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Lifetime Prevalence, Age of Risk, and Etiology of Comorbid Psychiatric Disorders in Tourette Syndrome

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Abstract:

Importance: Tourette syndrome (TS) is characterized by high rates of psychiatric comorbidity; however, few studies have fully characterized these comorbidities. Furthermore, most studies have included relatively few participants (<200), and none has examined the ages of highest risk for each TS-associated comorbidity or their etiologic relationship to TS.

Objective: To characterize the lifetime prevalence, clinical associations, ages of highest risk, and etiology of psychiatric comorbidity among individuals with TS.

Design, Setting, and Participants: Cross-sectional structured diagnostic interviews conducted between April 1, 1992, and December 31, 2008, of participants with TS (n = 1374) and TS-unaffected family members (n = 1142).

Main Outcomes and Measures: Lifetime prevalence of comorbid *DSM-IV-TR* disorders, their heritabilities, ages of maximal risk, and associations with symptom severity, age at onset, and parental psychiatric history.

Results: The lifetime prevalence of any psychiatric comorbidity among individuals with TS was 85.7%; 57.7% of the population had 2 or more psychiatric disorders. The mean (SD) number of lifetime comorbid diagnoses was 2.1 (1.6); the mean number was 0.9 (1.3) when obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD) were excluded, and 72.1% of the individuals met the criteria for OCD or ADHD. Other disorders, including mood, anxiety, and disruptive behavior, each occurred in approximately 30% of the participants. The age of greatest risk for the onset of most comorbid psychiatric disorders was between 4 and 10 years, with the exception of eating and substance use disorders, which began in adolescence (interquartile range, 15-19 years for both). Tourette syndrome was associated with increased risk of anxiety (odds ratio [OR], 1.4; 95% CI, 1.0-1.9; P = .04) and decreased risk of substance use disorders (OR, 0.6; 95% CI, 0.3-0.9; P = .02) independent from comorbid OCD and ADHD; however, high rates of mood disorders among participants with TS (29.8%) may be accounted for by comorbid OCD (OR, 3.7; 95% CI, 2.9-4.8; P < .001). Parental history of ADHD was associated with a higher burden of non-OCD, non-ADHD comorbid psychiatric disorders (OR, 1.86; 95% CI, 1.32-2.61; P < .001). Genetic

correlations between TS and mood (RhoG, 0.47), anxiety (RhoG, 0.35), and disruptive behavior disorders (RhoG, 0.48), may be accounted for by ADHD and, for mood disorders, by OCD.

Conclusions and Relevance: This study is, to our knowledge, the most comprehensive of its kind. It confirms the belief that psychiatric comorbidities are common among individuals with TS, demonstrates that most comorbidities begin early in life, and indicates that certain comorbidities may be mediated by the presence of comorbid OCD or ADHD. In addition, genetic analyses suggest that some comorbidities may be more biologically related to OCD and/or ADHD rather than to TS.

Introduction

Tourette syndrome (TS) is a childhood-onset neuropsychiatric disorder characterized by multiple motor tics and 1 or more vocal tics that persist for at least 1 year.^{1,2} Multiple comorbid psychiatric disorders have been reported in TS-affected individuals; when present, these conditions typically cause more distress and impairment than do tics.³⁻⁷ High rates of comorbid attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) have been well documented and are thought to be core components of the TS phenotype.^{4,8-11} Although elevated rates for mood disorders, nonobsessional anxiety disorders, and disruptive behavior disorders (DBDs) have also been reported,^{4,12-17} a significant gap in knowledge still exists regarding the range, prevalence, and clinical attributes of the non-OCD, non-ADHD comorbid disorders. The few available studies were limited by small sample sizes (<200 participants),^{3,7,18-20} small number of diagnoses examined, or reliance on symptom checklists and severity scales rather than DSM-based, structured diagnostic psychiatric assessments.^{18,21-24}

Despite methodologic limitations, these studies^{12,13,15} suggest that a high proportion of individuals with TS (61%-96%) have at least 1 comorbid psychiatric disorder. Unfortunately, there is no consensus regarding expected rates of the noncore (ie, non-OCD, non-ADHD) psychiatric disorders in TS-affected individuals; in addition, there is limited knowledge regarding typical age at onset, ages of highest risk, and association with impairment for these disorders.

Although the shared genetic susceptibility to OCD and ADHD in TS-affected families has been established,²⁵⁻²⁷ the etiologic relationships between TS and other psychiatric disorders have not been examined. Elevated rates of psychiatric comorbidity may arise from (1) shared genetic susceptibility with TS, (2) shared genetic susceptibility with comorbid OCD or ADHD, or (3) nongenetic factors (eg, shared environment). Together with quantifying the extent of concomitant occurrence, understanding the clinical and etiologic relationships between TS, OCD, ADHD, and other psychiatric comorbidities will help in understanding the sources of heterogeneity of this complex neuropsychiatric disorder. Therefore, the aims of the present study were to quantify psychiatric disorder burden, ages of highest risk, and underlying genetic relationship of psychiatric disorders in TS-affected individuals using the largest, most comprehensive data set available.

Methods

The study was described to all participants; adults provided written informed consent and children written assent before participating. Parents provided written consent for their children's participation. Institutional review board approval was obtained from all participating sites. The participants did not receive financial compensation. The eAppendix in the Supplement includes the inclusion and exclusion criteria and informed consent details.

Participants

Phenotypic data were collected for genetic studies from TS-affected individuals aged 6 years or older and their parents and siblings, ascertained from 802 independent families between April 1, 1992, and December 31, 2008. Recruitment primarily occurred from tic disorder specialty clinics in the United States, Canada, Great Britain, and the Netherlands as well as from the Tourette Syndrome Association of the United States.

Phenotypic Assessments

A psychiatrist, neurologist, or psychologist trained in the use of clinical research assessments evaluated all participants (D.L.P., Y.D., M.A.G., C.I., R.A.K., P.S., W.M.M., D.C.C., R.K., M.M.R., and C.A.M.).²⁸ Tics, OCD, and ADHD symptoms were assessed using a structured clinical interview specifically developed for TS genetic studies (eAppendix in the Supplement). The Structured Clinical Interview for *DSM-IV* Axis I Disorders–Non-Patient Edition, 2.0²⁹ (all sites except the University of Utah site) or the Schedule for Affective Disorders and Schizophrenia–Lifetime Version, Modified for the Study of Anxiety Disorders³⁰ (University of Utah site) was used to gather data on *DSM-IV-TR* diagnoses for adults. The Schedule for Affective Disorders and Schizophrenia for School-Age Children, the Lifetime Version³¹ (all sites except Johns Hopkins University School of Medicine or University of Toronto) or the Epidemiologic Version³² (Johns Hopkins University School of Medicine and University of Toronto sites) was used to collect data on *DSM-IV-TR* diagnoses in children and adolescents. Final diagnoses were assigned using a best-estimate process, which requires diagnostic consensus by at least 2 raters.^{28,33} We grouped individual disorders into *DSM-IV-TR*–based categories (eg, anxiety disorders) to aid in clinical interpretation. The eAppendix in the Supplement includes details regarding diagnostic instruments, rater training and reliability, age-at-onset determination, and the best-estimate process.

Statistical Analysis

For lifetime prevalence estimates of comorbid disorders and ages at onset, we limited the sample to the 1374 participants with TS. We also examined the lifetime prevalence of disorders among probands compared with their TS-affected first-degree relatives (eAppendix in the Supplement). To examine the association among TS, OCD, and ADHD with other comorbid disorders and for heritability analyses, we included all individuals, including TS-unaffected family members. We compared the rates of comorbid disorders by sex and age at interview using χ^2 and Fisher exact tests. We examined the relationship between psychiatric comorbidity and TS, OCD, and ADHD by comparing lifetime prevalence rates of comorbid disorders among participants with TS only, TS and OCD only (TS+OCD), TS and ADHD only (TS+ADHD), and TS with both OCD and ADHD (TS+OCD+ADHD) using χ^2 tests. We used generalized estimating equations to examine the association of TS, ADHD, and OCD (individually and in combination) with other comorbid disorders, controlling for family relationships, age at interview, and sex.

For each disorder, we graphed the number of individuals with each age at onset using violin plots along with the median value and corresponding interquartile range. Age of highest risk was defined as the age at which the cumulative risk exceeded 10% (lower bound) through the upper bound of the interquartile range.

Using generalized estimating equation models clustering on family and controlling for age at interview and sex, we tested the association between the presence of 1 or more comorbid disorder (excluding OCD and ADHD) with OCD and tic severity; OCD and ADHD; parental history of OCD, ADHD, and TS; and TS, OCD, and ADHD ages at onset. To improve clinical interpretation, we transformed continuous severity measures into 3 categories (low, medium, and high) and ages at onset into early and late onset so that there were approximately equal numbers of participants in each group. Variables from each generalized estimating equation model with a significance level of $P \leq .20$ were added simultaneously to a multivariate model.

We calculated the additive genetic and environmental correlations between TS and classes of comorbid disorders using the Sequential Oligogenic Linkage Analysis Routines (SOLAR, version 6.2.2)³⁴ (eAppendix and eFigure in the Supplement). For these analyses, TS was combined with chronic motor or vocal tic disorders (CMVTDs). We did not examine the heritability of psychotic or eating disorders because of the low prevalence rates or of elimination disorders because of missing parental data.

Results

Demographic Characteristics

The sample consisted of 1374 TS-affected individuals, including parents or siblings without a TS diagnosis who met the best estimate criteria for TS (583 [42.4%]), and 1142 TS-unaffected first-degree relatives. The subsample of TS-affected individuals showed a 3:1 male predominance (1006 [73.2%] male), and the mean (SD) age at assessment was 19.1 (13.5) years. Demographics and clinical characteristics of TS-affected and TS-unaffected participants are presented in eTable 1 in the Supplement.

Overall Burden of Psychiatric Comorbidity

Of the participants with TS, 85.7% met the criteria for 1 or more comorbid disorder (including OCD and ADHD) and 57.7% met the criteria for 2 or more comorbid disorders. Lifetime prevalence rates for classes of comorbid disorders are summarized in Table 1; rates of individual disorders by sex and age are presented in eTable 2 and eTable 3, respectively, in the Supplement. The mean (SD) number of lifetime disorders was 2.1 (1.6). When OCD and ADHD were excluded, 45.3% of the patients met the criteria for 1 or more comorbid disorder and 23.6% met the criteria for 2 or more comorbid disorders. The mean number of lifetime diagnoses, excluding OCD and ADHD, was 0.9 (1.3). There were no significant differences in the rates of comorbid diagnoses between probands and TS-affected relatives when controlling for age at assessment (eTable 4 in the Supplement); therefore, subsequent analyses combined these groups.

Prevalence of Specific Psychiatric Disorders

OCD and ADHD

The most common comorbid psychiatric disorders were OCD (50.0%) and ADHD (54.3%); 72.1% of the TS-affected participants met the criteria for either disorder. Females were more likely to have comorbid OCD (57.1% vs 47.5%; $P < .01$), and males were more likely to have comorbid ADHD (58.5% vs 42.3%; $P < .01$). Nearly one-third (29.5%) of the participants had TS+OCD+ADHD, 20.2% had TS+OCD, 22.4% had TS+ADHD, and 27.9% had TS

only. There was a significant interaction of sex and age with diagnostic group ($\chi^2 = 43.1$, $P < .001$; and $\chi^2 = 121.6$, $P < .001$, respectively).

Other Conditions

After OCD and ADHD, mood disorders, anxiety disorders, and DBDs were the most prevalent classes of psychiatric comorbidity, each affecting approximately 30% of TS-affected participants; psychotic disorders were the least common (<1%). The prevalence of individual disorders ranged from 0.5% (bipolar II disorder) to 26.1% (major depressive disorder) (eTables 2-5 in the Supplement). Females were more likely to have major depressive disorder, most anxiety disorders, and eating disorders. Males were more likely to have ADHD and DBD (oppositional defiant disorder or conduct disorder) (Table 1 and eTable 2 in the Supplement). Adults and adolescents were most likely to have OCD as well as mood, anxiety, eating, and substance use disorders, whereas children were more likely to have ADHD (eTable 3 in the Supplement).

There was a clear relationship between OCD, ADHD, and the other psychiatric comorbidities in TS-affected participants. Mood, anxiety, and substance use disorders were more prevalent among participants with TS+OCD and TS+OCD+ADHD than among those with TS-only or TS+ADHD. Disruptive behavior disorders and psychotic disorders were more prevalent among participants with TS+OCD+ADHD than among the other 3 groups (Figure 1 and eTable 5 in the Supplement). When these analyses were repeated for males and females separately using the diagnostic groups shown in Figure 1, patterns of significance for χ^2 analyses were comparable to those for all TS-affected participants combined, except for psychotic disorders, which is attributable to small sample sizes (eTable 5 in the Supplement).

To assess the relationships between TS, OCD, ADHD, and psychiatric comorbidity, we conducted a multivariate generalized estimating equation model in all individuals (eTable 6 in the Supplement). After controlling for OCD and ADHD, TS was independently associated with an increased risk of anxiety disorders (odds ratio [OR], 1.4; 95% CI, 1.0-1.9; $P = .04$) and a decreased risk of substance use disorder (OR, 0.6; 95% CI, 0.3-0.9; $P = .02$); there was no significant independent association between TS and mood disorder or DBD. Obsessive-compulsive disorder was independently associated with a 2-fold or greater risk of mood disorders (OR, 3.8; 95% CI, 2.9-4.9; $P < .001$),

anxiety disorders (OR, 2.8; 95% CI, 2.2-3.6; $P < .001$), DBDs (OR, 2.0; 95% CI, 1.4-2.9; $P < .001$), and substance use disorders (OR, 3.9; 95% CI, 2.5-6.0; $P < .001$). Attention-deficit/hyperactivity disorder was independently associated with an increased risk of anxiety disorders (OR, 1.5; 95% CI, 1.2-2.0; $P < .01$) and DBDs (OR, 4.0; 95% CI, 2.6-6.2; $P < .001$) but not substance use or mood disorders. There were no significant associations between TS, OCD, ADHD, and elimination or eating disorders. The results of these models build on those summarized in Figure 1 because they control for the age and sex of the participants.

Age of Highest Risk

The median age at onset for TS was 6 years (interquartile range, 4-8 years) (Figure 2 and eTable 7 in the Supplement). Attention-deficit/hyperactivity disorder and DBD had the youngest median age at onset and earliest ages of highest risk (5 years: interquartile ranges, 3-6 and 3-8, respectively). The high-risk period began at age 4 years for anxiety disorders, 7 years for mood disorders, and 13 years for substance use and eating disorders. Compared with males, females tended to have later ages at onset of TS, DBDs, anxiety disorders, and mood disorders (eTable 7 in the Supplement).

Clinical Correlates of Number of Psychiatric Disorders

High tic and moderate/high OCD symptom severity, lifetime prevalence of ADHD or OCD, and parental history of TS/CMVTD and ADHD were associated with having 1 or more noncore psychiatric comorbidity in univariate analyses (Table 2). In the multivariate model, only high tic severity (OR, 1.57; 95% CI, 1.11-2.21; $P = .01$), ADHD (OR, 1.51; 95% CI, 1.12-2.03; $P < .01$), OCD (OR, 1.77; 95% CI, 1.34-2.35; $P < .001$), and parental history of ADHD (OR, 1.55; 95% CI, 1.08-2.23; $P = .02$) remained significant. Obsessive-compulsive disorder severity was omitted from the multivariate model to avoid confounding with OCD diagnosis.

Genetic Relationships With TS

Consistent with previous findings,^{26,35} including those from a subset of the current sample, TS/CMVTD, OCD, and ADHD all demonstrated significant genetic correlations (eTable 8 in the Supplement). In addition, TS/CMVTD had significant genetic correlations with mood disorders (RhoG [SE], 0.47 [0.17]; $P = .004$), anxiety disorders (RhoG [SE], 0.35 [0.15]; $P = .02$), and DBDs (RhoG [SE], 0.40 [0.18]; $P = .02$); these correlations were not significant

when controlling for OCD and ADHD (eTable 9 in the Supplement). Mood disorders, anxiety disorders, and DBDs were also genetically correlated with ADHD; these correlations remained significant after controlling for TS/CMVTD and OCD (Table 3). Furthermore, mood disorders were significantly genetically correlated with OCD, even when controlling for TS/CMVTD and ADHD (Table 3).

Discussion

This study represents the most comprehensive examination to date of the extent and burden of comorbid psychiatric disorders in TS, and is the first to report ages of highest risk and etiological relationships with TS for a wide variety of psychiatric conditions. Our results have implications both clinically and for ongoing research into the causes and etiological relationships between these psychiatric disorders.

Clinical relevance

Consistent with previous studies^{3,4,12,15,36-39}, we identified a very high burden of psychiatric disorders. Our results suggest that the vast majority of children with TS can be expected to develop ≥ 1 comorbid psychiatric disorder over their lifetime, and more than half will develop two. In addition to high rates of OCD (50.0%) and ADHD (54.3%), we also found high rates of mood (29.8%), anxiety (36.1%), DBD (29.7%), and elimination disorders (16.2%). We found relatively low rates of psychotic disorders and substance abuse at the time of evaluation, although we do not have longitudinal data later on in life for the younger individuals, when such disorders typically manifest.

Importantly, this study is the first to report ages of highest risk for comorbid psychiatric disorders, as well as the relationship of demographic and clinical characteristics with overall disorder burden in TS. For most disorders, the age of greatest risk began before age 5, with high risk for anxiety and DBD continuing into adolescence, and risk for depressive disorders continuing into young adulthood. Previous research has demonstrated that TS symptoms typically emerge between the ages of 5 and 7 years^{13,40}, while ADHD generally appears 2 to 3 years earlier⁴¹, and OCD 5 to 6 years later⁴². In this study, DBD and ADHD began at or before age 5, prior to tic onset. In contrast to population-based epidemiologic studies^{43,44}, OCD and anxiety disorders also began early, typically within a year of onset of tics (with many cases beginning earlier); mood disorders had a more distributed age-of-onset pattern,

beginning as early as age 5, and becoming more frequent around ages 7-8. These results, in combination with the high likelihood of developing a mood, anxiety, or DBD, suggest that psychiatric assessments of TS-affected children should begin early and continue throughout adolescence and adulthood.

Our results also suggest that TS-affected children who also have OCD or a parent with ADHD in particular should be carefully evaluated over time for the development of mood, anxiety, and DBD, and adolescents, particularly those with OCD and/or ADHD, should also be monitored for the development of a substance use disorder. Similarly, TS-affected children with ADHD should be evaluated for other DBD and anxiety disorders. The association between high tic severity and the number of non-ADHD/non-OCD comorbidities is consistent with a previous study demonstrating an association between tic severity and non-OCD anxiety disorders¹².

Etiological relevance

The heritability estimates confirm previous research^{26,35} showing that TS, OCD, and ADHD are highly genetically related. However, for the first time, we also provide evidence of a strong genetic relationship between these TS-related phenotypes and mood, anxiety, and DBD. Of particular interest, our analyses suggest that the observed genetic correlations between TS and these disorders are better accounted for by an underlying genetic relationship with ADHD and, in the case of mood disorders, by an underlying genetic relationship with both ADHD and OCD. In non-TS samples, there is considerable evidence⁴⁵ to support shared genetic variance between ADHD and DBD, and some data⁴⁶ to support a shared genetic diathesis underlying ADHD and major depressive disorder. Genetic relationships between OCD and mood disorders have not previously been examined. Our findings are in line with a previous study that found no increased rates of ADHD⁴⁷ or other non-OCD disorders such as anxiety, affective, substance abuse and psychotic disorders,⁴⁸ among parents of probands with TS compared to controls, suggesting that these disorders segregate independently from TS. Our findings that parental history of ADHD predicts psychiatric disorder burden in TS-affected offspring, independent of parental history of TS and OCD, provides additional support for the observed genetic relationships between psychiatric disorders and ADHD.

Limitations

This study has several limitations. First, our data are cross-sectional, thus, we cannot assess causation (e.g., whether clinical characteristics predicted subsequent disorder onset). Second, the predominately clinic-based recruitment may have biased our sample to participants with more severe, comorbid, or familial TS, limiting generalizability. This concern is somewhat mitigated by the presence of parents and previously undiagnosed siblings with TS, who were typically less severely affected. Third, although consistent with previous studies, the total psychiatric burden identified is likely an underestimate, given that some disorders were not assessed (e.g., pervasive developmental disorders [PDDs]) and not everyone had passed the age of risk for all disorders. Specifically, parents were not routinely assessed for certain childhood disorders (e.g., elimination disorders) and children were not assessed for schizophrenia, although they were assessed for psychosis. Similarly, the lifetime rates of schizophrenia, bipolar disorder, and substance use disorders could be attenuated by an ascertainment bias (i.e., the children and adolescents in our sample may have developed these adult-onset disorders later in life). Fourth, ADHD severity was not uniformly assessed. Fifth, we did not have reliable data regarding recruitment method (i.e., TSA vs. specialty clinics), and characteristics of participants may vary by recruitment method. Sixth, PDDs were not systematically assessed or uniformly excluded; future studies should examine patterns of comorbidity between TS and PDDs⁴⁹. Finally, because the parent genetic study focused on sibling pairs and parent-child trios, the heritabilities may be underestimates, as the algorithm employed by SOLAR is best suited to analysis of multigenerational families.

Conclusions

This study provides important new data regarding the prevalence, predictors, and ages of highest risk for psychiatric illness among individuals affected with TS, as well as for the first time formally evaluating the etiological relationships between disorders other than OCD and ADHD. The key clinical findings, that mood, anxiety, and DBD are very common among TS-affected individuals, tend to begin early in life, and are highly associated with comorbid OCD and ADHD, are of direct and immediate relevance for practitioners. The genetic analyses advance our understanding of the etiological relationships between TS and other psychiatric disorders, and provide a framework for future studies aimed at better understanding the biology of these complex, inter-related syndromes.

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Figure 1

Lifetime Prevalence of Comorbid Disorders by Presence of OCD and ADHD Among Individuals with Tourette Syndrome. *Significance values reflect individual 4-by-2 χ^2 tests (i.e., TS/OCD/ADHD group by presence of the comorbid disorder).*

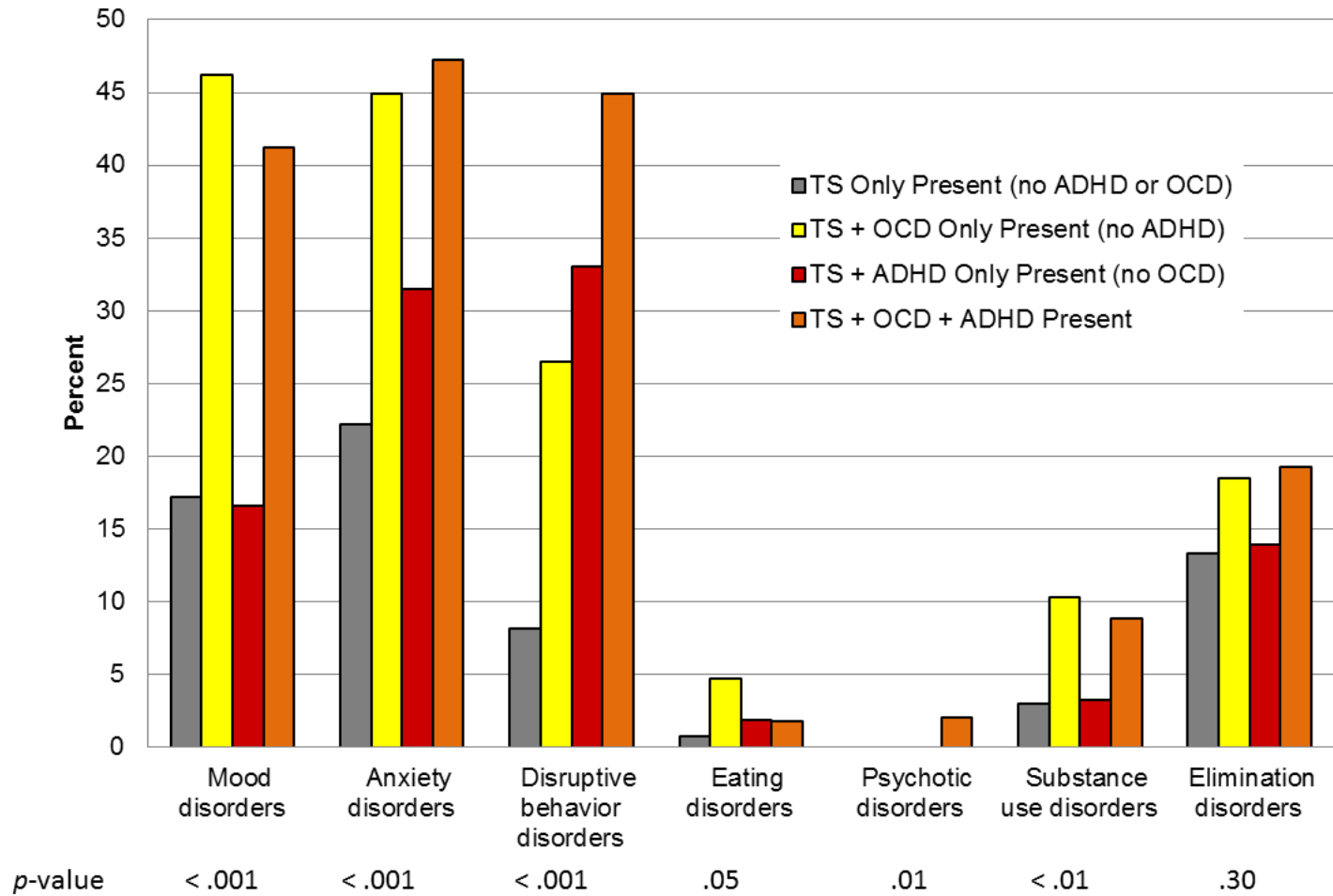


Figure 2

Ages-of-Onset for Comorbid Disorders Among Individuals with Tourette Syndrome. *Points and bars represent median ages-of-onset and interquartile ranges, respectively. Width of each plot is proportional to the number of individuals with the given age of onset.*

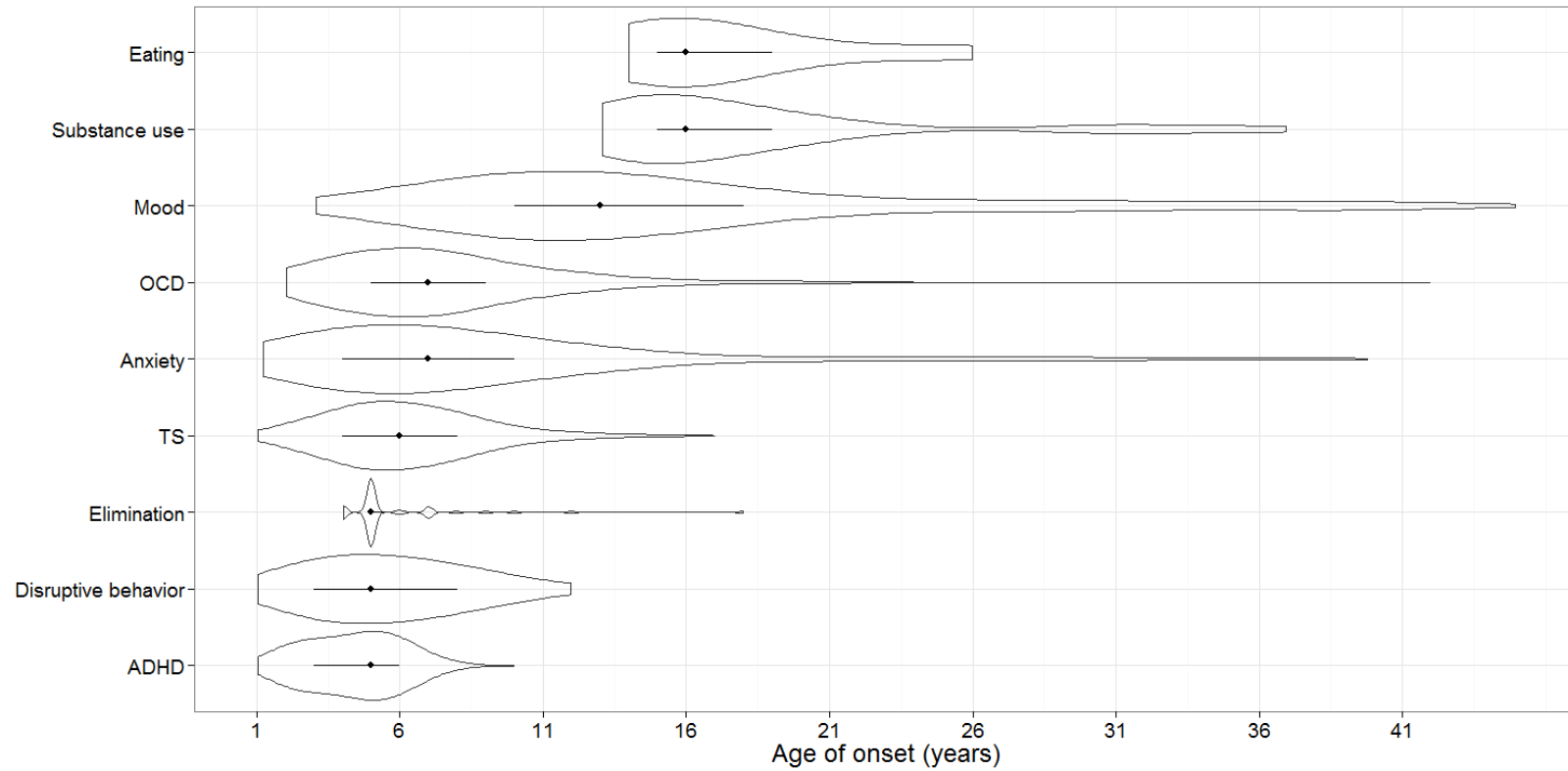


Table 1

Lifetime Prevalence of Psychiatric Disorders by Sex

Comorbid disorder	All TS-affected participants <i>n/total with available data (%)</i>	Sex		<i>p</i> -value
		Male <i>n/total with available data (%)</i>	Female <i>n/total with available data (%)</i>	
Obsessive compulsive spectrum disorders^a	904/1368 (66.1)	645/1001 (64.4)	259/367 (70.6)	.03
Attention-deficit/hyperactivity disorder	713/1314 (54.3)	564/962 (58.6)	149/352 (42.3)	< .001
Mood disorders^b	277/930 (29.8)	184/690 (26.7)	93/240 (38.8)	< .001
Anxiety disorders^c	343/949 (36.1)	225/703 (32.0)	118/246 (48.0)	< .001
Disruptive behavior disorders^d	185/622 (29.7)	157/493 (31.9)	28/129 (21.7)	.03
Eating disorders^e	19/937 (2.0)	2/693 (0.3)	17/244 (7.0)	< .001
Psychotic disorders^f	7/931 (0.8)	5/689 (0.7)	2/242 (0.8)	.88
Substance use disorders^g	59/948 (6.2)	42/701 (6.0)	17/247 (6.9)	.62
Elimination disorders^h	108/668 (16.2)	90/531 (17.0)	18/137 (13.1)	.28

Chi-squared or Fisher's exact test were used to compare rates of each disorder in males vs females.

Includes: ^a obsessive-compulsive disorder and subclinical obsessive-compulsive disorder, ^b major-depressive disorder, dysthymia, and bipolar disorder I and II, ^c generalized anxiety disorder, panic disorder, agoraphobia without panic, posttraumatic stress disorder, separation anxiety disorder, social phobia, and specific phobia, ^d oppositional-defiant and conduct disorders, ^e anorexia and bulimia nervosa, ^f schizophrenia and psychotic disorder, not otherwise specified, ^g alcohol and other substance use or dependence, excluding tobacco use, and ^h enuresis and encopresis.

Table 2Clinical Predictors of Having ≥ 1 Comorbid Disorder, Excluding OCD and ADHD

Characteristic (reference value)	Levels	OR (95% CI)	p-values
Symptom severity^a			
Tic severity tertiles (0-16)	17-21	1.18 (0.90—1.55)	.24
	22-30	1.87 (1.43—2.46)	<.001
OCD severity tertiles (0-2)	3-6	1.64 (1.26—2.13)	<.001
	7-12	2.86 (2.13—3.82)	<.001
Comorbid conditions			
ADHD (no ADHD)	ADHD present	1.93 (1.53—2.43)	<.001
OCD (no OCD)	OCD present	2.17 (1.75—2.70)	<.001
Parental history^b			
Parental history of TS/CMVTD (parental TS/CMVTD absent)	Parental TS/CMVTD present	1.33 (1.01—1.76)	.04
Parental history of OCD (parental OCD absent)	Parental OCD present	1.11 (0.84—1.47)	.46
Parental history of ADHD (parental ADHD absent)	Parental ADHD present	1.86 (1.32—2.61)	<.001
Age of onset			
TS age of onset (≥ 7 y)	< 7 y	1.02 (0.82—1.29)	.84
OCD age of onset (≥ 8 y)	< 8 y	1.10 (0.74—1.64)	.63
ADHD age of onset (≥ 5 y)	< 5 y	1.35 (0.90—2.01)	.14

Separate generalized estimating equations, clustering on family and controlling for age at interview and sex, were modeled with the presence of ≥ 1 comorbid disorder, other than ADHD or OCD, as the outcome and each clinical characteristic as the predictor variable.

^a Symptom severity scales for tics and obsessive-compulsive symptoms are described in the Supplemental Methods.

^b Parental history only available for probands and their full siblings.

ADHD, attention-deficit/hyperactivity disorder; CMVTD, chronic motor or vocal tic disorder; OCD, obsessive-compulsive disorder; TS, Tourette syndrome

Table 3

Bivariate Heritability of Comorbid Diagnoses with TS/CMVTD, OCD, and ADHD

		No additional diagnostic covariates ^a				Covarying for TS ^a				Covarying for OCD or ADHD ^{a,b}				Covarying for TS and OCD or ADHD ^{a,b}			
	Comorbid disorder	RhoG (SE)	RhoG p-value	RhoE (SE)	RhoE p-value	RhoG (SE)	RhoG p-value	RhoE (SE)	RhoE p-value	RhoG (SE)	RhoG p-value	RhoE (SE)	RhoE p-value	RhoG (SE)	RhoG p-value	RhoE (SE)	RhoE p-value
Bivariate heritability with ADHD	Mood	.77 (.14)	1.6 × 10 ⁻⁸	-.32 (.14)	2.6 × 10 ⁻²	.74 (.15)	3.9 × 10 ⁻⁷	.31 (.15)	.03	.68 (.18)	8.6 × 10 ⁻⁵	-.29 (.14)	.04	.70 (.18)	2.3 × 10 ⁻⁵	-.36 (.15)	.02
	Anxiety	.59 (.12)	3.2 × 10 ⁻⁶			.54 (.13)	5.0 × 10 ⁻⁵			.40 (.15)	7.7 × 10 ⁻³			.43 (.14)	3.2 × 10 ⁻³		
	Disruptive behavior	.68 (.15)	1.9 × 10 ⁻⁵			.66 (.16)	6.9 × 10 ⁻⁵			.62 (.17)	5.3 × 10 ⁻⁴			.61 (.17)	6.2 × 10 ⁻⁴		
Bivariate heritability with OCD	Mood	.59 (.13)	3.5 × 10 ⁻⁵	.34 (.11)	3.2 × 10 ⁻³	.53 (.15)	1.1 × 10 ⁻³	.40 (.11)	7.2 × 10 ⁻⁴	.47 (.17)	.01	.43 (.10)	1.3 × 10 ⁻⁴	.41 (.18)	.04	.48 (.11)	3.8 × 10 ⁻⁵
	Anxiety	.40 (.12)	2.7 × 10 ⁻³	.55 (.11)	4.2 × 10 ⁻⁶	.34 (.13)	.02	.55 (.11)	1.2 × 10 ⁻⁵			.60 (.10)	2.4 × 10 ⁻⁷			.62 (.11)	3.6 × 10 ⁻⁷
	Disruptive behavior																

Genetic and environmental correlation (RhoG and RhoE, respectively) between TS/CMVTD and groups of comorbid disorders were estimated; where RhoG was significant, ADHD and OCD were added separately as covariates to assess the independent association between TS/CMVTD and the given comorbid disorders. Subsequently, a series of bivariate analyses with ADHD and OCD were conducted for disorders with a significant RhoG with TS to determine the unique contributions of ADHD and OCD to the genetic correlation between TS and each of these disorders (mood, anxiety, and disruptive behavior disorders). Blank cells represent non-significant correlations (i.e., $p > 0.5$).

^a All analyses include sex, age, and sex-by-age as covariates.

^b In bivariate analyses with ADHD, OCD (not ADHD) was included as a covariate; conversely, in bivariate analyses with OCD, ADHD (not OCD) was included as a covariate.

ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; TS/CMVTD, Tourette syndrome/chronic motor and vocal tic disorder

Supplementary Online Material

eAppendix. Methods

eTable 1. Demographic and Clinical Characteristics of the Sample

eTable 2: Lifetime Prevalence of Psychiatric Disorders by Sex in Individuals with Tourette Syndrome

eTable 3. Lifetime Prevalence of Psychiatric Disorders by Age in Individuals with Tourette Syndrome

eTable 4. Lifetime Prevalence of Psychiatric Disorders by Proband Status in Individuals with Tourette Syndrome

eTable 5. Lifetime Prevalence of Psychiatric Disorders by Presence of OCD and ADHD in Individuals with Tourette Syndrome

eTable 6. Associations Among TS, OCD, ADHD and Other Comorbid Disorders

eTable 7. Ages of Onset for TS and Comorbid Disorders

eTable 8. Bivariate Heritability Estimates Among TS/CMVTD, OCD, And ADHD

eTable 9. Bivariate Heritability of Comorbid Diagnoses With TS/CMVTD

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Inclusion and exclusion criteria, informed consent

Inclusion criteria consisted of: age 6 years and older and a DSM-III-R, DSM-IV, or DSM-IV-TR diagnosis of Tourette syndrome (TS) (verified by the best estimate assessment, described in the text) in the proband. All participants were also required to have living parents for family-based genetic analyses, and parents were interviewed for corroborative history to supplement participant interviews regardless of participant age whenever possible. Exclusion criteria included tics caused by neurologic disorders other than TS and mental retardation (operationalized as an estimated IQ lower than 75 on a brief IQ scale, such as all or specific subscales of the Wechsler Intelligence Scale for Children—Revised¹). Pervasive developmental disorder (PDD) were also excluded during the first half of the study. However, due to time and resource limitations, we did not formally assess PDD in this sample. Only individuals with an established PDD diagnosis or with a suspected PDD based on medical record review were excluded; this exclusion criterion was removed from subsequent waves in part because it had not been operationalized.

Children ages 6 and up provided assent—parental permission was also obtained for all children under age 18. We decided to limit inclusion to age 6 years and older because of difficulties in obtaining reliable diagnostic information and blood for genetic testing from younger participants.

Tic and obsessive-compulsive severity scales

Tic severity scale

Tic symptoms were assessed using an instrument documented previously to be valid and reliable for the diagnosis of TS². Briefly, this battery includes demographic information, medical history, an inventory of lifetime tic symptoms, and ordinal severity scales modified from the Yale Global Tic Severity Scale (YGTSS)³. The YGTSS consists of items related to the frequency, intensity, and interference associated with motor and phonic tics, separately. For this study, items regarding the number and complexity of motor and phonic tics were not included in the questionnaire. The highest possible score of this abbreviated version of the YGTSS was 30. The wording of these items, including response choices, was identical to the published version of this scale.

Obsessive-compulsive severity scale

Participants in this sample were not administered the complete Yale-Brown Obsessive-Compulsive Scale^{4,5}; however, in addition to documenting specific obsessions and compulsions, they were asked the following 3 questions derived from the YBOCS regarding the time, interference, and distress associated with obsessions and compulsions when obsessive-compulsive symptoms were the worst. We used the sum of these 3 items in analyses as a measure of worst-ever obsessive-compulsive symptom severity; the highest possible score on this scale was 12.

1. *During the "worst ever" obsessive-compulsive period, how much time was occupied by these obsessive thoughts and/or compulsive behaviors?* (No time at all [score = 0], Less than one hour per day [score = 1], 1 to 3 hours per day [score = 2], More than 3 and up to 8 hours per day [score = 3], More than 8 hours per day [score = 4], No Response, N/A, Refused to Answer, Don't Know)
2. *During the "worst ever" obsessive-compulsive period, how much did obsessive thoughts and/or compulsive behaviors interfere with social or school functioning? Was there anything you couldn't do because of them?* (No interference [score = 0], Mild-slight interference [score = 1], Moderate-definite interference [score = 2], Severe interference [score = 3], Extreme interference [score = 4], No Response, N/A, Refused to Answer, Don't Know)
3. *During the worst ever obsessive-compulsive period, how much distress did obsessive thoughts and/or compulsive behaviors cause? How anxious (or upset) would you become if you could not perform a compulsion? How anxious (or upset) would you become from disturbing thoughts?* (No distress [score = 0], Mild-infrequent distress [score = 1], Moderate frequent and disturbing distress [score = 3], Severe very frequent and very disturbing distress [score = 4], Extreme near constant and disabling distress [score = 5], No Response, N/A, Refused to Answer, Don't Know)

Diagnostic instruments, rater training and reliability, age of onset, and best-estimate process

Diagnostic instruments

The two primary diagnostic instruments used were the Structured Clinical Interview for *DSM* Disorders (SCID) ⁶ for adults and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) ⁷ for children and adolescents. A subset of adult participants ascertained very early in the study from one site (192 participants, 22 of whom were probands) had assessments using the SADS-LA, as this instrument was being used in an unrelated study and the researchers wished to avoid undue subject burden.

For children and adolescents, parents and children were interviewed using the K-SADS-PL jointly or separately, depending on the family's preference. The source of information for each diagnostic interview was not systematically recorded; however, in all cases, interviewers were instructed to make reasonable efforts to consider child or adolescent input when appropriate. For adult probands, parents were interviewed whenever possible to corroborate data.

Rater training and reliability

Interviewer training varied in structure between the sites, but in all cases involved didactic instruction, observation of the assessment by experienced interviewers, and subsequent direct observation by experienced interviewers until assessors achieved proficiency. In addition, interviewers were required to administer each diagnostic interview to a master clinician at their site to receive approval to conduct the interview independently. A refresher training occurred approximately halfway through the study to maintain reliability. Reliability between interviewers was not assessed in a systematic way other than at the time of the two trainings. Instead, the focus of our efforts with regard to reliability was at the level of the best estimates (see below). However, a representative from each clinical site was required to attend weekly/semi-monthly clinician conference calls where challenging diagnoses were discussed as well as questions/clarifications regarding diagnostic instruments. The coordinating site also conducted intermittent quality control checks of submitted data over the course of the study and provided feedback to clinical sites.

Age of onset

Using all available data, age of onset was defined retrospectively as the earliest time point in which the participant had clinically significant symptoms for the disorder in question. Previous research provides evidence that individuals tend to recall age of symptom onset later than when criteria were actually met ⁸, suggesting that our age-of-onset data are perhaps even an underestimate of the true age at which comorbid disorders began. That is, due to recall bias, the exclusion of children younger than age 6 would likely bias the age of onset estimates towards later ages of onset.

Best-estimate process

Inter-rater reliability was established for the best estimate diagnoses at the beginning of the study using a series of test cases. Reliability of diagnoses was maintained via weekly clinician calls between best estimators, led by Dr. Mathews. All participants, including probands and family members, were reviewed by the same committee. Clinicians from sites that performed the assessments generally did not conduct the best estimates for participants from that site. If best estimators disagreed and could not reach consensus, the case was best estimated by a third reviewer. If consensus could not be reached by the three reviewers, the diagnosis in question was coded as "unable to code" and was not included in the analysis. Difficult diagnostic issues of general relevance to all best estimators were brought to the best estimate committee for discussion.

Comparing lifetime prevalence of comorbid disorders among probands and TS-affected relatives

Many of the comorbid disorders we are examining are familial; therefore, by combining probands and their TS-affected first-degree relatives we are introducing a potential source of confounding in our estimates of lifetime prevalence of each disorder. Because probands are unrelated to each other, prevalence rates limited to probands would theoretically more accurately represent the true lifetime prevalence rates of comorbid disorders in TS-affected individuals. In order to examine this possibility, we examined the association of each comorbid disorder and proband status (i.e., proband or TS-affected relative) in a series of binary logistic regression models. In a second set of models, we added age at time of interview, with the hypothesis that differences in lifetime prevalence of any comorbidity by proband status might be explained by age differences between probands and their relatives.

Heritability analyses

The heritability of a trait, such as a psychiatric disorder, represents the fraction of the total phenotypic variance accounted for by the additive genetic variance. All analyses included sex, age, and the sex-by-age interaction as covariates. TS and chronic motor or vocal tic disorder (CMVTD) were combined for these analyses. First, we estimated the univariate heritability of TS/CMVTD and comorbid disorders. Next, we estimated the genetic and environmental correlations (RhoG and RhoE, respectively) between TS/CMVTD and each of the comorbid disorders. To examine the independent effects of TS from OCD and ADHD, we added OCD and ADHD separately (and together if the RhoG remained significant at $p < .05$) as covariates in these bivariate analyses. Next, to directly examine the independent effects of comorbid OCD and ADHD on genetic correlation between TS/CMVTD and other comorbid disorders, we tested the bivariate relationship between OCD and ADHD with the other comorbid disorders for those disorders that showed a significant RhoG with TS/CMVTD. If those bivariate relationships yielded a significant RhoG, we then repeated the analyses controlling for TS/CMVTD and the other disorder, either OCD or ADHD (separately, and then together if the RhoG was significant when controlling for either OCD or ADHD separately). This algorithm is depicted in Supplemental Figure S1. This sequence of testing allowed us to examine the independent effects of OCD and ADHD in the genetic correlation between TS/CMVTD and other comorbid disorders. It should be noted, however, that because the sample contains only two generation families and no monozygotic or dizygotic twins, the RhoG cannot parse the contribution of heritability from common environment. Therefore, RhoG is more accurately the “familial” component; however, we have chosen to use the term “genetic correlation” in line with the common usage as employed by the authors of SOLAR.

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eTable 1. Demographic and Clinical Characteristics of the Sample

	Participants with TS (<i>n</i> = 1,374) ^a	First-degree relatives without TS (<i>n</i> = 1,142) ^a	All participants, including unaffected first-degree family members (<i>n</i> = 2,516) ^a
Age groups, %			
6 – 12	46.1	2.5	26.3
13 – 17	22.3	2.6	13.4
≥ 18	31.7	94.9	60.4
Age, M (SD)	19.1 (13.5)	41.6 (10.5)	29.3 (16.6)
Sex, %			
Female	26.8	52.6	38.5
Proband Status, %			
Proband	57.6	0	31.4
TS-affected family members, %			
Singleton	31.0	20.5	4.7
Multiplex	69.0	79.5	96.3
Symptom severity, M (SD)^b			
Tic severity	18.5 (6.4) [1287]	2.6 (3.9) [1072]	11.3 (9.6) [2359]
OCD severity	4.3 (3.4) [1264]	1.7 (2.6) [1085]	3.1 (3.3) [2349]
Parental history, %^c			
TS/CMVTD	57.6 [950]	55.4 [83]	57.4 [1033]
OCD	40.6 [946]	39.5 [76]	40.5 [1022]
ADHD	23.1 [932]	25.0 [72]	23.2 [1004]

^a The number of participants used to calculate each value are indicated in brackets when less than the total number of participants in that group.

^b Scales for symptom severity are described in the Supplemental Methods, above.

^c Parental history only available for probands and their siblings.

ADHD, attention-deficit/hyperactivity disorder; CMVTD, chronic motor or vocal tic disorder; OCD, obsessive-compulsive disorder; TS, Tourette syndrome

eTable 2: Lifetime Prevalence of Psychiatric Disorders by Sex in Individuals with Tourette Syndrome

Comorbid disorder	All TS-affected participants <i>n/total with available data (%)</i>	Sex		<i>p</i> -value
		Male <i>n/total with available data (%)</i>	Female <i>n/total with available data (%)</i>	
Obsessive compulsive disorder	682/1363 (50.0)	473/997 (47.4)	209/366 (57.1)	.002
Attention-deficit/hyperactivity disorder	713/1314 (54.3)	564/962 (58.6)	149/352 (42.3)	< .001
Mood disorders				
Major depressive disorder ^b	245/940 (26.1)	159/697 (22.8)	86/243 (35.4)	< .001
Dysthymia	28/927 (3.0)	18/688 (2.6)	10/239 (4.2)	.22
Bipolar I disorder	12/926 (1.3)	10/686 (1.5)	2/240 (0.8)	.74
Bipolar II disorder	3/642 (0.5)	2/188 (1.1)	1/454 (0.2)	.21
Any mood disorder ^a	277/930 (29.8)	184/690 (26.7)	93/240 (38.8)	< .001
Anxiety disorders				
Generalized anxiety disorder	104/931 (11.2)	62/689 (9.0)	42/242 (17.4)	< .001
Panic disorder	63/935 (6.7)	30/693 (4.3)	33/242 (13.6)	< .001
Agoraphobia without panic	9/931 (1.0)	9/689 (1.3)	0/242 (0)	.12
Posttraumatic stress disorder	19/587 (3.2)	5/414 (8.1)	14/173 (1.2)	< .001
Separation anxiety disorder	93/617 (15.1)	66/489 (13.5)	27/128 (21.1)	.03
Social phobia	84/935 (9.0)	31/244 (12.7)	53/691 (7.8)	.02
Specific phobia	140/930 (15.1)	83/691 (12.0)	57/239 (23.9)	< .001
Any anxiety disorder ^a	343/949 (36.1)	225/703 (32.0)	118/246 (48.0)	< .001
Disruptive behavior disorders				
Oppositional defiant disorder	179/610 (29.3)	152/484 (31.4)	27/126 (21.4)	.03
Conduct disorder	20/622 (3.2)	19/493 (3.9)	1/129 (0.8)	.09
Any disruptive behavior disorder ^a	185/622 (29.7)	157/493 (31.9)	28/129 (21.7)	.03
Eating disorders				
Anorexia nervosa	9/939 (1.0)	1/693 (0.1)	8/246 (3.3)	< .001

Comorbid disorder	All TS-affected participants <i>n/total with available data (%)</i>	Sex		<i>p</i> -value
		Male <i>n/total with available data (%)</i>	Female <i>n/total with available data (%)</i>	
Bulimia nervosa	12/937 (1.3)	1/693 (0.1)	11/244 (4.5)	< .001
Any eating disorder ^a	19/937 (2.0)	2/693 (0.3)	17/244 (7.0)	< .001
Psychotic disorders	7/931 (0.8)	5/689 (0.7)	2/242 (0.8)	.88
Substance use disorders				
Alcohol abuse/dependence	42/939 (4.5)	33/697 (4.7)	9/242 (3.7)	.51
Substance abuse/dependence ^c	38/946 (4.0)	26/699 (3.7)	12/247 (4.9)	.43
Any substance use disorder ^{a, c}	59/948 (6.2)	42/701 (6.0)	17/247 (6.9)	.62
Elimination disorders				
Enuresis	98/665 (14.7)	82/528 (15.5)	16/137 (11.7)	.26
Encopresis	18/558 (3.2)	16/438 (3.7)	2/120 (1.7)	.39
Any elimination disorder ^a	108/668 (16.2)	90/531 (17.0)	18/137 (13.1)	.28
Number of comorbid disorders, M (SD)	2.1 (1.6)	2.0 (1.5)	2.2 (1.8)	.14
Number of comorbid disorders, excluding ADHD and OCD, M (SD)	0.9 (1.3)	0.8 (1.2)	1.1 (1.5)	<.01

χ^2 , Fisher's exact test, or ANOVA were used as appropriate to compare rates or total number of disorders for each disorder in males vs females.

^a Cumulative numbers of participants who meet criteria for each group of disorders may not equal the sum of the component diagnoses because of comorbidity among the individual disorders.

^b Includes major depressive disorder with and without psychotic features

^c Does not include alcohol or nicotine

eTable 3. Lifetime Prevalence of Psychiatric Disorders by Age in Individuals with Tourette Syndrome

Comorbid disorder	All TS-affected participants <i>n/total with available data (%)</i>	Age (<i>n/total with available data (%)</i>)			<i>p</i> -value
		6-12 y	13-17 y	≥ 18 y	
Obsessive compulsive disorder	682/1363 (50.0)	270/627 (43.1)	172/302 (57.0)	240/434 (55.3)	< .001
Attention-deficit/hyperactivity disorder	713/1314 (54.3)	392/613 (63.9)	174/294 (59.2)	147/407 (36.1)	< .001
Mood disorders					
Major depressive disorder ^b	245/940 (26.1)	57/426 (13.4)	66/321 (20.6)	122/283 (43.1)	< .001
Dysthymia	28/927 (3.0)	6/424 (1.4)	4/229 (1.7)	18/274 (6.6)	< .001
Bipolar I disorder	12/926 (1.3)	5/424 (1.2)	3/229 (1.3)	4/273 (1.5)	.95
Bipolar II disorder	3/642 (0.5)	0/222 (0.0)	1/150 (0.7)	2/270 (0.7)	.45
Any mood disorder ^a	277/930 (29.8)	68/426 (16.0)	74/227 (32.6)	135/227 (59.5)	< .001
Anxiety disorders					
Generalized anxiety disorder	104/931 (11.2)	43/422 (10.2)	33/232 (14.2)	28/277 (10.1)	.23
Panic disorder	63/935 (6.7)	9/423 (2.1)	15/230 (6.5)	39/282 (13.8)	< .001
Agoraphobia without panic	9/931 (1.0)	6/421 (1.4)	3/230 (1.3)	0/280 (0.0)	.10
Posttraumatic stress disorder	19/587 (3.2)	2/186 (1.1)	1/135 (0.7)	16/266 (6.0)	< .01
Separation anxiety disorder	93/617 (15.1)	59/423 (13.9)	34/194 (17.5)	n/a	.25
Social phobia	84/935 (9.0)	22/423 (5.2)	10/231 (4.3)	52/281 (18.5)	< .001
Specific phobia	140/930 (15.1)	59/421 (14.0)	32/229 (14.0)	49/280 (17.5)	.39
Any anxiety disorder ^{a,c}	343/949 (36.1)	108/428 (25.2)	67/234 (28.6)	112/284 (39.4)	< .001
Disruptive behavior disorders					
Oppositional defiant disorder	179/610 (29.3)	129/419 (30.8)	50/191 (26.2)	n/a	.25
Conduct disorder	20/622 (3.2)	13/427 (3.0)	7/195 (3.6)	n/a	.81
Any disruptive behavior disorder ^a	185/622 (29.7)	133/427 (31.1)	52/195 (26.7)	n/a	.26
Eating disorders					
Anorexia nervosa	9/939 (1.0)	0/425 (0.0)	0/233 (0.0)	9/281 (3.2)	< .001

Comorbid disorder	All TS-affected participants <i>n/total with available data (%)</i>	Age (<i>n/total with available data (%)</i>)			<i>p</i> -value
		6-12 y	13-17 y	≥ 18 y	
Bulimia nervosa	12/937 (1.3)	0/425 (0.0)	2/233 (0.9)	10/279 (3.6)	< .001
Any eating disorder ^a	19/937 (2.0)	0/425 (0.0)	2/233 (0.9)	17/279 (6.1)	< .001
Psychotic disorders	7/931 (0.8)	3/421 (0.7)	0/230 (0.0)	4/280 (1.4)	.18
Substance use disorders					
Alcohol abuse/dependence	42/939 (4.5)	0/426 (0.0)	5/232 (2.2)	37/281 (13.2)	< .001
Substance abuse/dependence ^d	38/946 (4.0)	0/427 (0.0)	3/234 (1.3)	35/285 (12.3)	< .001
Any substance use disorder ^{a, d}	59/948 (6.2)	0/427 (0.0)	6/234 (2.6)	53/287 (18.5)	< .001
Elimination disorders					
Enuresis	98/665 (14.7)	67/465 (14.4)	31/200 (15.5)	n/a	.72
Encopresis	18/558 (3.2)	12/380 (3.2)	6/178 (3.4)	n/a	.89
Any elimination disorder ^a	108/668 (16.2)	73/468 (15.6)	35/200 (17.5)	n/a	.54
Number of comorbid disorders, M (SD)	2.1 (1.6)	2.0 (1.5)	2.3 (1.6)	2.0 (1.8)	0.04
Number of comorbid disorders, excluding ADHD and OCD, M (SD)	0.9 (1.3)	0.8 (1.1)	1.0 (1.3)	1.0 (1.4)	0.01

χ^2 , Fisher's exact test, or ANOVA were used as appropriate to compare rates or total number of disorders for each disorder across the 3 age groups.

^a Cumulative numbers of participants who meet criteria for each group of disorders may not equal the sum of the component diagnoses because of comorbidity among the individual disorders.

^b Includes major depressive disorder with and without psychotic features

^c Does not include separation anxiety

^d Does not include alcohol or nicotine

eTable 4. Lifetime Prevalence of Psychiatric Disorders by Proband Status in Individuals with Tourette Syndrome

Comorbid disorder	Proband status			OR (95% CI)	OR (95%CI), adjusted for age
	All TS-affected participants <i>n/total with available data</i> (%)	Proband <i>n/total with available data</i> (%)	Non-proband family member <i>n/total with available data</i> (%)		
Obsessive compulsive disorder	682/1363 (50.0)	303/579 (52.3)	379/784 (48.3)	0.85 (0.67-1.06)	.92 (.72-1.17)
Attention-deficit/hyperactivity disorder	713/1314 (54.3)	456/758 (60.2)	257/556 (46.2)	1.76 (1.41-2.19)***	1.07 (.83-1.39)
Mood disorders					
Major depressive disorder ^a	245/940 (26.1)	125/519 (24.1)	120/421 (28.5)	0.80 (0.60-1.07)	1.21 (.86-1.69)
Dysthymia	28/927 (3.0)	13/514 (2.5)	15/413 (3.6)	0.69 (0.32-1.46)	1.19 (.50-2.86)
Bipolar I disorder	12/926 (1.3)	6/513 (1.2)	6/413 (1.5)	0.80 (0.26-2.51)	.87 (.25-3.03)
Bipolar II disorder	3/642 (0.5)	0/262 (0)	3/380 (0.8)	n/a	n/a
Any mood disorder ^b	277/930 (29.8)	140/515 (27.2)	137/415 (33.0)	0.76 (0.57-1.00)	1.15 (.83-1.58)
Anxiety disorders					
Generalized anxiety disorder	104/931 (11.2)	55/515 (10.7)	49/416 (11.8)	0.90 (0.60-1.35)	.87 (.56-1.36)
Panic disorder	63/935 (6.7)	20/517 (3.9)	43/418 (10.3)	0.35 (0.20-0.61)***	.62 (.33-1.15)
Agoraphobia without panic	9/931 (1.0)	6/514 (1.2)	3/417 (0.8)	1.63 (0.41-6.56)	1.12 (.28-4.52)
Posttraumatic stress disorder	19/587 (3.2)	4/242 (1.7)	15/345 (4.4)	0.37 (0.12-1.13)	.65 (.19-2.19)
Separation anxiety disorder	93/617 (15.1)	61/398 (15.3)	32/219 (14.6)	1.06 (0.67-1.68)	1.06 (.66-1.68)
Social phobia	84/935 (9.0)	39/516 (7.6)	45/419 (10.8)	0.68 (0.43-1.07)	1.15 (.68-1.95)
Specific phobia	140/930 (15.1)	74/513 (14.4)	66/417 (15.8)	0.90 (0.63-1.29)	1.00 (.67-1.49)
Any anxiety disorder ^b	343/949 (36.1)	184/526 (35.0)	159/423 (37.6)	0.89 (0.68-1.17)	.94 (.71-1.26)
Disruptive behavior disorders					
Oppositional defiant disorder	179/610 (29.3)	123/397 (31.0)	56/213 (26.3)	1.26 (.87-1.83)	1.27 (.87-1.84)
Conduct disorder	20/622 (3.2)	11/404 (2.7)	9/218 (4.1)	.65 (.27-1.59)	.64 (.26-1.57)
Any disruptive behavior disorder ^b	185/622 (29.7)	127/404 (31.4)	58/218 (26.6)	1.26 (.88-1.82)	1.27 (.88-1.84)
Eating disorders					
Anorexia nervosa	9/939 (1.0)	4/520 (0.8)	5/419 (1.2)	.64 (.17-2.41)	1.42 (.31-6.56)
Bulimia nervosa	12/937 (1.3)	3/520 (0.6)	9/417 (2.2)	.26 (.07-.98)*	.53 (.12-2.27)
Any eating disorder ^b	19/937 (2.0)	6/520 (1.2)	13/417 (3.1)	.36 (.14-.96)*	.74 (.24-2.23)
Psychotic disorders	7/931 (0.8)	4/516 (0.8)	3/415 (0.7)	1.07 (.24-4.82)	1.12 (.22-5.81)
Substance use disorders					

Comorbid disorder	Proband status				OR (95% CI)	OR (95%CI), adjusted for age
	All TS-affected participants <i>n/total with available data (%)</i>	Proband <i>n/total with available data (%)</i>	Non-proband family member <i>n/total with available data (%)</i>			
Alcohol abuse/dependence	42/939 (4.5)	14/521 (2.7)	28/418 (6.7)	.38 (.20-.74)**	.88 (.41-1.92)	
Substance abuse/dependence ^c	38/946 (4.0)	12/523 (2.3)	26/423 (6.2)	.36 (.18-.72)**	.82 (.36-1.86)	
Any substance use disorder ^{b, c}	59/948 (6.2)	17/524 (3.2)	42/424 (9.9)	.31 (.17-.54)***	.74 (.37-1.47)	
Elimination disorders						
Enuresis	98/665 (14.7)	74/472 (15.7)	24/193 (12.4)	1.31 (.80-2.15)	1.32 (0.80-2.16)	
Encopresis	18/558 (3.2)	11/364 (3.0)	7/194 (3.6)	.83 (.32-2.18)	0.83 (0.32-2.18)	
Any elimination disorder ^p	108/668 (16.2)	78/474 (16.5)	30/194 (15.5)	1.08 (.68-1.70)	1.08 (0.68-1.71)	

In a series of logistic regression models, lifetime diagnosis of each comorbid disorder was defined as the dependent variable, and proband status (yes/no) was the independent variable. In a second series of models, age was added as an independent variable.

* p < .05, ** p < .01, p < .001

^a Includes major depressive disorder with and without psychotic features

^b Cumulative numbers of participants who meet criteria for each group of disorders may not equal the sum of the component diagnoses because of comorbidity among the individual disorders.

^c Does not include alcohol or nicotine

eTable 5. Lifetime Prevalence of Psychiatric Disorders by Presence of OCD and ADHD in Individuals with Tourette Syndrome

Comorbid disorder	All TS-affected participants <i>n/total with available data (%)</i>	Diagnostic category (<i>n/total with available data [%]</i>)				<i>p</i> -value
		TS Only Present (no ADHD or OCD)	TS + OCD Only Present (no ADHD)	TS + ADHD Only Present (no OCD)	TS + OCD + ADHD Present	
Mood disorders						
Major depressive disorder ^b	245/940 (26.1)	43/268 (16.0)	75/174 (43.1)	28/212 (13.2)	99/286 (34.6)	< .001
Dysthymia	28/927 (3.0)	6/264 (2.3)	3/168 (1.8)	8/210 (3.8)	11/285 (3.9)	.47
Bipolar I disorder	12/926 (1.3)	0/264 (0)	4/167 (2.4)	0/209 (0)	8/286 (2.8)	< .01
Bipolar II disorder	3/642 (0.5)	0/192 (0)	1/132 (0.8)	0/117 (0)	2/201 (1.0)	.47
Any mood disorder ^a	277/930 (29.8)	45/262 (17.2)	80/173 (46.2)	35/211 (16.6)	117/284 (41.2)	< .001
Anxiety disorders						
Generalized anxiety disorder	104/931 (11.2)	16/269 (6.0)	21/171 (12.3)	15/207 (7.3)	52/284 (18.3)	< .001
Panic disorder	63/935 (6.7)	5/268 (1.9)	26/173 (15.0)	5/212 (2.4)	27/282 (9.6)	< .001
Agoraphobia without panic	9/931 (1.0)	1/268 (0.4)	0/171 (0)	1/209 (0.5)	7/283 (2.5)	.03
Posttraumatic stress disorder	19/587 (3.2)	1/171 (0.6)	7/123 (5.7)	0/113 (0)	11/180 (6.1)	< .01
Separation anxiety disorder	93/617 (15.1)	12/157 (7.6)	16/82 (19.5)	22/173 (12.7)	43/205 (21.0)	< .01
Social phobia	84/935 (9.0)	22/269 (8.2)	21/171 (12.3)	10/209 (4.8)	31/286 (10.8)	.04
Specific phobia	140/930 (15.1)	21/267 (7.9)	32/171 (18.7)	30/209 (14.4)	57/283 (20.1)	< .001
Any anxiety disorder ^a	343/949 (36.1)	60/270 (22.2)	79/176 (44.9)	67/213 (31.5)	137/290 (47.2)	< .001
Disruptive behavior disorders						
Oppositional defiant disorder	179/610 (29.3)	13/157 (8.3)	21/83 (25.3)	57/171 (33.3)	88/199 (44.2)	< .001
Conduct disorder	20/622 (3.2)	1/158 (0.6)	2/83 (2.4)	5/176 (2.8)	12/205 (5.9)	.04
Any disruptive behavior disorder ^a	185/622 (29.7)	13/158 (8.2)	22/83 (26.5)	58/176 (33.0)	92/205 (44.9)	< .001
Eating disorders						
Anorexia nervosa	9/939 (1.0)	1/269 (0.4)	4/172 (2.3)	3/212 (1.4)	1/286 (0.4)	.11
Bulimia nervosa	12/937 (1.3)	1/268 (0.4)	5/172 (2.9)	1/212 (0.5)	5/285 (1.8)	.07

Comorbid disorder	All TS-affected participants <i>n/total with available data (%)</i>	Diagnostic category (<i>n/total with available data [%]</i>)				<i>p</i> -value
		TS Only Present (no ADHD or OCD)	TS + OCD Only Present (no ADHD)	TS + ADHD Only Present (no OCD)	TS + OCD + ADHD Present	
Any eating disorder ^a	19/937 (2.0)	2/268 (0.8)	8/172 (4.7)	4/212 (1.9)	5/285 (1.8)	.05
Psychotic disorders	7/931 (0.8)	0/268 (0)	1/172 (0)	0/211 (0)	6/280 (2.1)	.01
Substance use disorders						
Alcohol abuse/dependence	42/939 (4.5)	8/269 (3.0)	14/172 (8.1)	5/213 (2.4)	15/285 (5.3)	.03
Substance abuse/dependence ^c	38/946 (4.0)	4/268 (1.5)	13/174 (7.5)	3/213 (1.4)	18/291 (6.2)	< .001
Any substance use disorder ^{a, c}	59/948 (6.2)	8/269 (3.0)	18/174 (10.3)	7/213 (3.3)	26/292 (8.9)	< .01
Elimination disorders						
Enuresis	98/665 (14.7)	20/166 (12.0)	14/92 (15.2)	24/187 (12.8)	40/220 (18.2)	.31
Encopresis	18/558 (3.2)	2/146 (1.4)	5/81 (6.2)	6/153 (3.9)	5/178 (2.8)	.24
Any elimination disorder ^a	108/668 (16.2)	22/166 (13.3)	17/92 (18.5)	26/187 (13.9)	43/223 (19.3)	.30

Males with Tourette syndrome

Comorbid disorder	All TS-affected males <i>n/total with available data (%)</i>	Diagnostic category (<i>n/total with available data [%]</i>)				<i>p</i> -value
		TS Only Present (no ADHD or OCD)	TS + OCD Only Present (no ADHD)	TS + ADHD Only Present (no OCD)	TS + OCD + ADHD Present	
Any mood disorder	184/690 (26.7)	29/195 (14.9)	42/103 (40.8)	29/178 (16.3)	84/214 (39.3)	<.001
Any anxiety disorder	225/703 (32.0)	42/200 (21.0)	40/104 (38.5)	56/180 (31.1)	87/219 (39.7)	<.001
Any disruptive behavior disorder	157/493 (31.9)	11/124 (8.9)	15/51 (29.4)	49/153 (32.0)	82/165 (49.7)	<.001
Any eating disorder	2/693 (0.3)	0/199 (0)	0/101 (0)	1/179 (0.6)	1/214 (0.5)	.82
Any psychotic disorder	5/689 (0.7)	0/198 (0)	1/102 (1.0)	0/178 (0)	4/211 (1.9)	.07
Any substance use disorder^a	42/701 (6.0)	8/199 (4.0)	10/103 (9.7)	6/180 (3.3)	18/219 (8.2)	.04
Any elimination disorder	90/531 (17.0)	18/134 (13.4)	12/57 (21.1)	24/160 (15.0)	36/180 (20.0)	.32

Females with Tourette syndrome

Comorbid disorder	All TS-affected females <i>n/total with available data (%)</i>	Diagnostic category (<i>n/total with available data [%]</i>)				<i>p</i> -value
		TS Only Present (no ADHD or OCD)	TS + OCD Only Present (no ADHD)	TS + ADHD Only Present (no OCD)	TS + OCD + ADHD Present	
Any mood disorder	93/240 (38.8)	16/67 (23.9)	38/70 (54.3)	6/33 (18.2)	33/70 (47.1)	<.001
Any anxiety disorder	118/246 (48.0)	18/70 (25.7)	39/72 (54.2)	11/33 (33.3)	50/71 (70.4)	<.001
Any disruptive behavior disorder	28/129 (21.7)	2/34 (5.9)	7/32 (21.9)	9/23 (39.1)	10/40 (25.0)	.02
Any eating disorder	17/244 (7.0)	2/69 (2.9)	8/71 (11.3)	3/33 (9.1)	4/71 (5.6)	.24
Any psychotic disorder	2/242 (0.8)	0/70 (0)	0/70 (0)	0/33 (0)	2/69 (2.9)	.34
Any substance use disorder^a	17/247 (6.9)	0/70 (0)	8/71 (11.3)	1/33 (3.0)	8/73 (11.0)	.02
Any elimination disorder	18/137 (13.1)	4/32 (12.5)	5/35 (14.3)	2/27 (7.4)	7/43 (16.3)	.78

χ^2 or Fisher's exact test were used to compare rates of each disorder in males vs females and across the 3 age groups. Rates of OCD and ADHD are not included because the diagnostic categories specify the presence of these 2 disorders.

^a Cumulative numbers of participants who meet criteria for each group of disorders may not equal the sum of the component diagnoses because of comorbidity among the individual disorders.

^b Includes major depressive disorder with and without psychotic features

^c Does not include alcohol or nicotine

eTable 6. Associations Among TS, OCD, ADHD and Other Comorbid Disorders

		OR (95% CI) of each disorder					
		Mood	Anxiety	Disruptive behavior	Eating	Substance use	Elimination
Univariate analyses (TS, OCD, and ADHD each entered into separate models)	TS	1.7 (1.2—2.2), p<.01	2.1 (1.6—2.8), p<.001	1.5 (0.7—3.2), p=.25	2.2 (1.0—4.7), p<.05	0.9 (0.6—1.4), p=.78	0.8 (0.3—1.9), p=.65
	OCD	3.8 (3.0—4.8), p<.001	3.1 (2.5—3.9), p<.001	2.6 (1.8—3.7), p<.001	2.0 (.99—3.8), p=.053	3.5 (2.4—5.1), p<.001	1.5 (1.0—2.3), p=.04
	ADHD	1.5 (1.2—1.9), p<.01	2.1 (1.6—2.7), p<.001	4.6 (3.0—7.1), p<.001	1.4 (0.6—3.1), p=.43	1.6 (1.1—2.4), p=.02	1.3 (0.9—2.1), p=.19
Multivariate analyses: TS and OCD	TS	1.1 (0.8—1.5), p=.51	1.5 (1.1—2.1), p<.01	1.2 (0.5—2.4), p=.71	1.8 (0.8—4.1), p=.13	0.6 (0.4—0.9), p=.02	0.7 (0.3—1.7), p=.48
	OCD	3.7 (2.9—4.8), p<.001	3.0 (2.3—3.7), p<.001	2.5 (1.8—3.6), p<.001	1.7 (0.8—3.4), p=.17	4.2 (2.7—6.3), p<.001	1.5 (1.0—2.3), p=.04
Multivariate analyses: TS and ADHD	TS	1.5 (1.1—2.0), p<.01	1.8 (1.3—2.4), p<.001	1.0 (0.4—2.1), p=.96	2.1 (1.0—4.8), p=.06	0.8 (0.5—1.3), p=.44	0.7 (0.3—1.6), p=.41
	ADHD	1.4 (1.0—1.8), p=.02	1.8 (1.4—2.3), p<.001	4.6 (3.0—7.1), p<.001	1.1 (0.5—2.5), p=.81	1.7 (1.1—2.7), p=.01	1.4 (0.9—2.1), p=.17
Multivariate analyses: TS, OCD, and ADHD	TS	1.1 (0.8—1.5), p=.70	1.4 (1.0—1.9), p=.04	0.8 (0.4—1.8), p=.62	1.8 (0.8—4.2), p=.15	0.6 (0.3—0.9), p=.02	0.6 (0.3—1.5), p=.32
	ADHD	1.1 (0.8—1.4), p=.71	1.5 (1.2—2.0), p<.01	4.0 (2.6—6.2), p<.001	1.0 (0.4—2.2), p=.92	1.4 (0.9—2.2), p=.16	1.2 (0.8—2.0), p=.34
	OCD	3.8 (2.9—4.9), p<.001	2.8 (2.2—3.6), p<.001	2.0 (1.4—2.9), p<.001	1.7 (0.8—3.7), p=.17	3.9 (2.5—6.0), p<.001	1.5 (1.0—2.2), p=.07

To determine the association between TS and comorbid disorders, independent of ADHD and OCD, a series of univariate and multivariate generalized estimating equations were modeled with each comorbid disorder as the outcome and TS, ADHD, and/or OCD as the predictor variables. Both TS-affected and TS-unaffected individuals were included. All models included age at interview and sex as covariates.

ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; TS, Tourette syndrome

eTable 7. Ages of Onset for TS and Comorbid Disorders

Disorder	All TS-affected participants		TS-affected males		TS-affected females		Male vs female age of onset, p-value ^a
	N	Median (IQR) age of onset	N	Median (IQR) age of onset	N	Median (IQR) age of onset	
ADHD	569	5 (3-6)	469	4 (3-6)	100	5 (3-6)	.12
Disruptive behavior	85	5 (3-8)	76	5 (3-7)	9	8 (6-10)	.04
Elimination	48	5 (5-5.5)	39	5 (5-5)	9	5 (4-7)	.86
TS	1746	6 (4-8)	1300	6 (4-8)	446	6 (5-8)	<.01
Anxiety	234	7 (4-10)	160	6 (4-10)	74	8 (6-12)	<.01
OCD	579	7 (5-9)	560	7 (5-9)	174	7 (5-10)	.17
Mood	221	13 (10-18)	142	12 (9-16)	79	16 (12-25)	<.01
Substance use	47	16 (15-19)	36	16.5 (15-20)	11	15 (13-16)	.10
Eating	14	16 (15-19)	0	n/a	14	16 (15-19)	n/a

Abbreviation: IQR, interquartile range

^a Wilcoxon rank-sum (Mann-Whitney) test

eTable 8. Bivariate Heritability Estimates Among TS/CMVTD, OCD, And ADHD

Diagnoses	Number of participants included in analysis	RhoG (SE)	RhoG p-value	RhoE (SE)	RhoE p-value
OCD with TS/CMVTD	3182	.72 (.09)	5.6×10^{-11}	.31 (.13)	.03
ADHD with TS/CMVTD	3182	.54 (.09)	6.6×10^{-7}	.30 (.15)	.08
ADHD with OCD	3182	.67 (.09)	1.0×10^{-11}	.09 (.12)	.46

Notes: All analyses include sex, age, and sex-by-age as covariates. ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; RhoE, environmental correlation; RhoG, genetic correlation; TS/CMVTD, Tourette syndrome/chronic motor or vocal tic disorder

eTable 9. Bivariate Heritability of Comorbid Diagnoses with TS/CMVTD

Comorbid disorder	RhoG (SE)	RhoG <i>p</i> -value	RhoE (SE)	RhoE <i>p</i> -value	RhoG (SE)	RhoG <i>p</i> -value	RhoE (SE)	RhoE <i>p</i> -value	RhoG (SE)	RhoG <i>p</i> -value	RhoE (SE)	RhoE <i>p</i> -value	RhoG (SE)	RhoG <i>p</i> -value	RhoE (SE)	RhoE <i>p</i> -value
	No additional diagnostic covariates ^a				Covarying for ADHD ^a				Covarying for OCD ^a				Covarying for ADHD and OCD			
Mood	.47 (.17)	3.6E-3	-.14 (.17)	.40	.37 (.22)	.09	-.04 (.15)	.79	.16 (.25)	.53	-.07 (.14)	.63	n/a	n/a	n/a	n/a
Anxiety	.35 (.15)	.02	.24 (.16)	.15	.15 (.20)	.46	.29 (.14)	.04	.01 (.21)	.96	.24 (.14)	.10	n/a	n/a	n/a	n/a
Disruptive behavior	.40 (.18)	.02	-.20 (.38)	.59	.28 (.25)	.26	-.30 (.36)	.40	.23 (.22)	.30	-.06 (.37)	.87	n/a	n/a	n/a	n/a
Eating	1.0 (n/a)	.52	.29 (1.0)	.31	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Substance use	.22 (.32)	.48	-.17 (.26)	.52	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Elimination	1.0 (n/a)	.13	-.22 (1.0)	.43	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Genetic and environmental correlation (RhoG and RhoE, respectively) between TS/CMVTD and groups of comorbid disorders were estimated; where RhoG was significant, ADHD and OCD were added separately as covariates to assess the independent association between TS/CMVTD and the given comorbid disorders. Subsequently, a series of bivariate analyses with ADHD and OCD were conducted for disorders with a significant RhoG with TS to determine the unique contributions of ADHD and OCD to the genetic correlation between TS/CMVTD and each of these disorders (mood, anxiety, and disruptive behavior disorders).

^a All analyses include sex, age, and sex-by-age as covariates.

ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; TS/CMVTD, Tourette syndrome/chronic motor and vocal tic disorder

eFigure 1. Algorithm for Heritability Testing

