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

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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 (>500 kb), rare (<1%) copy number variants (CNVs) in OCD and the largest genome-wide CNV analysis in TS to date. **Method:** The primary analyses used a cross-disorder design for 2,699 case 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

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of these neurodevelopmental deletions were located in a single locus, 16p13.11 (5 case patient deletions: 0 control deletions, $p = .08$ in the current study, $p = .025$ compared to published controls). Three 16p13.11 deletions were confirmed de novo, providing further support for 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 individuals with 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. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(8):910–919. **Key Words:** Tourette syndrome, obsessive-compulsive disorder, copy number variation, genetics, 16p13.11

Obsessive-compulsive disorder (OCD) and Tourette syndrome (TS) are neurodevelopmental disorders with significant phenotypic and genetic overlap.[1,2] 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.[3] 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.[4] CNVs predisposing individuals to these disorders overlap substantially, highlighting the cross-disorder effects of this class of genetic variation.[5,6] 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, although specific gene variants have been difficult to identify.[7-9] Both disorders frequently co-occur in individuals,[10] and there is evidence for shared OCD/TS genetic risk from family studies,[9,11] with genetic correlation estimates ranging from 41% to 90%.[2,12] In OCD, locus-specific CNV analyses have been reported,[13,14] but no prior genome-wide CNV analysis has been performed. In TS, the 3 previous genome-wide surveys of CNVs have been limited by small sample sizes (<500 patients), and results differ with regard to whether there is an increased CNV burden in individuals with TS compared to controls.[15-17] No specific CNV region has received strong statistical support across studies, although exonic *NRXN1* deletions have been identified in 2 studies.[15,17]

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 3 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 multicenter collaborative genome-wide association study (genome-wide association study [GWAS]; described by Scharf *et al.*[18] and Stewart *et al.*[19]). Participants aged 18 years and older provided written, voluntary informed consent for participation in genetic studies. Individuals aged less than 18 years provided assent; parents provided written consent. 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, and S11, available online, for available clinical information regarding ID, ASD, attention-deficit/hyperactivity disorder [ADHD], and seizures). OCD and TS samples were collected independently but were genotyped jointly to facilitate cross-disorder analyses. All patients were genotyped on the Illumina Human610-Quadv1_B platform.

OCD. The initial OCD sample consisted of 1,565 case patients and 437 parent–child trios (n = 406 independent families, 31 affected siblings) recruited from 22 sites in the United States, Canada, Europe, Latin America,