Common and rare alleles of the serotonin transporter gene, SLC6A4, associated with Tourette disorder

Pablo R Moya1, Jens R Wendland1, Liza M Rubenstein1, Kiara R Timpano2, Gary A Heiman3, Jay A Tischfield3, Robert A King4, Anne M Andrews5, Samanda Ramamoorthy6, Francis J McMahon7, and Dennis L Murphy1

1Laboratory of Clinical Science, NIMH-Intramural Research Program, Bethesda, MD
2Department of Psychology, University of Miami, Coral Gables, FL
3Human Genetics Institute of New Jersey and Department of Genetics, Rutgers University, Piscataway, NJ
4Child Study Center of Yale University, New Haven, CT
5Semel Institute for Neuroscience and Human Behavior and California Nano Systems Institute, University of California, Los Angeles, CA
6Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA
7Human Genetics Branch, NIMH-Intramural Research Program, Bethesda, MD

Abstract

BACKGROUND—To evaluate the hypothesis that functionally over-expressing alleles of the serotonin transporter gene SLC6A4 are present in Tourette disorder (TD), just as we have found in obsessive compulsive disorder (OCD), we evaluated TD probands (N=151) and controls (N=858).

METHODS—We genotyped the refined 5-HTTLPR/rs25531 locus and the associated rs25532 variant in the SLC6A4 promoter plus the rare coding variant SERT I425V.

RESULTS—The higher-expressing 5-HTTLPR/rs25531 L_A allele was more prevalent in TD probands than controls (χ²=5.75, p=0.017, OR=1.35), and in a secondary analysis, surprisingly found to be significantly more frequent in probands with TD alone than in those with TD plus OCD (Fisher’s exact test, p=0.0006, OR=2.29). Likewise, the higher-expressing L_AC haplotype (5-HTTLPR/rs25531/rs25532) was more frequent in TD probands than controls (p=0.024, OR=1.33) and likewise in the TD alone versus TD plus OCD group (p=0.0013, OR=2.14). Further, the rare gain-of-function SERT I425V variant was found in three male siblings with TD and/or OCD and in their father. The cumulative count of SERT I425V thus becomes 1.57% in OCD/TD spectrum.
conditions vs. 0.15% in controls, with a recalculated, family-adjusted significance of \( \chi^2 = 15.03, p < 0.0001, \text{OR} = 9.0 \) (total worldwide genotyped=2914).

**CONCLUSIONS**—This report provides a unique combination of common and rare variants in one gene in TD, all found to be associated with *SLC6A4* gain of function. Thus, altered SERT activity represents a potential contributor to serotonergic abnormalities in TD. Present results call for replication in a similarly intensively evaluated sample.

**Keywords**

*SLC6A4; SERT; Tourette; serotonin; 5-HTTLPR; SERT I425V*

**INTRODUCTION**

Tourette disorder (TD) is a complex neurodevelopmental disorder characterized by chronic, fluctuating, involuntary motor and vocal tics. Comorbidity is a hallmark feature of TD, particularly with respect to obsessive-compulsive disorder (OCD) (up to 60%) and attention deficit hyperactivity disorder (ADHD) (~40%)\(^1\)\(^–\)\(^3\). These comorbidity patterns are striking in that individuals with a primary OCD or ADHD diagnosis have lower rates of comorbid TD (<10%, although still relatively high compared to the general population)\(^1\)\(^–\)\(^4\). Family studies show that tic disorders are increased in frequency in relatives of OCD probands and that the frequency of TD, TD plus OCD and also OCD alone are higher in the relatives of TD probands\(^5\). Taken together, these data suggest a possible etiological connection between these three disorders. Better understanding of this connection is of key importance since TD (0.3 – 1%), OCD (2.5%) and ADHD (5–10% in children, 2% in adults) are major health burdens, affecting all populations worldwide. While TD-related tics seem to diminish over the lifespan, OCD and to some extent ADHD can be life-long, impairing disorders which are only partially responsive to present treatments\(^6\)\(^–\)\(^8\).

Among specific genes recently investigated in neuropsychiatric disorders including OCD and ADHD, the serotonin transporter (SERT) gene, *SLC6A4* stands out. *SLC6A4* maps to chromosome 17q11.2 and is composed of 14 exons spanning 40 kb. The protein, SERT, has 603 amino acids and twelve transmembrane domains regulating the neurotransmitter reuptake and serotonin accumulation in multiple cell types. A 43 bp indel in the promoter region, the 5-HTTLPR (serotonin transporter-linked polymorphic region) modulates *SLC6A4* expression. At the 5-HTTLPR locus, the short (S) allele shows lower expression compared to the long (L) allele\(^9\). When the G allele of rs25531 is present with the 5-HTTLPR Long (L) allele, the resulting L\(_G\) allele has reduced expression comparable to the short (S) allele, rendering the L\(_A\) allele as the only truly high-expressing variant\(^10\).

Additional functional refinement of *SLC6A4* promoter variants was suggested by us in 2008, when we showed that the functional C>T rs25532 further modulates 5-HTTLPR/ rs25531 activity, indicating that L\(_{\text{AC}}\) is the truly highest-expressing haplotype\(^11\). Other functional polymorphisms known to affect *SLC6A4* expression and function in humans and other species include alternative splicing involving exons 1A, B and C; an intronic (STin2) VNTR, miR-15a/miR-16-mediated regulation as well as additional variant\(^12\)\(^–\)\(^15\). Since the first report describing the *SLC6A4* 5-HTTLPR affecting expression and being associated with anxiety-related personality traits\(^9\), there has been a constantly growing literature describing altered SERT expression and function associated with multiple disorders including anxiety spectrum disorders like OCD, bipolar disorder, depression, ADHD, autism and neurodevelopmental and peripherally-based disorders of cardiovascular, bone, gastrointestinal, endocrine and other systems\(^10, 15\)\(^–\)\(^18\).
The present report provides the first comprehensive assessment of TD probands and healthy controls for functional variants in the SLC6A4 gene. Based upon our prior investigations of these variants in OCD, we evaluated the primary hypothesis that TD and OCD might share similar gain-of-function contributions from these functional SLC6A4 gene variants. We investigated the multiallelic 5-HTTLPR/rs25531 locus found to be associated with OCD in case-control and family studies.\(^9,10,19\) We also evaluated contributions to TD from rs25532, investigated in OCD and also shown to have a greater-functioning C allele.\(^11\) Finally, we genotyped the rare SLC6A4 coding variant SERT I425V that produces enhanced SERT expression, serotonin uptake and impaired regulation.\(^20–24\) Thus, we considered whether a combination of common and rare alleles in SLC6A4 might comprise plausible contributions to TD.

**METHODS**

**Subjects**

Unrelated TD probands (N=151) were all European ancestry subjects from the New Jersey Center for Tourette Syndrome Sharing Repository maintained by the Rutgers University Cell and DNA Repository.\(^25\) Methods for clinical evaluations are described elsewhere.\(^25\) Briefly, consenting subjects (or their legal guardians) completed a self-report questionnaire which included sub-scale assessments on tic disorders (adapted from YGTSS),\(^26\) OC disorders (adapted from the Dimensional Yale-Brown Obsessive-Compulsive scale),\(^27\) and ADHD checklists (see\(^25\) for details). Final DSM-IV-TR diagnoses were made by an experienced child psychiatrist based upon review of the self-report questionnaires and by direct semi-structured interview. Cases were routinely “flagged” for atypical TD presentation or for potentially confounding conditions such as congenital abnormalities or others, as previously described.\(^25\) Healthy controls were from three independent sources: (1) human random control panels 1 and 2 (N=192) consisting of apparently healthy, UK European ancestry blood donors obtained from the European Collection of Cell Cultures (Sigma-Aldrich, St. Louis, MO, USA); (2) self-declared healthy US European ancestry subjects (N=200) obtained from the Coriell cell repository (Camden, NJ, USA), and (3) self-declared healthy volunteer undergraduate students of European ancestry (N=466) from a large Southeastern university who participated in a separate study of genes and personality in return for partial course credit. All studies were conducted under protocols approved by the Rutgers University Institutional Review Board for the TD probands and by the Human Subjects Committee at Florida State University. Written informed consent was obtained from all adult participants (or, at Rutgers, their legal guardians, with written assent for minors). As only the third control group was evaluated by self-report and standard scales, we cannot rule out the occurrence of TD or OCD within the control groups; however frequencies above the general population prevalence (0.3–1% and 2–3%, respectively) are unlikely and therefore should not have a significant impact on our results. None of the SLC6A4 polymorphisms (specifically including the 5-HTTLPR/rs25531 variants) significantly deviated from Hardy–Weinberg equilibrium as determined by contingency table statistics (data not shown). There were no differences in allele frequency across the three control populations, suggesting no evidence for population stratification. A definitive analysis of multiple ancestry-informative markers or through family-based studies to analyze population substructure was not feasible in the present work.

**Genotyping**—Deoxyribonucleic acid extraction and genotyping procedures for the 5-HTTLPR/rs25531 locus, rs25532 and I425V have been published previously by our group.\(^11,28\) The overall genotype completion rate exceeded 98% for each assay. Samples analyzed in duplicate and no-template-controls consistently yielded expected results.
Statistics—We analyzed 5-HTTLPR/rs25531 as a biallelic locus, treating L_A as one group and the combined L_G or S alleles as another. L_A alleles markedly differ from L_G on the basis of mRNA measurements and reporter expression activity that indicate L_G as functionally equivalent to S, complicating previous evaluations of ‘L’ alone10, 1128, 29. Haplotyping and conditional analyses were done as previously described11. Statistical analyses were performed using Fisher’s Exact Test (or the Chi-Square Test for larger sample groups) with significance set at p < 0.05 in two-tailed tests. For the I425V frequency estimate, a correction was made using the within-family coefficient of estimate as previously described by our group11. All test results are presented as nominal (uncorrected) p-values.

RESULTS

Three noteworthy, novel findings emerged from this first reported large study of SLC6A4 functional variants in TD probands (N=151) compared to controls (N=858):

A) An increased frequency of the greater-expressing L_A variant was found in TD probands compared to healthy controls (Table 1, \( \chi^2 = 5.75, p=0.017, \text{OR}=1.35, 95\% \text{ CI: 1.06 to 1.73})^{10, 11}. To investigate whether this association might be different in the presence of comorbid OCD, genotypes of TD probands with (N=63, 42\%) or without (N=88, 58\%) OCD were compared in a secondary analysis. The L_A allele was more frequent in probands with TD alone compared to those with TD plus OCD (Fisher’s exact test, p=0.0006, OR=2.29), indicating that the association between SLC6A4 and TD may be dominantly-driven by TD diagnosis (L_A allele frequency in TD plus OCD= 0.44; TD alone= 0.64). Significant associations for TD probands were not found at rs25532 with either allele; however, the L_AC haplotype was more frequent in TD probands than controls (Table 1, p=0.024, OR=1.33). To evaluate whether this association might be different in the presence of comorbid OCD, we performed a secondary analysis comparing genotypes in those TD probands with or without OCD. The greater expressing L_AC haplotype was more frequent in probands with TD alone compared to those with TD plus OCD (p=0.0013, OR=2.14), like that for the L_A variant alone11. Likewise, there was a greater frequency of the rs25532 C allele in the TD alone group vs. the TD plus OCD group (p=0.018, OR=2.31).

B) The rare SERT I425V variant that confers gain-of-function and impaired regulation was found in a TD proband with an additional diagnosis of OCD. Follow-up genotyping of this family indicated that his two male siblings were also I425V carriers: a sibling with OCD and chronic phonic tics not meeting full TD criteria, and a sibling with TD, ADHD, and subclinical OC symptoms not meeting full criteria for OCD (Figure 1). Their father, who had subclinical OC and TD symptoms, also had SERT I425V. Of note, all three siblings and their father had both the greater-expressing L_A allele and the L_AC haplotype, with two being rs25532 CC homozygotes (Figure 1). Without exception in the present study, as in all previous studies, SERT I425V carriers were also L_A (or L) carriers24, 30, 31. These findings contribute to the compilation of all publication reports to date of SERT I425V being reported in 27 individuals of whom 15 individuals from 8 families received diagnoses of OCD, OC personality disorder or TD. The cumulative count of SERT I425V thus becomes 1.57% in OCD/TD spectrum conditions vs. 0.15% in controls, with a recalculated, family-adjusted significance of \( \chi^2 = 15.03, p < 0.0001, \text{OR}=9.0 \) (total worldwide genotyped=2914).

C) An unusual aggregation of congenital renal disorders with SERT I425V was observed. Upon closer review of the clinical description of the family
segregating SERT I425V, we noted that the father and two of the siblings of this family were originally flagged for congenital urological anomalies. These original designations were “congenital renal syndrome” and “congenital familial renal atrophy”. This family was re-contacted to clarify their renal disorders as well as their tic and OC symptoms (See Figure 1 for updated descriptions). Two siblings were found to have chronic urinary reflux requiring ureteral re-implantation and one, a nephrectomy in childhood. Their father had long-term vesicoureteral reflux requiring ureteral reimplantation, with continuing reduced (~60%) renal function and hypertension.

**DISCUSSION**

This report describes associations between TD and SLC6A4 at two different levels: first, there is an association of TD with the SLC6A4 greater-expressing promoter region Lₐ allele, and also a haplotypic association of TD with the LₐC variant (5-HTTLPR/ rs25531/ rs25532). Also, connections between SLC6A4 and TD were observed with the new finding of the rare variant, SERT I425V, in three siblings, one with TD and OCD, one with TD alone, and one with OCD alone, and in their father (with subclinical OC symptoms). In addition, congenital renal system anomalies, all requiring surgical treatment, were found in two of these siblings and also in their father, all with SERT I425V.

Numerous genes involved in neurotransmitter systems and developmental sequences seem highly relevant to TD, OCD and ADHD, but only relatively few have been investigated. These include glutamate, dopamine, serotonin, and other transmitter system genes, neurotrophic factor genes, and genes suggested from animal models of TD-, OCD- and ADHD-related behaviors. Alterations in the serotonergic systems have been suggested in TD since very early cerebrospinal fluid studies and other neurobiological and neuropharmacological studies. The present findings suggesting specific involvement of the SLC6A4 gene and thus SERT activity in TD individuals do not seem to have been previously considered according to recent reviews. Two previous studies reported no association of the 5-HTTLPR and TD; however, in both studies the genotyping methodology only evaluated L vs. S variants in 5-HTTLPR that are now known to be erroneous due to the substantial modulatory effects of rs25531 and rs25532.

In most investigations of TD, dopaminergic dysfunctions and more recently histamine system abnormalities have been evaluated, but the serotonin system appears relatively neglected. The present study thus provides new support for the notion of altered serotonergic neurotransmission in TD. Both the SLC6A4 Lₐ variant and LₐC haplotype have previously been shown to confer increased SLC6A4 expression by our group and colleagues. By increasing serotonin clearance, both higher expressing SLC6A4 alleles and the gain-of-function SERT I425V variant would confer an hyposerotonergic status, condition that has been suggested in some studies beginning two decades ago; however, see. Such a hyposerotonergic state could upregulate postsynaptic 5-HT₂A receptors, as reported in TD. These changes in 5-HT₂A receptors could in turn facilitate dopamine release, and this would thus be in convergence with the dopamine hypothesis of TD, postulated by Singer and others. Almost all studies to date have suggested impairments of the serotonergic system in TD. In addition, multiple investigations support contributions from dopamine and serotonin to abnormalities in the cortico-striato-thalamo-cortical loop in both OCD and TD. Further research is needed to fully answer how common and rare SLC6A4 variants conferring increased SERT expression and function might contribute to TD.
Human SLC6A4 expression was originally ascertained as being regulated by the 5-HTTLPR promoter, in addition to coding region (I425V, G56A) and other variants.\cite{20, 21, 48–50} The impact of additional polymorphisms such as rs25531, rs25532, rs16965628,\cite{11} alternative splicing forms and miR15a/16-mediated translational control\cite{12, 13} might be responsible for the lack of replication in early human genetics association reports regarding initially identified SLC6A4 polymorphisms considered alone\cite{20, 48, 49}; in addition, gene x gene interactions related to the consequences of other genes observed to interact with SLC6A4 (e.g., ITGB3, BDNF, BMP) may have contributed to mixed single gene evaluations.\cite{51, 52}

In regard to SERT I425V in families with OCD, TD and other neuropsychiatric disorders, the total clinically-evaluated (N=5) or non-evaluated (N=2) first degree relatives of OCD or TD probands now includes 7 of 716 (0.97%) individuals genotyped\cite{24, 30}, a significantly greater proportion than found in controls (3 of 1958, 0.15%; $\chi^2=7.48; p<0.006; \text{OR}=1.5$). In addition, five individuals with SERT I425V were fathers or siblings of individuals with SERT I425V who declined or could not participate in these studies (e.g., due to suicide N=4); three others with SERT I425V were each parents of two to four siblings with OCD in independent families\cite{24, 30, 31}. Also of relevance, three individuals with SERT I42V have been diagnosed with anorexia nervosa, three with autism or Asperger's syndrome and three with tic disorder, all disorders with overlapping features of perseverative, repetitive behaviors like OCD and TD\cite{24, 30}. Among all controls genotyped (N=1958), one diagnostically evaluated and two non-evaluated individuals from independent families had I425V (0.15%, Table 2). This compares to a figure of 0.084% in the 1000 Genomes Project for SERT I425V (rs28914832) (http://www.1000genomes.org/)\cite{53}. A recent report described three parents with SERT I425V, none of whom transmitted this variant to their OCD-affected children\cite{31}. One parent had OCD, one OCPD and the other skin-picking disorder. Of note, skin-picking disorder co-occurs with OCD in some instances and sometimes occurs as part of a constellation of grooming disorders considered as OCD spectrum disorders genetically associated with familial OCD\cite{54–56}. As summarized in Table 2, these new data add support to the notion that TD and OCD have some genetic overlap as spectrum conditions in which SERT I425V as well as common SLC6A4 polymorphisms (5-HTTLPR, rs25531 and rs25532) may be relevant, contributing, and perhaps even causative gene variants associated with TD, OCD and related neuropsychiatric disorders.

SERT I425V leads to greater SERT surface availability, increased transport of serotonin, disrupted regulation via a PKG/cGMP-linked pathway, and also altered binding of some inhibitory ligands.\cite{20, 21, 46, 48} However, the molecular consequences of SERT I425V have thus far been only investigated in heterologous expression cell systems (HeLa and COS-7 cells)\cite{20, 21, 48}. The recently available transgenic SERT I425V mice should make possible the study of this variant in vivo [Ramamoorthy, S et. al., in preparation]. These mice with expected SERT over-expression and altered SERT regulation will be especially valuable in developmental studies as well as providing means to explore additional SERT-related disorders, including TD.

This is the first reported association of common SLC6A4 alleles and a haplotype plus the rare, highly penetrant SERT I425V with TD. Three of four individuals with SERT I425V also had in a congenital renal system disorder. Present results call for examination of this possible connection between SERT I425V and renal anomalies in other families with this variant, perhaps related to the existence of a 'intrarenal serotonin system' that includes serotonin synthesis in the proximal tubule, SERT-mediated excretion and multiple renal serotonin receptors.\cite{57–59}

We did not correct our results for multiple testing since we and others have previously shown that the SLC6A4 variants investigated here are not independent: The rs25532 T allele
has not been observed on rs25531 G background (i.e. S_G or L_G when considering 5-HTTLPR/rs25531)\textsuperscript{11}. Of note, the minor G allele of rs25531 has been found to occur almost always in phase with the L allele of 5-HTTLPR\textsuperscript{10, 11}. In all previous reports, and just as we have found in the present results, the SERT I425V variant has been always found in subjects having the 5-HTTLPR/rs2551 L\textsubscript{A} (or L) allele\textsuperscript{20–23, 30, 31}.

An important limitation in our case-control association study is its susceptibility to population stratification. We addressed this issue by matching ethnicities between cases and controls. Although considered by some authors to be relatively uncommon\textsuperscript{60}, spurious associations can only be definitively ruled out by genotyping multiple ancestry-informative markers or through family-based studies, which were not feasible in the present work.

A complex impact of serotonin changes on early development in rodents has been investigated for some years\textsuperscript{61}. The deleterious consequences of a single gene knockout of SERT or of specific serotonin receptors and studies of prenatal or early postnatal exposure to serotonin reuptake inhibitors have been established in mice\textsuperscript{62}; [Andrews et al., under review]. These include altered extinction fear plus stress- and anxiety-related responses, head twitch responses (which may be tic-like)\textsuperscript{63}, motor dysfunction and more -all of which may be relevant to neuropsychiatric disorders including TD, OCD and ADHD\textsuperscript{49, 62, 64}. OCD has been most clearly associated with the 5-HTTLPR/rs25531, plus rs25532 and SERT I425V variants (as has ADHD, to some extent), although earlier reports suggested mixed results, particularly when only 5-HTTLPR was studied or when TD was excluded from the OCD samples\textsuperscript{10, 11, 31, 65, 66}. The present findings indicate that multiple variants in SLC6A4 are involved in TD, just like those found in OCD – two disorders characterized by obligatory/unwanted movements, behaviors or thoughts. These new results call for replication in a similarly intensively evaluated sample. A number of recent reviews have strengthened the case for SLC6A4 contributions to different neuropsychiatric disorders including affective disorders and suicide plus anxiety related-traits, particularly when life events and other environmental antecedents are taken into account\textsuperscript{16, 67–69}. A related G × E hypothesis might apply to TD: the combined burden of TD associated with OCD or ADHD in addition might provide compounded gene/multiple disorders/environmental interactions akin to that found with the combinations of SLC6A4 variants with traumatic/stressful life events on the risk for behavioral disorder outcomes, as recently examined in several reviews\textsuperscript{16, 67–69}.

Acknowledgments

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Figure 1.
Pedigree of Family D with SLC6A4 SERT I425V in three siblings with TD/OCD and in their father, showing also SLC6A4 5-HTTLPR/rs25531/rs25532 variants.
TABLE 1

Summary of Genotypes and Alleles in TD Probands and Controls; Alleles and Haplotype Analysis by Functional Grouping (see Methods).

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<th>TD Probands</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Total individuals</td>
<td>150</td>
<td>855</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>N (%)</td>
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<td></td>
</tr>
<tr>
<td>L_A L_A</td>
<td>51 (34.0)</td>
<td>203 (23.7)</td>
<td></td>
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<tr>
<td>L_A L_G</td>
<td>6 (4.0)</td>
<td>60 (7.0)</td>
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<tr>
<td>L_G L_G</td>
<td>0</td>
<td>4 (0.5)</td>
<td></td>
</tr>
<tr>
<td>L_A S</td>
<td>61 (40.7)</td>
<td>369 (43.0)</td>
<td></td>
</tr>
<tr>
<td>L_G S</td>
<td>7 (4.7)</td>
<td>48 (5.6)</td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>25 (16.7)</td>
<td>171 (19.9)</td>
<td></td>
</tr>
<tr>
<td>Total alleles</td>
<td>300</td>
<td>1710</td>
<td></td>
</tr>
<tr>
<td>L_A</td>
<td>169 (56.3)</td>
<td>835 (48.8)</td>
<td></td>
</tr>
<tr>
<td>S, L_G</td>
<td>131 (43.7)</td>
<td>875 (54.2)</td>
<td>$\chi^2=5.75$, OR=1.35 $p=0.017$</td>
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<tr>
<td>Haplotypes</td>
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</tr>
<tr>
<td>L_AC</td>
<td>(49.3)</td>
<td>(38.3)</td>
<td></td>
</tr>
<tr>
<td>L_AT, S, L_G</td>
<td>(50.6)</td>
<td>(61.7)</td>
<td>$\chi^2=5.08$, OR=1.33 $p=0.024$</td>
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TABLE 2

SERT I425V in Genotyped OCD, TD and Controls

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>SERT I425V</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total OCD/OCPD or TD</td>
<td>956</td>
<td>15</td>
<td>1.57**</td>
</tr>
<tr>
<td>Total diagnostically-evaluated [N=1] healthy or non-evaluated [n=2] controls</td>
<td>1958</td>
<td>3</td>
<td>0.15</td>
</tr>
</tbody>
</table>

OCD/OCPD or TD (with family correction) vs. Controls:

χ²=15.03, p < 0.0001, OR=9.0