higher in total OCS and its three dimensions than did females. These results were consistent with previous studies that used various scales measuring for OCS and OCD (Richter et al., 1994). Interestingly, both the current study and that of Lensi et al. (1996) found that gender differences were especially large in the dimension of Obsessions. It should be noted that age of onset for OCD has been found to differ by gender, with males having an earlier onset. For example, a recent study of a Chinese clinical OCD sample found that male patients showed an average onset age of around 20 years while females around 27 years (Li et al., 2009). Considering that the current sample had an average age of 20 years, the gender differences in OCS we found may be specific to this age group.

Second, the current study found that different sections of the *SLC6A4* gene were related to OCS for males and females. The promoter region's polymorphism (*5-HTTLPR)* was related to females' OCS, but the haplotype block containing the gene (and to some extent, *STin2*) was related to males' OCS. This intriguing finding is in line with the growing literature of gender-specific genetic effects on behaviors and neural correlates of behaviors (Cahill, 2006). Biological and physiological differences between the sexes in sex chromosomes (X- and Y-linked genes and proteins), gonadal hormone secretions (Ngun et al., 2011), and autosomal chromosomes and general neurochemical mechanisms (Bocklandt and Vilain, 2007; Sanchez and Vilain, 2010) can all contribute to gender differences in behaviors. Recent studies have documented specific examples of gender-modulated genetic effects of catechol-o-methyltransferase (*COMT*) on personality traits (Chen et al., 2011), and those of the monoamine oxidase A (*MAOA*) on brain circuitry underlying aggression (Buckholtz and Meyer-Lindenberg 2008) and harm avoidance (Buckholtz et al., 2008). For the *SLC6A4* gene, researchers have found gender-specific associations of *5-HTTLPR* with psychiatric disorders such as depression (Baune et al., 2008; Brummett et al., 2008) and anxiety (Mizuno et al., 2006). A clinical pharmacological study also found gender-specific effects of *5-HTTLPR* on treatment effectiveness of selective serotonin reuptake inhibitors (SSRIs) on depression (Smits et al., 2008), suggesting intrinsic gender-specific biochemical and physiological differences in the function of *5-HTTLPR*. In terms of OCS/OCD, our results on *5-HTTLPR* were in line with a recent case–control review study in which the *l* allele of *5-HTTLPR* was shown to be significantly associated with OCD in females (Dickel et al., 2007). The link between the *l* allele and OCD is consistent with the hypothesis that abnormally low serotonin neurotransmission in the brain plays an important role in the pathology of OCD since the *l* allele has been reported to be associated with high *SLC6A4* expression, consequently leading to a relatively low serotonin neurotransmission (Greenberg et al., 1999; Heils et al., 1996; Hranilovic et al., 2004). Clinical and pharmacological studies found that selective serotonin reuptake inhibitors (SSRIs), which facilitate serotonin neurotransmission, are effective choices for medical treatments of OCD (Geller et al., 2003; Goddard et al., 2008). OCD patients also showed abnormally reduced serotonin transporter availability in limbic and paralimbic brain areas, especially in the late-onset OCD patients (Hasselbalch et al., 2007; Hesse et al., 2011). Not all studies, however, found this pattern of results. For example, the only other study conducted with a community sample found that the OCPD trait was linked to the *s* allele among females, but the *l* allele among males (Blom et al., 2011). A number of differences between this study and the current study, including ethnicity, age range of the two samples, and different measures used, may have contributed to this inconsistency. As mentioned earlier, substantial diversities in the allele frequencies of *5-HTTLPR* in different ethnic populations may indicate different behavioral adaptive functions of the *SLC6A4* polymorphisms in different cultures and different living environments (Chiao and Blizinsky, 2010). Much more research is needed to understand the dynamic interactions between genes and environments.

In contrast to *5-HTTLPR*, both *STin2* and the haplotype block (*rs1042173*| *rs4325622*| *rs3794808*| *rs140701*| *rs4583306*| *rs2020942*) showed male-specific genetic effects on OCS. Male *10R* carriers (mostly *10R/12R*) of *STin2* showed higher scores on Cleanliness dimension than did the *non-10R* males. Male non-*CGAAGG/CGAAGG* carriers showed higher scores on total OCS and Cleanliness than did male *CGAAGG/CGAAGG* carriers. Few previous studies have examined *STin2* and none studied the haplotype in terms of their potential associations with OCS or OCD. A recent study found that *9R/10R* was significantly associated with OCD in European ancestry females (Voyiaziakis et al., 2011), consistent with our results albeit

for a different gender. Two other case–control studies, one with Spanish (Baca-Garcia et al., 2007) and the other with Japanese (Ohara et al., 1999) showed that the *12R* allele was associated with the clinical patient group consisting of OCD, panic, phobias and general anxiety disorders in the former study and *12R/12R* and *10R/12R* were associated with OCD as compared to other psychiatric patients and controls in the latter study. However, these two studies did not analyze data by gender.

As for the specific evolutionary, biochemical or physiological mechanisms of the gender × haplotype interactions on OCS, we can only make some reasonable speculations. From the *HapMap* data (www.hapmap.org; also see Supplementary Figure S1), the current haplotype block belongs to a huge highly-linked region spanning part of the *SLC6A4* gene, the whole *NSrp70* gene (also termed the *CCDC55*gene) (Kim et al., 2011), and the *EFCAB5* gene. This large linkage disequilibrium (LD) block suggested that it has experienced strong recent selection (Wang et al., 2006). The haplotype linked to lower OCS showed stronger LD than the haplotype linked to higher OCS, suggesting positive selection for low OCS. Although evolutionary psychologists (Abed and de Pauw, 1998) have speculated that moderate versions of compulsive behavior (e.g., frequent checks of hygiene and the presence of enemies, hoarding) might have had evolutionary advantages during early periods of human evolution, our study suggests recent deselection of compulsive behaviors. It should be noted that, however, that because this is a large LD block, the selection of a particular haplotype at this locus may have acted on any of the three genes in the block. Future research can address this intriguing conjecture of recent deselection of OCS/OCD and the role of other genes.

Finally, because the *SLC6A4* gene has been linked to several affective disorders, it was not clear whether its associations with OCS/OCD were due to the latter's shared variance with other disorders. In this study, we reanalyzed our data by controlling for several common confounding factors such as depression, anxiety, and stressful life events, and showed that the *SLC6A4* gene's link may be specific to OCS/OCD, particularly its Cleanliness dimension. Future studies should take into consideration the different subtypes of OCS/OCD.

Three main limitations of the current study need to be mentioned. First, the current study did not genotype tri-allelic *5-HTTLPR*. A single nucleotide polymorphisms *rs25331* on the *l* allele results in three alleles: l_A, l_G and *s* (Hu et al., 2006; Wendland et al., 2008), in which l_G and *s* both reduce *SLC6A4* expression. Nevertheless, the frequency of the minor *G* allele of *rs25531* in Asians was estimated to be 9.1% (Zhang et al., 2009). Thus, although the current study did not differentiate l_G and l_A (*s/s*: $n = 298$, *l/s*: $n = 219$; *l/l* = 52), the low frequencies of the *l* allele and the *G* allele of *rs25531* were not expected to dramatically alter the results. Second, this was a gene-behavior association study in normal college students. The biochemical and physiological functions of the haplotype block (*rs1042173*| *rs4325622*| *rs3794808*| *rs140701*| *rs4583306*| *rs2020942*) and the linked functional loci were not explored in the present study. Previous studies found that variations in intron or noncoding regions can also exert transcriptional suppression of the genes, influence mRNA secondary structure (Nackley et al., 2006), and regulate gene expression and splicing (Zhang et al., 2007). Such biochemical work needs to be conducted specifically for the haplotype identified in the current study. Third, the present study was conducted with one ethnic group (i.e., Han Chinese college students) to avoid potential population stratification problem. These results should be compared to the results of other ethnic populations in the future. Finally, we limited our sample to a homogeneous group of college students. Psychologists have lamented for decades on the "college sophomore" phenomenon in social psychological research (Henry, 2008; Sears, 1986). Because of potential gene–environment interactions, it is not clear whether our results can be generalized to other age groups. Nevertheless, college enrollment (or selection effects) may have more to do with characteristics such as intelligence, motivation, and ideologies than with OCS, because OCS covers many areas of daily life that are common inside and outside of the college environment. Furthermore, college enrollment is gradually becoming the norm rather than the exception even in China. That said, future behavioral and genetic studies of OCS should directly compare college and non-college students and provide information about the role of environments in OCS and in modulating the effects of genes on OCS.

In conclusion, the current study observed the gender-specific effects of the *SLC6A4* polymorphisms on OCS in normal Chinese college students. These effects were independent of depression, anxiety and stressful life events. The haplotype block (*rs1042173*| *rs4325622*| *rs3794808*| *rs140701*| *rs4583306*| *rs2020942*) spanning from intron 3 to 3′ UTR and *STin2* in intron 2 showed male-specific genetic effects on OCS, with the non-*CGAAGG/CGAAGG* genotypes associated with higher OCS scores. Male *10R* carriers of *STin2* had higher Cleanliness scores compared to male *non-10R* carriers. In contrast, *5-HTTLPR* showed female-specific genetic effects, with the *l/l* and *l/s* genotypes linked to higher OCS scores. These findings provided specific evidence for the gender-specific role of the *SLC6A4* gene in the continuum of OCS, confirmed the contributions of disturbed serotonin neurotransmission to the pathology of OCD, and should be of relevance to the diagnosis and treatment of OCD.

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Contributors

Chuansheng Chen, Robert K. Moyzis, Qi Dong, Jun Li, Gui Xue designed the study. Qinghua He, Xuemei Lei, Jin Li, He Li, Chunhui Chen, Bi Zhu, Zhongyu Cao, Xiongying Chen, wrote the protocol and collected genetic and behavioral data. Sufang Li took part in collecting of genetic data. Xuemei Lei undertook the analysis and managed the literature searches and wrote the first draft of the manuscript. Anna Shan Chun Hsu took part in editing the manuscript. All authors contributed to have approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.jpsychires.2012.05.002.

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