

# UCSF

## UC San Francisco Previously Published Works

### Title

Copy Number Variation in Obsessive-Compulsive Disorder and Tourette Syndrome: A Cross-Disorder Study

### Permalink

<https://escholarship.org/uc/item/221498r1>

### Journal

Journal of the American Academy of Child & Adolescent Psychiatry, 53(8)

### ISSN

0890-8567

### Authors

McGrath, Lauren M  
Yu, Dongmei  
Marshall, Christian  
[et al.](#)

### Publication Date

2014-08-01

### DOI

10.1016/j.jaac.2014.04.022

Peer reviewed



Published in final edited form as:

*J Am Acad Child Adolesc Psychiatry*. 2014 August ; 53(8): 910–919. doi:10.1016/j.jaac.2014.04.022.

## Copy Number Variation in Obsessive-Compulsive Disorder and Tourette Syndrome: A Cross-Disorder Study

*A full list of authors and affiliations appears at the end of the article.*

### Abstract

**Objective**—Obsessive-compulsive disorder (OCD) and Tourette syndrome (TS) are heritable, neurodevelopmental disorders with a partially shared genetic etiology. This study represents the first genome-wide investigation of large (>500kb), rare (<1%) copy number variants (CNVs) in OCD and the largest genome-wide CNV analysis in TS to date.

**Method**—The primary analyses utilized a cross-disorder design for 2,699 patients (1,613 ascertained for OCD, 1,086 ascertained for TS) and 1,789 controls. Parental data facilitated a de novo analysis in 348 OCD trios.

**Results**—Although no global CNV burden was detected in the cross-disorder analysis or in secondary, disease-specific analyses, there was a 3.3-fold increased burden of large deletions previously associated with other neurodevelopmental disorders ( $p=.09$ ). Half of these neurodevelopmental deletions were located in a single locus, 16p13.11 (5 patient deletions: 0 control deletions,  $p=0.08$  in current study,  $p=0.025$  compared to published controls). Three 16p13.11 deletions were confirmed de novo, providing further support to the etiological significance of this region. The overall OCD de novo rate was 1.4%, which is intermediate between published rates in controls (0.7%) and in autism or schizophrenia (2–4%).

**Conclusion**—Several converging lines of evidence implicate 16p13.11 deletions in OCD, with weaker evidence for a role in TS. The trend toward increased overall neurodevelopmental CNV burden in TS and OCD suggests that deletions previously associated with other neurodevelopmental disorders may also contribute to these phenotypes.

### Keywords

Tourette syndrome; obsessive-compulsive disorder; copy number variation; genetics; 16p13.11

---

© 2014 American Academy of Child & Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved

Correspondence to Jeremiah Scharf, MD, PhD, Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114; jscharf@partners.org.

∞Deceased

Dr. K. Wang served as the statistical expert for this research.

Supplemental material cited in this article is available online.

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

## INTRODUCTION

Obsessive-compulsive disorder (OCD) and Tourette syndrome (TS) are neurodevelopmental disorders with significant phenotypic and genetic overlap.<sup>1,2</sup> One promising avenue for identifying cross-disorder genetic risk factors in neurodevelopmental disorders is the study of genomic copy number variants (CNVs), segments of DNA ranging from 1 kilobase to several megabases that show deletions or duplications compared to a reference.<sup>3</sup> The association of large, rare CNVs with neurodevelopmental disorders including autism spectrum disorders (ASD), schizophrenia, and intellectual disability (ID) has been one of the most important recent advances in psychiatric genomics.<sup>4</sup> CNVs predisposed to these disorders overlap substantially, highlighting the cross-disorder effects of this class of genetic variation.<sup>5,6</sup> Given this robust literature, an important, unanswered question is whether large, rare CNVs are also relevant for the genetic architecture of OCD and TS.

Both OCD and TS are highly heritable and have long been suspected to share genetic liability, though specific gene variants have been difficult to identify.<sup>7-9</sup> Both disorders frequently co-occur in individuals,<sup>10</sup> and there is evidence for shared OCD/TS genetic risk from family studies,<sup>9,11</sup> with genetic correlation estimates ranging from 41–90%.<sup>2,12</sup> In OCD, locus-specific CNV analyses have been reported,<sup>13,14</sup> but no prior genome-wide CNV analysis has been performed. In TS, the three previous genome-wide surveys of CNVs have been limited by small sample sizes (<500 cases), and results differ with regard to whether there is an increased CNV burden in TS compared to controls.<sup>15-17</sup> No specific CNV region has received strong statistical support across studies, although exonic *NRXN1* deletions have been identified in two studies.<sup>15,17</sup>

Given the evidence for shared genetic underpinnings of OCD and TS and cross-disorder effects of specific neurodevelopmental CNVs, along with the need for large samples when investigating rare events, we chose a cross-disorder design that combined OCD and TS samples into a single case group, with follow-up analyses examining the individual disorders. This study is the first genome-wide CNV analysis in OCD and the largest to date in TS, and addressed three key questions. First, is there an increased burden of large, rare CNVs in OCD/TS? Second, are the recurrent and/or de novo CNVs implicated in other neurodevelopmental disorders also etiologically relevant for OCD/TS? Third, is there evidence of association between any specific genomic region and OCD/TS?

## METHOD

### Participants

Individuals with OCD or TS were recruited for a multi-center collaborative genome-wide analyses (GWAS, described in<sup>18 and 19</sup>). Participants ages 18 and older provided written, voluntary informed consent for participation in genetic studies. Individuals under age 18 provided assent; written parental consent was also obtained. The study was approved by the Ethics Committees of all participating sites. Recruitment sites varied in screening and exclusions related to other neurodevelopmental disorders; see supplementary tables S9, S10, S11, available online, for available clinical information regarding ID, ASD, ADHD, and seizures. OCD and TS samples were collected independently but were genotyped jointly to

facilitate cross-disorder analyses. All cases were genotyped on the Illumina Human610-Quadv1\_B platform.

**OCD**—The initial OCD sample consisted of 1,565 patients and 437 parent-child trios (n=406 independent families, 31 affected siblings) recruited from 22 sites in the US, Canada, Europe, Latin America, and South Africa, predominantly through OCD specialty clinics. In total, 1,971 independent patients with OCD (including trio probands) were eligible for analysis. 1,613 patients with OCD (82%) survived quality control (QC), and were included in the final analyses. Mean age of OCD symptom onset was 13.8 years (SD=9.1). 327 cases and 21 affected siblings had parents available for de novo analysis (n=348 total trios). TS or chronic tics (CT) were assessed in 57% of OCD probands using *DSM-IV-TR* criteria. Of those assessed, TS was present in 10% of patients with OCD, and an additional 5% had CT.

**TS**—The initial TS sample consisted of 1,235 individuals recruited from 19 sites in the US, Canada, Europe, and Israel. Participants with *DSM-IV-TR*-diagnosed TS were recruited primarily from TS specialty clinics or from the Tourette Syndrome Association (TSA). 1,086 (88%) individuals passed sample-level QC. Mean age of tic onset was 6.3 years (SD=3.5). OCD as defined by *DSM-IV-TR* criteria was assessed in 88% of cases; OCD was present in 46% of assessed TS individuals.

**Controls**—Ancestry-matched controls (n=720) were collected in parallel with their respective cases for the French-Canadian (n=269), German (n=224), South African (n=188), and Dutch (n=39) samples. These controls were screened for TS and OCD and genotyped with cases on the Illumina Human610-Quadv1\_B<sup>20,21</sup>, (referred to here as ‘Hap610 controls’).

1,279 additional European-ancestry controls were obtained through the Database of Genotypes and Phenotypes (dbGaP) from the Studies of Addiction: Genetics and Environment (SAGE) cohort.<sup>20</sup> SAGE controls were excluded for lifetime substance dependence but were not screened for other psychopathology. The SAGE controls were genotyped on the Illumina Human-Hap1Mv1\_C (referred to here as ‘Hap1M controls’).

### CNV Calling and Quality Control (QC)

Data from the Hap610 (cases and controls) and Hap1M (controls) platforms were processed and cleaned separately using standard procedures (see Supplementary Methods, available online). CNV calls were generated with PennCNV (version 2010-05-01)<sup>21</sup> and iPattern<sup>22,23</sup> using hg18 genomic coordinates. Analyses were limited to autosomal events. Trio analyses utilized the trio functions in PennCNV to improve calling accuracy and to estimate the likelihood of a de novo event.<sup>21</sup>

Both sample and CNV-specific QC was conducted by examining distributions of QC metrics informed by comparable published CNV analyses, e.g.,<sup>22,24,25</sup>. Since distributions were similar for calls from PennCNV and iPattern, the same QC thresholds were used for both algorithms to maximize comparability (see Supplementary Methods, available online). QC-filtered PennCNV and iPattern callsets were merged at the sample level using CNVision

(<http://futo.cs.yale.edu/mw/index.php/CNVision>). Only calls with >50% overlap based on the union of the CNV region were included in the analysis. Overlap percentages were higher for the Hap1M (86%–98%) compared to the Hap610 chip (59%–82%; Table S1, available online). Due to the presence of a batch effect within the Hap610 samples, analyses were restricted to large (>500kb) events, the size at which batch effects were no longer observed (Figure S1, Table S2, available online). All CNVs were also filtered for rare events (<1% frequency in the Database of Genomic Variants).

### Ancestry Matching

The patient-control sample was predominantly composed of individuals self-reporting European (EU) ancestry (n=4410), but did include a small number of individuals from Brazil, Mexico, and Costa Rica (n=78) to maximize the power to detect rare events. However, a sensitivity analysis restricted to genetically-defined EU ancestry (n=4276) via multidimensional scaling (Figures S2, S3, available online) confirmed that results were not biased by population stratification.

### Statistical Analysis

CNV burden, region-specific analyses, and permutations were performed in PLINK using the rare CNV functions.<sup>26</sup> The primary case-control analyses grouped OCD and TS cases versus Hap610 and Hap1M controls to maximize sample sizes. No additional covariates were included, though follow-up analyses were stratified by EU ancestry. To evaluate whether OCD and TS patients harbor large, pathogenic CNVs that have been repeatedly implicated in other neurodevelopmental disorders, we assembled a curated list of CNVs drawn from the ASD, schizophrenia, and ID literature, including 47 regions of interest (all >500kb<sup>22,24,27,28</sup>; Table S3, available online).

### Quantitative PCR (qPCR) Validation

Validation of neurodevelopmental or putative de novo CNVs was performed with SYBR green qPCR. Two qPCR primers per CNV were designed against NCBI build hg18 sequence to obtain converging evidence for the called event. If one primer pair failed or gave ambiguous results, an additional primer pair was run to resolve the discrepancy (Supplementary Methods, available online).

## RESULTS

After filtering and QC, the final sample consisted of 2,699 patients (1,086 ascertained for TS and 1,613 ascertained for OCD), and 1,789 controls.

### Overall CNV Burden Analysis

There was no significant difference in burden of large, rare CNVs between patients with OCD/TS and controls for CNV rate (average number of CNVs per person), CNV proportion (proportion of samples carrying 1 CNV), gene rate (the average number of genes spanned by a CNV), or by restricting to CNVs containing exons (Tables 1, S4, S5, S6; Tables S4–6 appear online). Similarly, no increased CNV burden was identified in secondary, disorder-

specific analyses (OCD versus controls or TS versus Controls; Tables S7, S8, available online).

### Neurodevelopmental CNV Burden Analysis

Given that various neurodevelopmental disorders have previously been associated with large, rare, recurrent CNVs in specific regions of the genome<sup>4</sup>, we examined 47 known, pathogenic neurodevelopmental loci for an excess of large, rare CNVs in OCD/TS cases compared to controls (Tables 2, 3, S3, S9; Tables S3 and S9 are available online). We found a 3.3-fold, trend-level increase in large deletions overlapping these loci for patients with TS/OCD ( $p=.09$ ; Table 2). In contrast, there was no enrichment of duplication events (patient/control ratio 1.16,  $p=0.46$ ) and no difference in overall CNV size within these regions ( $p=.31$ ).

In disorder-specific analyses, the neurodevelopmental deletion burden was larger in OCD (case/control ratio=4.44,  $p=0.04$ , one-sided) than in TS (case/control ratio=1.65,  $p=0.49$ , one-sided) (Tables S7, S8). The most frequently observed neurodevelopmental CNVs were located at 16p13.11, 22q11, and *PARK2* (Figure 1, Tables 3, S4, S5; Tables S4, S5 are available online).

### Laboratory Validation

We confirmed 10 of 11 neurodevelopmental deletion events (91%) with qPCR; the one unconfirmed deletion was near the 9q34 telomere and was excluded from the neurodevelopmental burden analysis (see Supplementary Methods, available online). We also confirmed 12 of 14 duplication events (86%) with 1 or 2 sets of primers. The two remaining duplications could not be confirmed but had qPCR results trending towards duplication. Of note, the LRR and BAF plots (Figure S6, available online) strongly supported all CNV events with the exception of the unconfirmed 9q34 deletion.

### Region-Specific analyses

Half of the 10 large neurodevelopmental deletions were in the same genomic region on 16p13.11 (patient:control ratio=5:0, one-sided Fisher's exact  $p=0.08$ ) (Figure 1, Table 3). Using previously published estimates to more accurately calculate the control rate for 16p13.11 deletions (3/8329)<sup>28</sup>, we found a statistically significant excess in the OCD/TS cases (one-sided Fisher's exact  $p=0.025$ ). Of note, the rate of 16p13.11 deletions in this sample (0.19%) was comparable to published rates from large samples of children with neurodevelopmental disorders ( $n$ 's ~15,000) referred for genetic testing (0.11%–0.14%).<sup>28,29</sup> Interestingly, the clinical phenotype of the 5 16p13.11 deletions did not respect traditional diagnostic boundaries: 3 patients had OCD without tics, 1 had TS without OCD, and 1 had OCD+CT. None of the patients had ASD, ID, or a seizure disorder (Table S10, available online). All 16p13.11 deletions were validated with qPCR.

16p13.11 was also the top recurrent region in genome-wide, region-specific analyses combining deletions and duplications (patient:control ratio=7:1, one-sided empirical  $p=0.13$ ; genome-wide permutation corrected  $p=0.86$ ). This region-specific effect was driven by deletions; no excess of 16p13.11 duplications was found in patients with OCD/TS compared

either to sample controls (patient:control ratio=2:1, one-sided Fisher's exact  $p=0.65$ ) or to published controls (10/8329)<sup>28</sup> (one-sided Fisher's exact  $p=0.83$ ).

We also examined genome-wide, region-specific associations in each disorder separately, combining deletions and duplications. In OCD, 16p13.11 again emerged as the locus with the most notable patient:control excess (6:1; one-sided empirical  $p=0.046$ , genome-wide permutation-corrected  $p=0.35$ ). In TS, the 3p26.3 region had the largest patient:control excess (7:2 ratio of duplications 50kb upstream of *CNTN6*; 1-sided empirical  $p=0.018$ , genome-wide permutation-corrected  $p=0.15$ ); exonic *CNTN6* regions had a more equivocal patient-control ratio (8:6; 1-sided empirical  $p=0.11$ , genome-wide permutation-corrected  $p=0.99$ ; see Figure S7, available online).

### De Novo Analyses

The OCD parent-proband trios (total trios=348) were examined for the presence of large (>500kb), rare, de novo CNVs. We detected 5 high confidence, de novo CNVs at 4q24, 7p21.1-7p21.2, 16p13.11, 17q12, and 22q11.21, resulting in a de novo rate of 1.44% (Figure S8, available online). Three of these CNVs were in known pathogenic neurodevelopmental loci: 16p13.11, 17q12, 22q11.21 (Table S3, available online). All 5 events were validated in silico and by qPCR (Table S11, available online).

Given that 16p13.11 contained both a de novo CNV and the largest patient/control difference across the genome, we undertook further investigation of the de novo status of other 16p13.11 patient CNVs in our sample. Parental DNA was available for 1 of the 5 16p13.11 deletions (TS only), which we confirmed as de novo using qPCR. We also re-examined trios removed during QC for evidence of large 16p13.11 events and found one additional deletion (OCD only) with a statistically significant in silico probability of being de novo,  $p=5.68 \times 10^{-14}$  that we subsequently validated using qPCR (Figure S8, available online). This increased the total number of 16p13.11 deletions from 5 to 6, 3 of which were de novo (2 OCD only, 1 TS only; see Table S10, available online). The de novo status of 2 16p13.11 deletions could not be determined because parental DNA was not available; 1 deletion was inherited.

## DISCUSSION

In this GWA of large, rare CNVs in OCD and TS, although there was no global increase in CNV burden, we did find suggestive evidence for an increased burden of known, pathogenic neurodevelopmental deletions in patients with OCD/TS compared to controls. The 3.3-fold increased risk associated with this finding only reached trend-level significance, potentially due to the conservative bias toward the null introduced by having the majority of controls genotyped on a more sensitive, higher-density genotyping array than patients.

Deletions at 16p13.11, which contributed disproportionately to the neurodevelopmental burden, have been implicated in a wide range of disorders, including ID/developmental delay<sup>28,29</sup>, seizures<sup>30,31</sup>, and, less strongly, ASD.<sup>32</sup> The confirmation of three de novo events among our 6 patients with OCD/TS 16p13.11 deletions, as well as the absence of comorbid ID, seizures, or ASD in the patients assessed, suggests that these events may be

pathogenic in our sample and that the phenotypic spectrum of 16p13.11 deletions should be expanded to include OCD and TS. Importantly, the phenotypic profiles indicate that 16p13.11 deletions are primarily associated with OCD (4 OCD only, 1 OCD+CT, 1 TS only). The presence of a patient with TS but without OCD raises the possibility of a pleiotropic effect of this locus, though this hypothesis remains preliminary, as it is based only on a single patient. It is also likely that additional genetic and environmental factors shape the ultimate phenotypic outcome of these CNV events, including patterns of comorbidity.

Three of the 5 large de novo CNVs reported in this study were located in regions previously associated with other neurodevelopmental disorders. The de novo events at 16p13.11 and 22q11 also had additional supporting patient events in the same locus, whereas the deletion at 17q12 was a singleton event in a patient with OCD. The final 2 de novo events were singleton deletions at novel loci: 4q24 and 7p21.1-7p21.2. The clinical significance of both events remains unclear, although pathogenic CNVs have been documented in both regions ([www.iscaconsortium.org](http://www.iscaconsortium.org)),<sup>33</sup> including a report of a patient with Saethre-Chotzen syndrome and co-occurring TS and OCD.<sup>34</sup>

The overall de novo rate in the OCD trio sample was 1.44% for large CNVs (> 500kb), which is intermediate between estimates in healthy controls (0.7%)<sup>27</sup> and estimates in ASD (1.8% multiplex, 3.9% simplex)<sup>27</sup> and schizophrenia (2–3%).<sup>35–37</sup> Additional studies with larger samples and more sensitive CNV calling will be needed to refine this estimate.

Previous CNV studies have implicated *NRXN1* deletions in TS.<sup>15,17</sup> We detected one 600kb *NRXN1* deletion in a patient with OCD (TS status unknown) (chr2:50185814–50799877, hg18) that was called by iPattern and qPCR-validated, although it did not pass initial QC because <50% of the region was called by PennCNV. We also observed 3 22q11 duplications, all patients with OCD (2 OCD only, 1 OCD+CT), 1 de novo deletion (OCD only), and 1 control duplication (Figure S4, available online). The de novo 22q11 deletion was smaller (~700kb) than the canonical 1.5-3Mb 22q11 deletion associated with velocardiofacial and DiGeorge syndrome (OMIM 192430, 188400), whereas the duplications ranged in size from 700kb-2MB. Although the 3:1 22q11 CNV duplication excess in our sample is not significant, it is notable that three other 22q11 duplications, including 1 de novo event, have previously been reported in TS cases,<sup>16,17,38,39</sup> and thus this region warrants further study.

The results of this study should be interpreted in the context of some limitations. First, the majority of controls were genotyped on a higher resolution array (Hap1M) than patients (Hap610), resulting in a conservative bias toward the null hypothesis due to better CNV detection in controls than patients. This effect is evident when comparing the higher CNV rates in Hap610 controls to Hap1M controls (Table 1). However, a comparison of Hap610 cases to Hap610 controls did not reveal overall burden differences within the limits of this restricted sample size (Table S12, available online).

Second, we were unable to call CNVs smaller than 500kb due to genotyping batch effects. Although previous research has shown that >500kb events are most likely to be



pathogenic,<sup>22,25</sup> we may have missed smaller pathogenic CNVs in this sample. Third, albeit the largest for OCD and TS to date, our sample is still small compared to large-scale investigations of CNVs in other disorders.<sup>4,28,29</sup> For this reason and because the number of patients with OCD/TS and rare, pathogenic CNVs appears to be small, we recommend caution in interpreting these results, pending further studies in larger OCD/TS samples that can refine the global and neurodevelopmental CNV burden estimates.

Fourth, missing data on TS/CT and OCD comorbidity in some individuals prevented us from dividing patients into mutually exclusive subgroups (TS only, OCD only, OCD+TS) for analysis. Instead, we identified CNVs in the combined OCD/TS sample and then reviewed the diagnostic profile of each patient with a CNV. Moreover, TS and OCD participants were not universally screened for other neurodevelopmental disorders, though we documented this information when available (Tables S9, S10, S11, available online). Without comprehensive screening, we cannot exclude 2 possibilities regarding cases with neurodevelopmental CNVs: (1) the primary TS/OCD diagnosis was misclassified (i.e., stereotypies or restricted interests/repetitive behaviors in the context of ASD were misdiagnosed as TS or OCD, respectively) and (2) cases with complex comorbidities were more likely to harbor neurodevelopmental CNVs. All assessments were completed by internationally-recognized expert clinicians, reducing the likelihood of misclassification. However, some individuals with neurodevelopmental CNVs may have had subtle or unassessed ASD, ADHD, cognitive impairment, or psychotic symptoms.

These results suggest that deletions associated with other neurodevelopmental disorders may also contribute to OCD and TS. Converging lines of evidence specifically implicate 16p13.11 deletions, with stronger evidence for OCD than TS. While it is premature to make clinical recommendations based on these observations, we note that tic and obsessive-compulsive symptoms often occur in the context of other neurodevelopmental disorders, such as ASD and ID, where practice parameters do recommend chromosomal microarray testing.<sup>40</sup> Future studies should help to refine clinical guidelines as to whether CNV testing might be indicated for children with TS and/or OCD in general or be restricted to those with multiple co-occurring neurodevelopmental disorders.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Authors

Dr. Lauren M. McGrath, PhD, Ms. Dongmei Yu, MS, Dr. Christian Marshall, PhD, Dr. Lea K. Davis, PhD, Ms. Bhooma Thiruvahindrapuram, MSc, Mr. Bingbin Li, HBSc, Ms. Carolina Cappi, MSc, Ms. Gloria Gerber, BA, Messr. Aaron Wolf, BA, Dr. Frederick A. Schroeder, PhD, Ms. Lisa Osiecki, BA, Dr. Colm O'Dushlaine, PhD, Messr. Andrew Kirby, BA, Dr. Cornelia Illmann, PhD, Messr. Stephen Haddad, MS, Ms. Patience Gallagher, BS, Dr. Jesen A. Fagerness, JD, Dr. Cathy L. Barr, PhD, Dr. Laura Bellodi, MD, Dr. Fortu Benarroch, MD, Dr. O. Joseph Bienvenu, MD, PhD, Dr. Donald W. Black, MD, Dr. Michael H. Bloch, MD, MS, Dr. Ruth D. Bruun, MD,

Dr. Cathy L. Budman, MD, Ms. Beatriz Camarena, MSc, Dr. Danielle C. Cath, MD, Dr. Maria C. Cavallini, MD, Dr. Sylvain Chouinard, MD, Dr. Vladimir Coric, MD, Dr. Bernadette Cullen, MB, BCh, BAO, Dr. Richard Delorme, MD, PhD, Dr. Damiaan Denys, MD, PhD, Dr. Eske M. Derks, PhD, Dr. Yves Dion, MD, Dr. Maria C. Rosário, MD, PhD, Dr. Valsama Eapen, MD, PhD, Dr. Patrick Evans, PhD, Dr. Peter Falkai, MD, Dr. Thomas Fernandez, MD, Ms. Helena Garrido, MA, Dr. Daniel Geller, MD, Dr. Hans J. Grabe, MD, Dr. Marco A. Grados, MD, MPH, Dr. Benjamin D. Greenberg, MD, PhD, Dr. Varda Gross-Tsur, MD, Dr. Edna Grünblatt, PhD, Dr. Gary A. Heiman, PhD, Dr. Sian M.J. Hemmings, PhD, Dr. Luis D. Herrera, MD, MPH, Dr. Ana G. Hounie, MD, PhD, Dr. Joseph Jankovic, MD, Dr. James L. Kennedy, MD, Dr. Robert A. King, MD, Dr. Roger Kurlan, MD, Dr. Nuria Lanzagorta, PsyD, Dr. Marion Leboyer, MD, PhD, Dr. James F. Leckman, MD, Mr. Leonhard Lennertz, MSc, Dr. Christine Lochner, PhD, Dr. Thomas L. Lowe, MD, Dr. Gholson J. Lyon, MD, PhD, Dr. Fabio Macciardi, MD, PhD, Dr. Wolfgang Maier, MD, Dr. James T. McCracken, MD, Dr. William McMahon, MD, Dr. Dennis L. Murphy, MD, Dr. Allan L. Naarden, MD, Dr. Benjamin M. Neale, PhD, Dr. Erika Nurmi, MD, PhD, Dr. Andrew J. Pakstis, PhD, Dr. Michele T. Pato, MD, Dr. Carlos N. Pato, MD, PhD, Dr. John Piacentini, PhD, Dr. Christopher Pittenger, MD, PhD, Dr. Yehuda Pollak, PhD, Dr. Victor I. Reus, MD, Dr. Margaret A. Richter, MD, Dr. Mark Riddle, MD, Dr. Mary M. Robertson, MD, PhD, Dr. David Rosenberg, MD, Dr. Guy A. Rouleau, MD, Dr. Stephan Ruhrmann, MD, Dr. Aline S. Sampaio, MD, PhD, Dr. Jack Samuels, PhD, Dr. Paul Sandor, MD, Ms. Brooke Sheppard, MSc, Dr. Harvey S. Singer, MD, Jan H. Smit, PhD, Dr. Dan J. Stein, MD, PhD, Dr. Jay A. Tischfield, PhD, Dr. Homero Vallada, MD, PhD, Dr. Jeremy Veenstra-VanderWeele, MD, Dr. Susanne Walitza, MD, Ms. Ying Wang, MSc, Dr. Jens R. Wendland, MD, Dr. Yin Yao Shugart, PhD, Dr. Euripedes C. Miguel, MD, PhD, Dr. Humberto Nicolini, MD, PhD, Dr. Ben A. Oostra, PhD, Dr. Rainald Moessner, MD, Dr. Michael Wagner, PhD, Dr. Andres Ruiz-Linares, MD, PhD, Dr. Peter Heutink, PhD, Dr. Gerald Nestadt, MD, Dr. Nelson Freimer, MD, Dr. Tracey Petryshen, PhD, Dr. Danielle Posthuma, PhD, Dr. Michael A. Jenike, MD, Dr. Nancy J. Cox, PhD, Dr. Gregory L. Hanna, MD, Dr. Helena Brentani, MD, PhD, Dr. Stephen W. Scherer, PhD, Dr. Paul D. Arnold, MD, PhD, Dr. S. Evelyn Stewart, MD, Dr. Carol A. Mathews, MD, Dr. James A. Knowles, MD, PhD, Dr. Edwin H. Cook, MD, Dr. David L. Pauls, PhD, Dr. Kai Wang, PhD, and Dr. Jeremiah M. Scharf, MD, PhD

Drs. McGrath, Illmann, Fagerness, Geller, Jenike, Neale, Petryshen, Pauls, Scharf, Schroeder, Stewart, Mss. Yu, Gerber, Osiecki, Gallagher, and Messrs. Wolf, Haddad, and Kirby are with Massachusetts General Hospital. Dr. Stewart is also with the University of British Columbia. Dr. McGrath is also with American University. Dr. Scharf is also with Brigham and Womens Hospital, Boston, MA. Drs. O'Dushlaine, McGrath, Neale, Petryshen, Scharf, and Ms. Yu are also with the Harvard-MIT Broad Institute. Drs. Marshall, Scherer, Barr, Richter, Arnold, Sandor, Ms. Thiruvahindrapuram and Mr. Li are with the University of Toronto and the Hospital for Sick Children. Drs. Sandor and Barr are also with the Toronto Western Research Institute, University Health Network, Toronto. Dr. Kennedy is with the Centre for Addiction and Mental Health. Drs. Davis, Evans, and Cox are with the

University of Chicago. Drs. Vallada, Miguel, and Brentani and Ms. Cappi are with the University of São Paulo Medical School. Dr. Bellodi is with the Università Vita-Salute San Raffaele. Dr. Benarroch is with Hadassah-Hebrew University Medical Center. Drs. Bienvenu, Cullen, Grados, Samuels, Singer, Nestadt, Riddle, and Ms. Wang are with Johns Hopkins University School of Medicine. Dr. Black is with the University of Iowa College of Medicine. Drs. Bloch, Coric, Fernandez, Leckman, Pakstis, Pittenger, and King are with the Yale University School of Medicine. Drs. Bruun and Budman are with North Shore-Long Island Jewish Medical Center. Dr. Budman is also with Hofstra University School of Medicine, Hempstead, NY. Dr. Bruun is also with New York University Medical Center, New York. Ms. Camarena is with the Instituto Nacional de Psiquiatría Ramon de la Fuente Muñiz. Dr. Cath is with Utrecht University and VU University Medical Center, Amsterdam. Dr. Cavallini is with the Ospedale San Raffaele. Drs. Chouinard and Dion are with the University of Montreal. Drs. Delorme and Leboyer are with the Robert Debre University Hospital and the French National Science Foundation. Dr. Delorme is also with Institut Pasteur, Paris. Dr. Leboyer is also with Institut Mondor de Recherche Biomédicale, Créteil, France. Dr. Denys is with the Netherlands Institute for Neuroscience. Drs. Denys and Derks are with the Academic Medical Center, Amsterdam. Drs. Rosário, Hounie, and Sampaio are with the Federal University of São Paulo. Dr. Sampaio is also with Universidade Federal da Bahia, Salvador, Bahia, Brazil. Dr. Eapen is with the University of New South Wales. Dr. Falkai is with the University of Munich. Dr. Herrera and Ms. Garrido are with the Hospital Nacional de Niños. Ms. Garrido is also with Clinica Herrera Amighetti, Avenida Escazú, San José, Costa Rica. Dr. Grabe is with the University Medicine Greifswald. Dr. Greenberg is with Brown Medical School. Drs. Gross-Tsur and Pollak are with Shaare Zedek Medical Center. Drs. Grünblatt and Walitza are with the University of Zurich. Dr. Walitza is also with the University of Würzburg. Drs. Heiman and Tischfield are with Rutgers University. Dr. Jankovic is with Baylor College of Medicine. Dr. Kurlan is with the Atlantic Neuroscience Institute. Drs. Lanzagorta and Nicolini are with the Carracci Medical Group. Mr. Lennertz and Drs. Maier, Moessner, and Wagner are with the University of Bonn. Drs. Lochner and Hemmings are with the University of Stellenbosch. Drs. Lowe, Reus, Mathews and Ms. Sheppard are with the University of California at San Francisco School of Medicine. Dr. Lyon is with the Cold Spring Harbor Laboratory. Dr. Macciardi is with University of California Irvine. Drs. McCracken, Piacentini, Nurmi, and Freimer are with the UCLA School of Medicine. Dr. Freimer is also with Semel Institute for Neuroscience and Human Behavior, UCLA. Dr. McMahon is with the University of Utah. Drs. Murphy, Wendland and Shugart are with the NIMH Intramural Research Program. Dr. Naarden is with Medical City Dallas Hospital. Drs. M. Pato, C. Pato, Knowles, and Wang are with the Zilkha Neurogenetic Institute. Dr. Richter is with Sunnybrook Health Sciences Centre. Drs. Robertson and Ruiz-Linares are with University College London. Dr. Rosenberg is with Wayne State University and Detroit Medical Center. Dr. Rouleau is with the Montreal Neurological Institute. Dr. Ruhrmann is with the University of Cologne. Dr. Stein is with the University of Cape Town. Dr. Veenstra-VanderWeele is with Vanderbilt University. Dr. Oostra is with

Erasmus Medical Center. Dr. Heutink is with the German Center for Neurodegenerative Diseases and VU University Medical Center Amsterdam. Dr. Posthuma is with VU University Amsterdam and Erasmus University Medical Centre, Rotterdam. Dr. Hanna is with the University of Michigan. Dr. Cook is with the University of Illinois at Chicago

## Affiliations

Drs. McGrath, Illmann, Fagerness, Geller, Jenike, Neale, Petryshen, Pauls, Scharf, Schroeder, Stewart, Mss. Yu, Gerber, Osiecki, Gallagher, and Messrs. Wolf, Haddad, and Kirby are with Massachusetts General Hospital. Dr. Stewart is also with the University of British Columbia. Dr. McGrath is also with American University. Dr. Scharf is also with Brigham and Womens Hospital, Boston, MA. Drs. O'Dushlaine, McGrath, Neale, Petryshen, Scharf, and Ms. Yu are also with the Harvard-MIT Broad Institute. Drs. Marshall, Scherer, Barr, Richter, Arnold, Sandor, Ms. Thiruvahindrapuram and Mr. Li are with the University of Toronto and the Hospital for Sick Children. Drs. Sandor and Barr are also with the Toronto Western Research Institute, University Health Network, Toronto. Dr. Kennedy is with the Centre for Addiction and Mental Health. Drs. Davis, Evans, and Cox are with the University of Chicago. Drs. Vallada, Miguel, and Brentani and Ms. Cappi are with the University of São Paulo Medical School. Dr. Bellodi is with the Università Vita-Salute San Raffaele. Dr. Benarroch is with Hadassah-Hebrew University Medical Center. Drs. Bienvenu, Cullen, Grados, Samuels, Singer, Nestadt, Riddle, and Ms. Wang are with Johns Hopkins University School of Medicine. Dr. Black is with the University of Iowa College of Medicine. Drs. Bloch, Coric, Fernandez, Leckman, Pakstis, Pittenger, and King are with the Yale University School of Medicine. Drs. Bruun and Budman are with North Shore-Long Island Jewish Medical Center. Dr. Budman is also with Hofstra University School of Medicine, Hempstead, NY. Dr. Bruun is also with New York University Medical Center, New York. Ms. Camarena is with the Instituto Nacional de Psiquiatría Ramon de la Fuente Muñiz. Dr. Cath is with Utrecht University and VU University Medical Center, Amsterdam. Dr. Cavallini is with the Ospedale San Raffaele. Drs. Chouinard and Dion are with the University of Montreal. Drs. Delorme and Leboyer are with the Robert Debre University Hospital and the French National Science Foundation. Dr. Delorme is also with Institut Pasteur, Paris. Dr. Leboyer is also with Institut Mondor de Recherche Biomédicale, Créteil, France. Dr. Denys is with the Netherlands Institute for Neuroscience. Drs. Denys and Derks are with the Academic Medical Center, Amsterdam. Drs. Rosário, Hounie, and Sampaio are with the Federal University of São Paulo. Dr. Sampaio is also with Universidade Federal da Bahia, Salvador, Bahia, Brazil. Dr. Eapen is with the University of New South Wales. Dr. Falkai is with the University of Munich. Dr. Herrera and Ms. Garrido are with the Hospital Nacional de Niños. Ms. Garrido is also with Clinica Herrera Amighetti, Avenida Escazú, San José, Costa Rica. Dr. Grabe is with the University Medicine Greifswald. Dr. Greenberg is with Brown Medical School. Drs. Gross-Tsur and Pollak are with Shaare Zedek Medical Center. Drs. Grünblatt and Walitza are with the University of Zurich. Dr. Walitza is also with the University of Würzburg. Drs.

Heiman and Tischfield are with Rutgers University. Dr. Jankovic is with Baylor College of Medicine. Dr. Kurlan is with the Atlantic Neuroscience Institute. Drs. Lanzagorta and Nicolini are with the Carracci Medical Group. Mr. Lennertz and Drs. Maier, Moessner, and Wagner are with the University of Bonn. Drs. Lochner and Hemmings are with the University of Stellenbosch. Drs. Lowe, Reus, Mathews and Ms. Sheppard are with the University of California at San Francisco School of Medicine. Dr. Lyon is with the Cold Spring Harbor Laboratory. Dr. Macciardi is with University of California Irvine. Drs. McCracken, Piacentini, Nurmi, and Freimer are with the UCLA School of Medicine. Dr. Freimer is also with Semel Institute for Neuroscience and Human Behavior, UCLA. Dr. McMahon is with the University of Utah. Drs. Murphy, Wendland and Shugart are with the NIMH Intramural Research Program. Dr. Naarden is with Medical City Dallas Hospital. Drs. M. Pato, C. Pato, Knowles, and Wang are with the Zilkha Neurogenetic Institute. Dr. Richter is with Sunnybrook Health Sciences Centre. Drs. Robertson and Ruiz-Linares are with University College London. Dr. Rosenberg is with Wayne State University and Detroit Medical Center. Dr. Rouleau is with the Montreal Neurological Institute. Dr. Ruhrmann is with the University of Cologne. Dr. Stein is with the University of Cape Town. Dr. Veenstra-VanderWeele is with Vanderbilt University. Dr. Oostra is with Erasmus Medical Center. Dr. Heutink is with the German Center for Neurodegenerative Diseases and VU University Medical Center Amsterdam. Dr. Posthuma is with VU University Amsterdam and Erasmus University Medical Centre, Rotterdam. Dr. Hanna is with the University of Michigan. Dr. Cook is with the University of Illinois at Chicago

## Acknowledgments

This work was supported by grants from the David Judah Fund, the Tourette Syndrome Association, the International OCD Foundation, and NIH (U01NS40024; DLP/JMS/TSA International Consortium for Genetics; R01NS16648, R01MH079489, and MH073250 [DLP]; K23MH085057 [JMS]; T32MH16259 [LMM]; NS037484 and P30NS062691 [NBF]; K20MH01065 and R01MH58376 [GLH]; R01MH092293 [GAH/RAK/JAT]). Additional support came from American Recovery and Re-investment Act (ARRA) awards NS40024-07S1 and NS16648-29S1 (DLP). This work was also supported by grants from the New Jersey Center for Tourette Syndrome and Associated Disorders, NIMH (R01MH092293; GAH/RAK/JAT), the German Research Foundation (Fa 241/6-1; DFG), the Ontario Mental Health Foundation (MAR and JLK), and T32MH018268 (JFL). Funding support for the Study of Addiction: Genetics and Environment (SAGE) was provided through the NIH Genes, Environment and Health Initiative (GEI; U01 HG004422). SAGE is one of the genome-wide association studies funded as part of the Gene Environment Association Studies (GENEVA) under GEI. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01 HG004446). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Support for collection of datasets and samples was provided by the Collaborative Study on the Genetics of Alcoholism (COGA; U10 AA008401), the Collaborative Genetic Study of Nicotine Dependence (COGEND; P01 CA089392), and the Family Study of Cocaine Dependence (FSCD; R01 DA013423). Funding support for genotyping, which was performed at the Johns Hopkins University Center for Inherited Disease Research, was provided by the NIH GEI (U01HG004438), the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the NIH contract "High throughput genotyping for studying the genetic contributions to human disease" (HHSN268200782096C). The datasets used for the analyses described in this manuscript were obtained from dbGaP at [http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000092.v1.p1](http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000092.v1.p1) through dbGaP accession number phs000092.v1.p. None of the funding agencies for this project had any influence on a) the design or conduct of the study; b) management, analysis or interpretation of the data; or c) preparation, review or approval of the manuscript.

The authors thank the families, patients, and control volunteers who participated in this research. The authors would like to acknowledge additional members of the Tourette Syndrome Association International Consortium for Genetics (TSAICG) and the International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC), including Denise A. Chavira, PhD, Karin Egberts, MD, Eduardo Fournier, MS, Simon L. Girard,

MSc, Jubel Morgan, RN, Tobias Renner, MD, Roxana Romero, MA, John Walkup, MD, and Herman G. Westenberg, PhD (deceased), for their contributions to this research.

## References

1. Grados MA. The genetics of obsessive-compulsive disorder and Tourette's syndrome: what are the common factors? *Curr Psychiatry Rep.* 2009; 11:162–166. [PubMed: 19302771]
2. Davis LK, Yu D, Keenan CL, et al. Partitioning the heritability of Tourette syndrome and obsessive compulsive disorder reveals differences in genetic architecture. *PLoS genetics.* Oct.2013 9(10):e1003864. [PubMed: 24204291]
3. Cook EH Jr, Scherer SW, Cook EH. Copy-number variations associated with neuropsychiatric conditions. *Nature.* 2008; 455:919–923. [PubMed: 18923514]
4. Malhotra D, Sebat J. CNVs: harbingers of a rare variant revolution in psychiatric genetics. *Cell.* 2012; 148:1223–1241. [PubMed: 22424231]
5. Thapar A, Cooper M. Copy number variation: what is it and what has it told us about child psychiatric disorders? *Journal of the American Academy of Child and Adolescent Psychiatry.* 2013; 52:772–774. [PubMed: 23880486]
6. Pescosolido MF, Gamsiz ED, Nagpal S, Morrow EM. Distribution of disease-associated copy number variants across distinct disorders of cognitive development. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2013; 52:414–430. e414. [PubMed: 23582872]
7. van Grootheest DS, Cath DC, Beekman AT, Boomsma DI. Twin studies on obsessive-compulsive disorder: a review. *Twin Res Hum Genet.* 2005; 8:450–458. [PubMed: 16212834]
8. Bolton D, Rijsdijk F, O'Connor TG, Perrin S, Eley TC. Obsessive-compulsive disorder, tics and anxiety in 6-year-old twins. *Psychological medicine.* 2007; 37:39–48. [PubMed: 16999878]
9. O'Rourke JA, Scharf JM, Yu D, Pauls DL. The genetics of Tourette syndrome: a review. *Journal of psychosomatic research.* 2009; 67:533–545. [PubMed: 19913658]
10. Scharf JM, Miller LL, Mathews CA, Ben-Shlomo Y. Prevalence of Tourette syndrome and chronic tics in the population-based Avon longitudinal study of parents and children cohort. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2012; 51:192–201. e195. [PubMed: 22265365]
11. Pauls DL. The genetics of obsessive-compulsive disorder: a review. *Dialogues in clinical neuroscience.* 2010; 12(2):149–163. [PubMed: 20623920]
12. Mathews CA, Grados MA. Familiarity of Tourette syndrome, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder: heritability analysis in a large sib-pair sample. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2011; 50:46–54. [PubMed: 21156269]
13. Delorme R, Moreno-De-Luca D, Gennetier A, et al. Search for copy number variants in chromosomes 15q11-q13 and 22q11.2 in obsessive compulsive disorder. *BMC Med Genet.* 2010; 11:100. [PubMed: 20565924]
14. Walitza S, Bove DS, Romanos M, et al. Pilot study on HTR2A promoter polymorphism, –1438G/A (rs6311) and a nearby copy number variation showed association with onset and severity in early onset obsessive-compulsive disorder. *Journal of Neural Transmission.* 2012; 119:507–515. [PubMed: 21874579]
15. Sundaram SK, Huq AM, Wilson BJ, Chugani HT. Tourette syndrome is associated with recurrent exonic copy number variants. *Neurology.* 2010; 74:1583–1590. [PubMed: 20427753]
16. Fernandez TV, Sanders SJ, Yurkiewicz IR, et al. Rare copy number variants in tourette syndrome disrupt genes in histaminergic pathways and overlap with autism. *Biological psychiatry.* 2012; 71:392–402. [PubMed: 22169095]
17. Nag A, Bochukova EG, Kremeyer B, et al. CNV analysis in Tourette syndrome implicates large genomic rearrangements in COL8A1 and NRXN1. *PLoS One.* 2013
18. Scharf JM, Yu D, Mathews CA, et al. Genome-wide association study of Tourette's syndrome. *Molecular psychiatry.* Jun; 2013 18(6):721–728. [PubMed: 22889924]
19. Stewart SE, Yu D, Scharf JM, et al. Genome-wide association study of obsessive-compulsive disorder. *Molecular psychiatry.* Jul; 2013 18(7):788–798. [PubMed: 22889921]

20. Bierut LJ, Agrawal A, Bucholz KK, et al. A genome-wide association study of alcohol dependence. *Proceedings of the National Academy of Sciences of the United States of America*. Mar 16; 2010 107(11):5082–5087. [PubMed: 20202923]
21. Wang K, Li M, Hadley D, et al. PennCNV: an integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. *Genome research*. 2007; 17:1665–1674. [PubMed: 17921354]
22. Pinto D, Pagnamenta AT, Klei L, et al. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature*. 2010; 466:368–372. [PubMed: 20531469]
23. Pinto D, Darvishi K, Shi X, et al. Comprehensive assessment of array-based platforms and calling algorithms for detection of copy number variants. *Nature biotechnology*. 2011; 29:512–520.
24. Williams NM, Zaharieva I, Martin A, et al. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet*. 2010; 376:1401–1408. [PubMed: 20888040]
25. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*. 2008; 455:237–241. [PubMed: 18668038]
26. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *American journal of human genetics*. 2007; 81:559–575. [PubMed: 17701901]
27. Sanders SJ, Ercan-Sencicek AG, Hus V, et al. Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron*. 2011; 70:863–885. [PubMed: 21658581]
28. Cooper GM, Coe BP, Girirajan S, et al. A copy number variation morbidity map of developmental delay. *Nature Genetics*. 2011; 43:838–846. [PubMed: 21841781]
29. Kaminsky EB, Kaul V, Paschall J, et al. An evidence-based approach to establish the functional and clinical significance of copy number variants in intellectual and developmental disabilities. *Genet Med*. 2011; 13:777–784. [PubMed: 21844811]
30. de Kovel CG, Trucks H, Helbig I, et al. Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies. *Brain*. 2010; 133:23–32. [PubMed: 19843651]
31. Heinzen EL, Radtke RA, Urban TJ, et al. Rare deletions at 16p13.11 predispose to a diverse spectrum of sporadic epilepsy syndromes. *American journal of human genetics*. 2010; 86:707–718. [PubMed: 20398883]
32. Ullmann R, Turner G, Kirchhoff M, et al. Array CGH identifies reciprocal 16p13.1 duplications and deletions that predispose to autism and/or mental retardation. *Human Mutation*. 2007; 28:674–682. [PubMed: 17480035]
33. Firth HV, Richards SM, Bevan AP, et al. DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. *American journal of human genetics*. 2009; 84:524–533. [PubMed: 19344873]
34. Kerbeshian J, Burd LJ, Martsof JT. Psychiatric comorbidity in a girl with Saethre-Chotzen syndrome. *Psychiatric Genetics*. 2008; 18:258–259. [PubMed: 18797404]
35. Kirov G, Pocklington AJ, Holmans P, et al. De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Molecular psychiatry*. 2012; 17:142–153. [PubMed: 22083728]
36. Malhotra D, McCarthy S, Michaelson JJ, et al. High frequencies of de novo CNVs in bipolar disorder and schizophrenia. *Neuron*. 2011; 72:951–963. [PubMed: 22196331]
37. Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M. Strong association of de novo copy number mutations with sporadic schizophrenia. *Nature Genetics*. 2008; 40:880–885. [PubMed: 18511947]
38. Robertson MM, Shelley BP, Dalwai S, Brewer C, Critchley HD. A patient with both Gilles de la Tourette's syndrome and chromosome 22q11 deletion syndrome: clue to the genetics of Gilles de la Tourette's syndrome? *Journal of Psychosomatic Research*. 2006; 61:365–368. [PubMed: 16938515]
39. Clarke RA, Fang ZM, Diwan AD, Gilbert DL. Tourette syndrome and klippel-feil anomaly in a child with chromosome 22q11 duplication. *Case Rep Med*. 2009; 2009:361518. [PubMed: 20069037]

40. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *American journal of human genetics*. 2010; 86:749–764. [PubMed: 20466091]

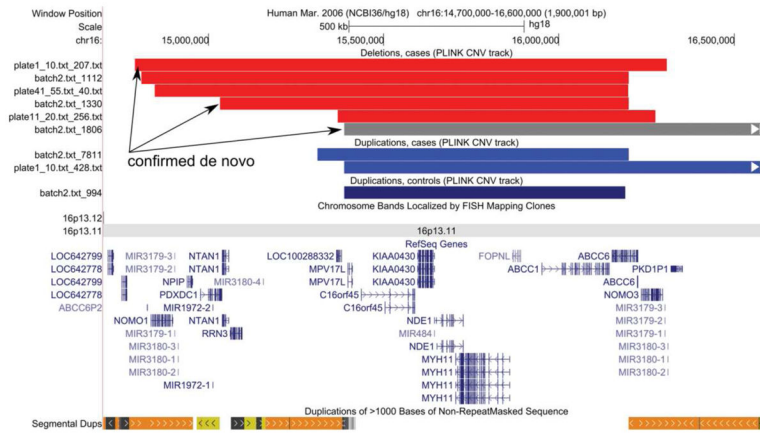
## Disclosure

Dr. O’Dushlaine has received funding from the Stanley Center for Psychiatric Research. Dr. Black has received a research grant from AstraZeneca and has received royalties from American Psychiatric Publishing, UpToDate, and Oxford University Press. Dr. Bloch has received grant or research support from the National Institutes of Health (NIH) K23 Award, the Trichotillomania Learning Center, TSA, the Patterson Foundation, the National Alliance for Research on Schizophrenia and Depression, the Rembrandt Foundation, and the American Academy of Child and Adolescent Psychiatry Research Initiative Junior Investigator Award. Dr. Budman is currently receiving funding for Tourette syndrome clinical trials from Otsuka Pharmaceutical and has received research funding in the past year from Psyadon Pharmaceuticals. She is also a speaker for the TSA-CDC partnership and was on the National Medical Advisory Board for TSA in the past year. Dr. Cath has received speaker’s honoraria from Pfizer pharmaceuticals and a research grant from the TSA foundation. Dr. Denys is a member of the advisory board of Lundbeck and has received occasional consultant fees from Medtronic for educational purposes. Dr. Rosário has received a grant from CNPq (Brazilian National Council) and has received research grants and/or consultancy honoraria from Novartis and Shire. Dr. Fernandez has received research funding from NIMH (K08 MH099424-01), the Simons Foundation, Allison Foundation, and Shire. Dr. Geller has received research support from NIMH and teaching honorarium from the American Academy of Child and Adolescent Psychiatry. Dr. Grabe has received research grants from the German Research Foundation and the Federal Ministry of Education and Research Germany. He has also received speakers’ honoraria from Bristol-Myers Squibb, Eli Lilly and Co., and Servier, and travel funds from Eli Lilly and Co., AstraZeneca, and Servier. Dr. Greenberg has received research funding from F. Hoffman la Roche Pharmaceuticals, Ltd. Dr. Kennedy has received honoraria from Roche, Eli Lilly and Co., and Novartis. Dr. King has received research support from NIH and Grifols, LLC. Dr. Leckman has received grant or research support from the National Institute of Mental Health (NIMH), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), TSA, GRIFOLS (formerly Talecris Biotherapeutics), and the Klingenstein Third Generation Foundation. He has served on the speakers’ bureau of TSA. He has received royalties from John Wiley and Sons, McGraw Hill, and Oxford University Press. He has received donations to clinical and research programs by the Associates of the Yale Child Study Center. Dr. Macciardi has received payments and travel refunds from Pharma Company TEVA for a couple of meetings in 2012. Dr. McCracken has received speaker honoraria from the TSA and research grants from Otsuka, Roche, Seaside Therapeutics, NICHD, and NIMH. He has served as a consultant to Roche. Dr. Piacentini has received grant or research support from NIMH, Pfizer Pharmaceuticals through the Duke Clinical Research Institute CAPTN Network, and TSA. He has served as a consultant to the Coleman Research Group and NIMH. He has served on the speakers’ bureau of TSA and the International Obsessive Compulsive Disorder Foundation. He has received book royalties from Guilford Press and Oxford University Press. He is a co-author of the Child



OCD Impact Scale-Revised (COIS-R), the Child Anxiety Impact Scale (CAIS), the Parent Tic Questionnaire (PTQ), and the Premonitory Urge for Tics Scale (PUTS) assessment tools, all of which are in the public domain, therefore no royalties are received. He has received financial support from the Furlotti Family Foundation to develop a computerized child OCD treatment program. Dr. Pittenger has received honoraria for consulting from F. Hoffman la Roche Pharmaceuticals, Ltd. Dr. Richter has received honoraria from Lundbeck and has received research funding from Great-West Life Assurance Company of Canada and Eli Lilly Canada Ltd. Dr. Robertson has received grants from Tourette's Action-UK, TSA-USA. She has received honoraria from Janssen-Cilag, and book royalties from Wiley-Blackwell, David Fulton/Granada/Taylor Francis, Oxford University Press, and Jessica Kingsley Publishers. She is a patron of Tourette's Action (UK), sits on the medical advisory boards of the Italian Tourette Syndrome Association and the Tourette Syndrome Foundation of Canada, and is Honorary Life President of ESSTS (European Society for the Study of Tourette's Syndrome). Dr. Rosenberg has received consulting fees from Shire and research support from Children's Hospital of Michigan Foundation and NIH. Dr. Sandor has received honoraria and research support from GlaxoSmithKline, Astra, Solway, Otsuka, Psyadon, TSA, Tourette Syndrome Foundation of Canada, and NIH. Dr. Stein has received research grants and/or consultancy honoraria from AMBRF, Biocodex, Lundbeck, National Responsible Gambling Foundation, Novartis, Servier, and Sun. Dr. Veenstra-VanderWeele has consulted with Novartis and Roche Pharmaceuticals. He has received research funding from Novartis, Roche, Seaside Therapeutics, Forest, Sunovion, and SynapDx. Dr. Walitza has received lecture honoraria from Janssen Cilag, AstraZeneca, and Eli Lilly and Co. She has received research support from the Swiss National Science Foundation (SNF), Deutsche Forschungsgemeinschaft, EU FP7, and HSM Hochspezialisierte Medizin of the Kanton, Zurich, Switzerland. Dr. Wendland is a past employee of F. Hoffmann-La Roche and a current employee of Pfizer. Dr. Nicolini has received grant/research support from Servier, Transcept, and Pherin. He has served as a consultant or on advisory boards for Servier, Transcept, Sanofi, and MSD. He has also served on speakers' bureaus for MSD. Dr. Scherer has received funding from the government of Ontario. Dr. Arnold has received an unrestricted research grant from DNA Genotek. Dr. Stewart has received research support from the International OCD Foundation, the Anxiety Disorder Association of America, a Harvard Scholar Award, the Canadian Institutes of Health Research, the University of British Columbia, the Child and Family Research Institute, the British Columbia Mental Health and Addictions Research Institute, and the Michael Smith Foundation for Health Research. Dr. Mathews has received speaker honoraria and a research grant from the TSA and a research grant from the International OCD Foundation. Dr. Knowles has received research support from NIH, the International OCD Foundation, and Della Martin Foundation, and speaker's honoraria from Illumina, Inc. Dr. Cook has served as a consultant for and has had a research contract with Seaside Therapeutics. Dr. K. Wang is co-founder and shareholder of Tute Genomics, a bioinformatics consulting company. Dr. Scharf has received research support, honoraria, and travel support from TSA. He is also a member of the TSA Scientific Advisory Board. Ms. Yu has received research support from TSA and NIH. Mr. Fagerness was employed by Genomind. Drs. McGrath, Marshall, Davis, Schroeder, Illmann, Barr, Bellodi, Benarroch, Bienvenu, Bruun, Cavallini, Chouinard, Coric, Cullen, Delorme, Derks, Dion, Eapen, Evans, Falkai, Grados, Gross-Tsur, Grünblatt,

Heiman, Hemmings, Herrera, Hounie, Jankovic, Kurlan, Lanzagorta, Leboyer, Lochner, Lowe, Lyon, Maier, McMahon, Murphy, Naarden, Neale, Nurmi, Pakstis, M. Pato, C. Pato, Pollak, Reus, Riddle, Rouleau, Ruhrmann, Sampaio, Samuels, Singer, Smit, Tischfield, Vallada, Shugart, Miguel, Oostra, Moessner, Wagner, Ruiz-Linares, Heutink, Nestadt, Freimer, Petryshen, Posthuma, Jenike, Cox, Hanna, Brentani, Pauls, and Mr. Thiruvahindrapuram, Mr. Li, Ms. Cappi, Ms. Gerber, Mr. Wolf, Ms. Osiecki, Mr. Kirby, Mr. Haddad, Ms. Gallagher, Ms. Camarena, Ms. Garrido, Mr. Lennertz, Ms. Sheppard, and Ms. Y. Wang report no biomedical financial interests or potential conflicts of interest.



**Figure 1.** 16p13.11 region with 8 patient and 1 control copy number variants (CNVs). Note: red denotes deletions; blue, duplications. Gray denotes the de novo deletion that did not survive strict quality control (QC) filters but was validated in silico and by qPCR.

Table 1

Global Burden Analysis of Large (>500kb), Rare (<1%) Copy Number Variants (CNVs) in Cases Ascertained for Obsessive-Compulsive Disorder (OCD) or Tourette Syndrome (TS) Compared to Controls

Description	Combined OCD/TS n=2699	Hap610 Controls n=561	Hap1M Controls n=1228	Case/Control Ratio	P-Value <sup>a</sup>
All CNVs	186	39	111		
> 500kb					
#CNVs	186	39	111		
Rate	0.069	0.070	0.090	0.82	0.97
Proportion	0.067	0.068	0.086	0.84	0.95
Gene Rate	7.23	5.16	6.25	1.21	0.19
Deletions					
#CNVs	60	7	31		
Rate	0.022	0.012	0.025	1.05	0.45
Proportion	0.022	0.012	0.025	1.03	0.48
Gene Rate	6.29	4.00	4.39	1.46	0.14
Duplications					
#CNVs	126	32	80		
Rate	0.047	0.057	0.065	0.75	0.99
Proportion	0.046	0.055	0.063	0.75	0.99
Gene Rate	7.63	5.42	6.75	1.20	0.26

Note: gene rate = average number genes spanned by CNVs; proportion = proportion of samples with 1 CNV; rate = average number of CNVs per person.

<sup>a</sup> one-sided, empirical *p*-value

**Table 2**

Neurodevelopmental Burden Analysis of Large, Rare Copy Number Variants (CNVs) in Patients with Obsessive-Compulsive Disorder (OCD) or Tourette Syndrome (TS) Compared to Controls

<b>Description</b>	<b>Combined OCD/TS n=2699</b>	<b>Hap610 Controls n=561</b>	<b>Hap1M Controls n=1228</b>	<b>Patient/Control Ratio</b>	<b>P-Value<sup>a</sup></b>
All CNVs	24	2	8		
> 500kb	Rate/Proportion <sup>b</sup>	0.0089	0.0036	1.59	0.14
Deletions	#CNVs	10	0		
> 500kb	Rate/Proportion <sup>b</sup>	0.0037	0	3.31	0.09
Duplications	#CNVs	14	2		
>500kb	Rate/Proportion <sup>b</sup>	0.0052	0.0036	1.16	0.46

<sup>a</sup> One-sided, empirical *p*-value

<sup>b</sup> Rate and proportion are identical because no samples had >1 large, neurodevelopmental CNV.

**Table 3**

Large, Rare Case Number Variants (CNVs) in Patients and Controls Overlapping Previously Identified Neurodevelopmental Loci

Chr	Region	Deletions				Duplications				p-value <sup>1</sup>
		Patients (OCD only/TS only/OCD+TS/CT) n=2699	Controls n=1789	p-value <sup>a</sup>	Patients (OCD only/TS only/OCD+TS/CT) n=2699	Controls n=1789	p-value <sup>a</sup>	Patients (OCD only/TS only/OCD+TS/CT) n=2699	Controls n=1789	
2	2p15-16.1	0	0	--	0	1	--	0	1	1.00
2	2q11.2	1 (0/0/1)	0	0.60	0	0	--	0	0	--
3	CNTN4	1 (0/0/1)	1	0.84	1 (0/0/1)	0	--	1 (0/0/1)	0	0.60
3	3q29	0	0	--	0	1	--	0	1	1.00
6	PARK2	1 (1/0/0)	0	0.60	3 (2/0/1)	0	--	3 (2/0/1)	0	0.22
7	7q11.23	0	0	--	1 (0/0/1)	0	--	1 (0/0/1)	0	0.60
12	12q14	0	0	--	0	1	--	0	1	1.00
15	15q11-q13	0	0	--	2 (0/0/2)	0	--	2 (0/0/2)	0	0.36
15	15q24	0	1	1.00	0	0	--	0	0	--
16	16p13.11	5 (4/1/0)	0	0.08	2 (2/0/0)	1	--	2 (2/0/0)	1	0.65
16	16p11.2	0	0	--	1 (1/0/0)	2	--	1 (1/0/0)	2	0.94
17	NFI	0	0	--	1 (0/1/0)	0	--	1 (0/1/0)	0	0.60
17	17q12	1 (1/0/0)	0	0.60	0	1	--	0	1	1.00
22	22q11.21	1 (1/0/0)	0	0.60	3 (2/0/1)	1	--	3 (2/0/1)	1	0.48

Note: Chr = chromosome; CT = chronic tics; OCD = obsessive-compulsive disorder; TS = Tourette syndrome.

<sup>a</sup>Fisher's exact 1-sided p-value.