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Comprehensive Family-Based Association Study of the Glutamate Transporter Gene SLC1A1 in Obsessive-Compulsive Disorder

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Abstract

SLC1A1 encodes a neuronal glutamate transporter and is a promising candidate gene for obsessive-compulsive disorder (OCD). Several independent research groups have reported significant associations between OCD and single nucleotide polymorphisms (SNPs) in this gene. Previously, we evaluated 13 SNPs in, or near, SLC1A1 and reported a strong association signal with rs301443, a SNP 7.5 kb downstream of the gene (Shugart et al., 2009). The aims of the current study were first, to further investigate this finding by saturating the region around rs301443; and second, to explore the entire gene more thoroughly with a dense panel of SNP markers. We genotyped an additional 111 SNPs in or near SLC1A1, covering from 9kb upstream to 84kb downstream of the gene at average spacing of 1.7kb per SNP, and conducted family-based association analyses in 1,576 participants in 377 families. We found that none of the surrounding markers were in linkage disequilibrium with rs301443, nor were any associated with OCD. We also found that SNP rs4740788, located about 8.8 kb upstream of the gene, was associated with OCD in all families ($P=0.003$) and in families with male affecteds ($P=0.002$). A 3-SNP haplotype (rs4740788-rs10491734-rs10491733) was associated with OCD in the total sample ($P=0.00015$) and in families with male affecteds ($P=0.0007$). Although of nominal statistical significance considering the number of comparisons, these findings provide further support for the involvement of SLC1A1 in the pathogenesis of OCD.

Keywords

obsessive-compulsive disorder; glutamate transporter; candidate gene

Introduction

SLC1A1 is a neuronal glutamate transporter gene and is a promising candidate gene for obsessive-compulsive disorder (OCD) (Leckman and Kim, 2006). This gene is expressed in the cortex, striatum, and thalamus, where it is important for glutamate neurotransmission (Kanai and Hediger, 2004). Neuroimaging studies have found that glutamatergic concentrations are lower in the anterior cingulate and greater in the caudate in pediatric OCD patients compared to controls, and that glutamatergic levels in the caudate decrease to control levels following treatment with serotonin reuptake inhibitors (Rosenberg et al., 2000; Rosenberg et al., 2004). The first genome-wide linkage scan of OCD found suggestive evidence of linkage of early-onset OCD to a region of chromosome 9p24 that includes this gene (Hanna et al., 2002); a linkage peak very close to this region was subsequently found in 50 OCD pedigrees, and pedigree-based analyses identified two markers associated with OCD in this region (Willour et al., 2004).

Four research groups have reported associations between OCD and SNPs in SLC1A1. Dickel et al. (2006) reported association with two SNPs, and also detected a deletion in a flanking region of the gene in a large multigenerational family. In addition, they identified a 2-SNP haplotype which was under-transmitted in male probands but not female probands. Arnold et al. (2006) found an association with three SNPs in this gene in families of patients with OCD. Further, they conducted a haplotype-based association analysis considering two SNPs jointly and detected significant over-transmission to male but not female offspring. Stewart et al. (2007) reported an association between a 3-SNP haplotype of SLC1A1 and OCD in families with male probands. It is noteworthy that SNPs in this haplotype overlap with those reported by Dickel et al. (2006). More recently, a large case-control study found that two 3-SNP haplotypes in SLC1A1 were significantly correlated with expression of the gene, and they were significantly associated with OCD in both male and female cases (Wendland et al., 2009).

In a family-based association study, our group examined the association between OCD and 13 SNPs within, or in proximity to, this gene (Shugart et al., 2009). Although we did not replicate findings for the significant SNPs found in the previous studies, we did detect a strong association signal with another SNP, rs301443, about 7.5 kb downstream of the gene (odds ratio=3.5, 95% CI=2.7-4.5). This relationship was much stronger in families with male than female affecteds.

The aims of the current study were first, to further investigate this finding by saturating the region around rs301443; and second, to explore the entire gene more thoroughly with a dense panel of SNP markers. We genotyped an additional 111 SNPs in or near SLC1A1, covering from 9kb upstream to 84kb downstream of the gene, at average spacing of 1.7kb per SNP, and conducted family-based association analyses in 377 previously-studied families.

Materials and Methods

Study sample

The OCD Collaborative Genetics Study (OCGS) is an NIMH-funded collaboration among investigators at six sites in the U.S. (Brown University, Columbia University, Johns Hopkins

University, Massachusetts General Hospital, University of California at Los Angeles, and the National Institute of Mental Health). The methods of the study are described in detail elsewhere and summarized below (Samuels et al., 2006).

The OCGS ascertained families with OCD-affected sibling pairs and extended these when possible through affected first- and second-degree relatives. Subjects were recruited into the study from outpatient and inpatient clinics, referrals from clinicians in the community, web sites, media advertisements, self-help groups, and annual conventions of the Obsessive Compulsive Foundation (OCF). To qualify as “affected”, a subject had to meet Diagnostic and Statistical Manual DSM-IV OCD diagnostic criteria at some time in his/her life (American Psychiatric Association, 1994). Probands were included if, in addition to meeting DSM-IV criteria, their first onset of obsessions and/or compulsions occurred before 18 years of age. Probands with schizophrenia, severe mental retardation, Tourette syndrome (TS), or secondary OCD (OCD occurring exclusively in the context of depression) were excluded. Subjects had to be at least 7 years old to participate in the study. Written, informed consent (or assent, for children) to study procedures was obtained before the clinical interview. The protocol was approved by the institutional review board at each site.

Diagnostic assessment

Diagnostic evaluations were conducted by psychiatrists and PhD-level psychologists experienced with clinical evaluations using the OCGS assessment package, modified and developed for the study, as a semi-structured format for the evaluation of psychopathology. The OCD section was adapted from the Schedule for Affective Disorders and Schizophrenia-Lifetime Anxiety version (Mannuzza et al., 1986) and included detailed screening questions; the Yale Brown Obsessive Compulsive Scale and Symptom Checklist (Goodman et al., 1989), and additional questions on onset, course, and treatment of symptoms. A similar section was developed for assessing tics, Tourette disorder, and other tic disorders. The Structured Clinical Interview for DSM-IV (Spitzer et al., 1997) was used to assess other major Axis I diagnoses. In adults, items from the Structured Instrument for the Diagnosis of DSM-IV Personality Disorders (Pohl, 1997) were used to assess the presence of specific personality disorders. The Family Informant Schedule and Criteria (Mannuzza et al., 1985) was used to obtain additional information about each subject from a knowledgeable informant. For subjects who had received psychiatric treatment, consent was obtained to review relevant medical records and to contact treatment providers, if such information was deemed useful for making diagnoses. Examiners completed a narrative formulation for each case.

The JHU diagnostic assignment checklist was used to collate all the clinical information from a variety of sources (the semi-structured direct interview, case formulation, informant interview, and medical records). The checklist presents logical algorithms with specified rules, allowing assignment of definite, probable, absent, or unknown for each disorder. All psychiatric diagnoses were made according to strict DSM-IV criteria (American Psychiatric Association, 1994). At each site, each case was reviewed independently by two expert diagnosticians who reviewed all case materials. Assessments from all other sites were reviewed at JHU to ensure diagnostic conformity. If all required criteria for a disorder were met, then a ‘definite’ diagnosis was given. If any required criterion was clearly not met, then the diagnosis was considered ‘absent’. If it seemed likely that the subject had the diagnosis, but the diagnosticians could not be certain of a given criterion required for definite diagnosis, then the diagnosis was made at the ‘probable’ level. If the diagnosticians could not be sure of the presence or absence of a given diagnosis, then that diagnosis was coded as “unknown.”

Molecular genotyping

Blood samples were collected from all affected probands, their parents, and their affected relatives. If available, blood samples from unaffected relatives also were collected to help determine phase for computing identity by descent (IBD) sharing probabilities.

SNP markers were genotyped using the Illumina BeadArray system with the GoldenGate assay at the deCODE service laboratory. A total of 124 SNPs were selected from the Illumina1M chip, covering from 9kb upstream to 84kb downstream of SLC1A1, with an average spacing of 1.7kb, in addition to the 13 SNPs genotyped previously in this sample (Shugart et al., 2009). Two of the SNPs were not successfully genotyped, and 11 were excluded because of low minor allele frequency (<0.008); therefore, 111 SNPs were included in the analysis. Seventeen of the SNPs were within 20kb of rs301443, with average spacing of 1.3 kb. (The LD structure of the 124 SNPs is illustrated in Supplement Figure 1). Three of the SNPs had call rates between 85-90%, and all others had call rates above 90%. All SNPs presented in Table I had call rates above 98%.

In addition to error checking performed by the service site, PEDCHECK was used for more complicated genotype error checking for each individual in the data set (O'Connell and Weeks, 1998). Those genotypes with a posterior probability of being incorrect of greater than 75% were removed from the analysis, as recommended by Douglas et al. (2002). In addition, we used the PLINK program (Purcell et al., 2007) to check for Mendelian inconsistencies. A total of 100 genotypes were removed; these genotypic errors appear to be randomly distributed and were not consistently observed in the same set of families. PLINK also was used to check for deviations from Hardy-Weinberg equilibrium. SNPs with $P \leq 0.001$ were to be excluded from the analysis, although none were found to exceed this threshold. Only founders were considered for the Hardy-Weinberg calculations; their offspring were not included.

A total of 1,576 participants in 377 families were genotyped in this study. A total of 999 of these individuals (377 affected males and 622 affected females) were diagnosed with definite or probable OCD and were included in the genetic association analyses.

Statistical Analysis

We used PBAT for these family-based association analyses (Lange et al., 2004). PBAT allows inclusion of extended pedigrees as well as nuclear families, and also allows users to choose the assumed mode of inheritance. Although the mode of inheritance is unknown, segregation analysis of families collected in the Johns Hopkins OCD Family Study suggested that OCD segregates in a dominant manner (Nestadt et al., 2000a); thus, we chose to use the dominant model for all the analyses conducted in this study for both single SNP and haplotype-based association analyses. We used the PBAT implementations for Windows XP that are available at the website of Dr. Christoph Lange (www.biostat.harvard.edu/~clange/default.htm).

We conducted PBAT analysis on the 111 genotyped SNPs. We first analyzed the entire data set and then stratified the data by the sex of the affecteds in each family. In the male-only dataset, we coded the affection status of female affecteds as "unknown" and, in the female-only dataset, we coded the affection status of male affecteds as "unknown", allowing us to compare the contribution to the association signal of the families with male affecteds with that of the families with female affecteds (Shugart et al., 2009). Genotype relative risk estimates were calculated for the heterozygous and two homozygous genotypes, because the GRR software allows computation of these estimates only for the additive model. No adjustment was made for the number of statistical comparisons.

Results

Of the 111 SNPs genotyped, 7 were associated with OCD with a P -value < 0.01 in analyses which included all families, only families with male affecteds, or only families with female affecteds (Table I). None of the SNPs adjacent to rs301443 were associated with OCD. SNP rs4740788 was associated in the total sample ($P=0.003$), with genetic relative risk of 1.88 (95% CI, 1.38-2.57) for the heterozygous (GA) and 2.87 (95% CI, 0.90-9.26) for the homozygous (GG) genotypes. This SNP also was associated with OCD in the families with male affecteds ($P=0.002$), but not in the families with female affecteds. Three additional SNPs, rs10758631, rs16921669, and rs4740796, were associated only in the families with male affecteds ($P<0.006$). SNPs rs10491734 and rs7856675 were associated with OCD in the total sample ($P=0.005$ and $P=0.003$, respectively). One SNP, rs928209, was associated with OCD only in the families with female affecteds ($P=0.005$).

We then conducted haplotype analysis in PBAT to test for associations between OCD and the SNPs identified above. We used the “solid spine of LD” approach in Haploview to define haplotype blocks. None of the genotyped SNPs was found to be in linkage disequilibrium with rs301443. A haplotype composed of 3 SNPs (rs4740788-rs10491734-rs10491733) was associated with OCD in the total sample ($P=0.00015$), and in the families with male affecteds ($P=0.0007$). Another haplotype composed of 2 SNPs (rs7856675-rs3780415) was associated in families with male affecteds ($P=0.003$), but not in analyses including all families, or only families with female affecteds; however, other SNPs in this block were not individually associated with OCD.

Discussion

We previously reported that rs301443, located about 7.5 kb downstream of SLC1A1, was strongly associated with OCD in these families, and we suggested that this SNP may be located in a region involved in the regulation of SLC1A1 expression (Shugart et al., 2009). In the current study, none of the genotyped SNPs adjacent to rs301443 was found to be in linkage disequilibrium with it. Therefore, this SNP remains an important candidate variant for OCD in these families. Interestingly, individuals with autism spectrum disorders often exhibit compulsive-like repetitive behaviors, and modest associations have been reported for SNPs in SLC1A1 and these disorders (Brune et al., 2008; Gadow et al., 2010). Moreover, a recent case-control study reported that a SNP in the JMJD2C gene in 9p24 is associated with autism spectrum disorders, although rs301443 is much closer to SLC1A1 than to JMJD2C (Kanttojärvi et al., 2010).

We also found that SNP rs4740788, located roughly 8.8 kb upstream of the gene, was associated with OCD in all families and in families with male affecteds. Further, we found that a haplotype including this SNP (rs4740788-rs10491734-rs10491733) was associated with OCD in the total sample and in the families with male affecteds. Willour et al. (2004) and Wendland et al. (2009) also reported associations with markers upstream of the gene; it would be useful to determine the degree of linkage disequilibrium between markers found in these and the current study. We hypothesize that rs4740788 or nearby SNPs may represent another region involved in regulation of the SLC1A1 gene and may influence the development of OCD through expression of the neuronal glutamate transporter. Two mutation screens have failed to find any known functional mutations in exons or flanking intronic regions of SLC1A1 in OCD pedigrees (Veenstra-VanndereWeele et al., 2001; Wang et al., 2009), although the latter study identified a “potentially functional variant” in a proband and affected mother in one family (Wang et al., 2009).

Previous family-based association studies have reported that the association between OCD and variants in SLC1A1 are specific to families with male probands or to male affecteds (Dickel et al., 2006; Arnold et al., 2006; Stewart et al., 2007; Shugart et al., 2009), although this was not found in a more recent case-control study (Wendland et al., 2009). Male-specific associations with OCD have been reported for alleles of other genes, for example, catechol-O-methyltransferase (COMT) (Karayiorgou et al., 1997 and 1999; Pooley, Fineberg, and Harrison, 2007), although the findings have been inconsistent (Alsobrook et al., 2002). A male-specific association between OCD and monoamine oxidase A (MAO-A) also has been reported (Karayiorgou et al., 1999), although another study found an association only in women (Camerena et al., 2001). Sex-specific genetic associations have been reported for several other psychiatric disorders and may reflect regulation of gene expression by sex hormones (Goes et al. 2010; Harrison and Tunbridge, 2008; Carroll et al., in press).

This study was designed to explore SLC1A1 for unidentified variants associated with OCD, and we genotyped and analyzed 111 SNPs. We did not correct for multiple comparisons, and we recognize that the findings, while nominally significant, would not have remained statistically significant at the $P < 0.05$ level after correction. Even though one of the largest family-based association studies of OCD to date, our study may not have sufficient power to detect, as statistically significant, variants of modest effect. Nevertheless, these findings, in an important candidate gene for OCD, are worthy of investigation in future studies.

There is evidence that the genetic etiology of OCD is complex, and the results reported here and in previous studies are consistent with substantial allelic heterogeneity in the association between OCD and SLC1A1. Moreover, associations of OCD with additional functional candidate genes have been reported (Nestadt et al., 2010). Elucidating the genetic etiology of OCD also is complicated by the clinical heterogeneity of the disorder, which may reflect etiologic heterogeneity (Miguel et al., 2005). For example, our group reported evidence for significant linkage of compulsive hoarding to chromosome 14 in OCD families (Samuels et al., 2007), as well as evidence for gene-gene interaction between regions on chromosomes 9p and 14q (Liang et al., 2008). Interestingly, Wendland et al. (2009) reported a SNP in the SLC1A1 gene that was correlated with gene expression and was significantly associated with hoarding in OCD (Wendland et al., 2009). These findings merit further investigation of the role of the SLC1A1 gene in the development of specific clinical subtypes and dimensions of OCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The D prime of the 13 SNPs. Haplotype blocks are defined by the solid spine approach implemented in Haploview.

TABLE I

PBAT Analysis Results for SNPs Associated with OCD at $P < 0.01$

Marker	Location (NCBI36)	Allele	Frequency	All		Female		Male	
				HW parents	P-value	HW parents	P-value	HW parents	P-value
rs4740788	4471668	G	0.094	0.9308	0.0032668	0.931	0.3411712	0.931	0.0021976
rs10491734	4472706	A	0.479	0.9993	0.0052122	0.999	0.0345472	0.999	0.1106539
rs928209	4532890	G	0.432	0.9867	0.0283636	0.987	0.0048930	0.987	0.9559737
rs10758631	4536319	A	0.471	0.9337	0.0537302	0.934	0.9142463	0.934	0.0052842
rs7856675	4545305	A	0.922	0.9960	0.0027002	0.996	0.0546679	0.996	0.0522041
rs301443	4584919	C	0.663	0.9990	0.0000670	0.999	0.0767045	0.999	0.0002732
rs16921669	4625232	A	0.057	0.7910	0.3863275	0.791	0.2189218	0.791	0.0044464
rs4740796	4626900	G	0.055	0.7910	0.3863275	0.791	0.2189218	0.791	0.0044464

HW = Hardy Weinberg