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

Xuemei Lei [a,b], Chuansheng Chen [b,**], Qinghua He [d], Chunhui Chen [a], Robert K. Moyzis [c], Gui Xue [a,d], Xiongying Chen [a], Zhongyu Cao [a], Jin Li [a], He Li [a], Bi Zhu [a], Anna Shan Chun Hsu [b], Sufang Li [a], Jun Li [a], Qi Dong [a,*]

[a] *State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China*
[b] *Department of Psychology and Social Behavior, 4201 Social & Behavioral Sciences Gateway, University of California, Irvine, CA 92697-7085, USA*
[c] *Department of Biological Chemistry and Institute of Genomics and Bioinformatics, University of California, Irvine, CA, USA*
[d] *Department of Psychology, University of Southern California, Los Angeles, CA 90089, USA*

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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

* Corresponding author. Tel.: +86 010 58807615; fax: +86 010 58808470.
** Corresponding author. Tel.: +1 949 824 4184; fax: +1 949 824 3002.
E-mail addresses: cschen@uci.edu (C. Chen), dongqi@bnu.edu.cn (Q. Dong), bnuxuemei@gmail.com (X. Lei).

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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.