

## Research

## Original Investigation

# Lifetime Prevalence, Age of Risk, and Genetic Relationships of Comorbid Psychiatric Disorders in Tourette Syndrome

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**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.

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**T**ourette 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.<sup>1,2</sup> Multiple comorbid psychiatric disorders have been reported in TS-affected individuals; when present, these conditions typically cause more distress and impairment than do tics.<sup>3-7</sup> 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.<sup>4,8-11</sup> Although elevated rates for mood disorders, nonobsessional anxiety disorders, and disruptive behavior disorders (DBDs) have also been reported,<sup>4,12-17</sup> 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),<sup>3,7,18-20</sup> small number of diagnoses examined, or reliance on symptom checklists and severity scales rather than *DSM*-based, structured diagnostic psychiatric assessments.<sup>18,21-24</sup>

Despite methodologic limitations, these studies<sup>12,13,15</sup> 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,<sup>25-27</sup> 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.).<sup>28</sup> 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, 2.0<sup>29</sup> (all sites except the University of Utah site) or the Schedule for Affective Disorders and Schizophrenia-Lifetime Version, Modified for the Study of Anxiety Disorders<sup>30</sup> (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 Version<sup>31</sup> (all sites except Johns Hopkins University School of Medicine or University of Toronto) or the Epidemiologic Version<sup>32</sup> (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.<sup>28,33</sup> 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  $\chi^2$  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  $\chi^2$  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 me-

Table 1. Lifetime Prevalence of Psychiatric Disorders by Sex

Comorbid Disorder	No./Total No. With Available Data (%)			P Value <sup>a</sup>
	All TS-Affected Participants	Sex		
		Male	Female	
Obsessive-compulsive spectrum <sup>b</sup>	904/1368 (66.1)	645/1001 (64.4)	259/367 (70.6)	.03
Attention-deficit/hyperactivity	713/1314 (54.3)	564/962 (58.6)	149/352 (42.3)	<.001
Mood <sup>c</sup>	277/930 (29.8)	184/690 (26.7)	93/240 (38.8)	<.001
Anxiety <sup>d</sup>	343/949 (36.1)	225/703 (32.0)	118/246 (48.0)	<.001
Disruptive behavior <sup>e</sup>	185/622 (29.7)	157/493 (31.8)	28/129 (21.7)	.03
Eating <sup>f</sup>	19/937 (2.0)	2/693 (0.3)	17/244 (7.0)	<.001
Psychotic <sup>g</sup>	7/931 (0.8)	5/689 (0.7)	2/242 (0.8)	.88
Substance use <sup>h</sup>	59/948 (6.2)	42/701 (6.0)	17/247 (6.9)	.62
Elimination <sup>i</sup>	108/668 (16.2)	90/531 (17.0)	18/137 (13.1)	.28

Abbreviation: TS, Tourette syndrome.

<sup>a</sup> The  $\chi^2$  or Fisher exact test was used to compare rates of each disorder in males vs females.

<sup>b</sup> Obsessive-compulsive disorder and subclinical obsessive-compulsive disorder.

<sup>c</sup> Major depressive disorder, dysthymia, and bipolar disorder I and II.

<sup>d</sup> Generalized anxiety disorder, panic disorder, agoraphobia without panic, posttraumatic stress disorder, separation anxiety disorder, social phobia, and specific phobia.

<sup>e</sup> Oppositional defiant and conduct disorders.

<sup>f</sup> Anorexia and bulimia nervosa.

<sup>g</sup> Schizophrenia and psychotic disorder, not otherwise specified.

<sup>h</sup> Alcohol and other substance use or dependence, excluding tobacco use.

<sup>i</sup> Enuresis and encopresis.

dian 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)<sup>34</sup> (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

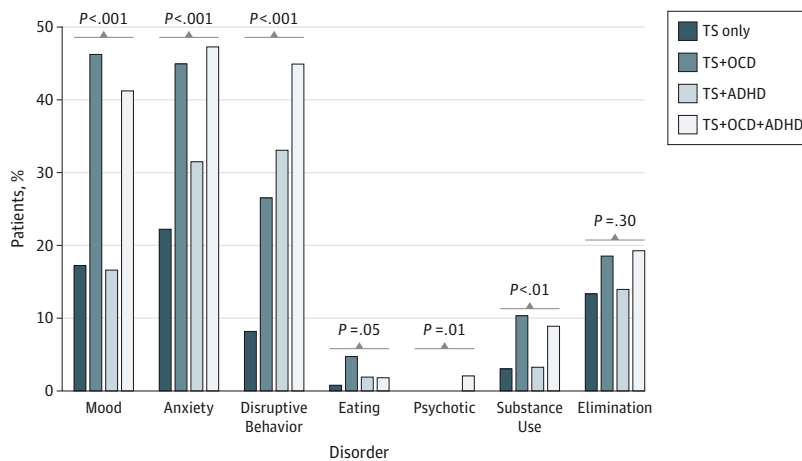
Of the participants with TS, 85.7% met the criteria for 1 or more comorbid disorder (including OCD and ADHD) and 57.7% met the criteria for 2 or more comorbid disorders. Lifetime prevalence rates for classes of comorbid disorders are summarized in Table 1; rates of individual disorders by sex and age 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

Figure 1. Lifetime Prevalence of Comorbid Disorders by the Presence of Obsessive-Compulsive Disorder (OCD) and Attention-Deficit/Hyperactivity Disorder (ADHD) Among Individuals With Tourette Syndrome (TS)



Significance values reflect individual  $4 \times 2 \chi^2$  tests (ie, TS, OCD, and ADHD grouped by the presence of the comorbid disorder).

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  $\chi^2$  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.

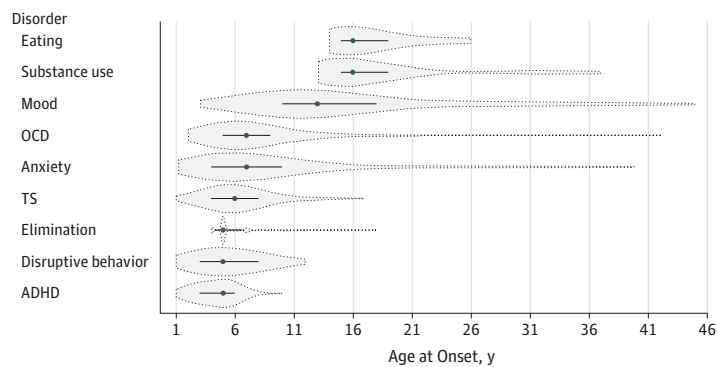
#### Age of Highest Risk

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 non-core 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 his-

Figure 2. Ages at Onset for Comorbid Disorders Among Individuals With Tourette Syndrome (TS)



Data points and bars represent median ages at onset and interquartile ranges, respectively. The width of each plot is proportional to the number of individuals with the given age at TS onset. ADHD indicates attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder.

Table 2. Clinical Predictors of Having 1 or More Comorbid Disorder<sup>a</sup>

Characteristic (Reference Value)	Level	OR (95% CI)	P Value
Symptom severity <sup>b</sup>			
Tic severity tertile (0-16)	17-21	1.18 (0.90-1.55)	.24
	22-30	1.87 (1.43-2.46) <sup>c</sup>	<.001 <sup>c</sup>
OCD severity tertile (0-2)	3-6	1.64 (1.26-2.13) <sup>c</sup>	<.001 <sup>c</sup>
	7-12	2.86 (2.13-3.82) <sup>c</sup>	<.001 <sup>c</sup>
Comorbid condition			
ADHD (no ADHD)	ADHD present	1.93 (1.53-2.43) <sup>c</sup>	<.001 <sup>c</sup>
OCD (no OCD)	OCD present	2.17 (1.75-2.70) <sup>c</sup>	<.001 <sup>c</sup>
Parental history <sup>d</sup>			
TS/CMVTD (parental TS/CMVTD absent)	Parental TS/CMVTD present	1.33 (1.01-1.76) <sup>c</sup>	.04 <sup>c</sup>
OCD (parental OCD absent)	Parental OCD present	1.11 (0.84-1.47)	.46
ADHD (parental ADHD absent)	Parental ADHD present	1.86 (1.32-2.61) <sup>c</sup>	<.001 <sup>c</sup>
Age at onset, y			
TS (≥7)	<7	1.02 (0.82-1.29)	.84
OCD (≥8)	<8	1.10 (0.74-1.64)	.63
ADHD (≥5)	<5	1.35 (0.90-2.01)	.14

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CMVTD, chronic motor or vocal tic disorder; OCD, obsessive-compulsive disorder; OR, odds ratio; TS, Tourette syndrome.

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

<sup>b</sup> Symptom severity scales for tics and obsessive-compulsive symptoms are described in the eMethods in the Supplement.

<sup>c</sup> Statistically significant.

<sup>d</sup> Parental history was available only for probands and their full siblings.

tory 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,<sup>26,35</sup> 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

To our knowledge, 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 the ages of highest risk and etiologic relationships with TS for a wide variety of psychiatric conditions. Our results have implications both clinically and for ongoing research into the causes and etiologic relationships between these psychiatric disorders.

### Clinical Relevance

Consistent with previous studies,<sup>3,4,12,15,36-39</sup> 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 or more comorbid psychiatric disorder during their lifetime, and more than half will develop 2 disorders. In addition to high rates of OCD (50.0%) and ADHD (54.3%), we identified high rates of mood disorders (29.8%), anxiety disorders (36.1%), DBDs (29.7%), and elimination

Table 3. Bivariate Heritability of Comorbid Diagnoses With TS/CMVTD, OCD, and ADHD<sup>a</sup>

Comorbid Disorder	No Additional Diagnostic Covariate <sup>b</sup>				Covariate											
	RhoG (SE)		P Value		TS <sup>b</sup>				OCD or ADHD <sup>b,c</sup>				TS and OCD or ADHD <sup>b,c</sup>			
	RhoG (SE)	P Value	RhoE (SE)	P Value	RhoG (SE)	P Value	RhoE (SE)	P Value	RhoG (SE)	P Value	RhoE (SE)	P Value	RhoG (SE)	P Value	RhoE (SE)	P Value
<b>ADHD</b>																
Mood	0.77 (0.14)	1.6 × 10 <sup>-8</sup>	-0.32 (0.14)	2.6 × 10 <sup>-2</sup>	0.74 (0.15)	3.9 × 10 <sup>-7</sup>	0.31 (0.15)	.03	0.68 (0.18)	8.6 × 10 <sup>-5</sup>	-0.29 (0.14)	.04	0.70 (0.18)	2.3 × 10 <sup>-5</sup>	-0.36 (0.15)	.02
Anxiety	0.59 (0.12)	3.2 × 10 <sup>-6</sup>			0.54 (0.13)	5.0 × 10 <sup>-5</sup>			0.40 (0.15)	7.7 × 10 <sup>-3</sup>			0.43 (0.14)	3.2 × 10 <sup>-3</sup>		
Disruptive behavior	0.68 (0.15)	1.9 × 10 <sup>-5</sup>			0.66 (0.16)	6.9 × 10 <sup>-5</sup>			0.62 (0.17)	5.3 × 10 <sup>-4</sup>			0.61 (0.17)	6.2 × 10 <sup>-4</sup>		
<b>OCD</b>																
Mood	0.59 (0.13)	3.5 × 10 <sup>-5</sup>	0.34 (0.11)	3.2 × 10 <sup>-3</sup>	0.53 (0.15)	1.1 × 10 <sup>-3</sup>	0.40 (0.11)	7.2 × 10 <sup>-4</sup>	0.47 (0.17)	.01	0.43 (0.10)	1.3 × 10 <sup>-4</sup>	0.41 (0.18)	.04	0.48 (0.11)	3.8 × 10 <sup>-5</sup>
Anxiety	0.40 (0.12)	2.7 × 10 <sup>-3</sup>	0.55 (0.11)	4.2 × 10 <sup>-6</sup>	0.34 (0.13)	.02	0.34 (0.11)	1.2 × 10 <sup>-5</sup>			0.60 (0.10)	2.4 × 10 <sup>-7</sup>			0.62 (0.11)	3.6 × 10 <sup>-7</sup>
Disruptive behavior																

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CMVTD, chronic motor and vocal tic disorder; OCD, obsessive-compulsive disorder; OR, odds ratio; RhoE, environmental correlation; RhoG, genetic correlation; TS, Tourette syndrome.

<sup>a</sup> RhoG and RhoE between TS/CMVTD and groups of comorbid disorders were estimated; if 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 was conducted for disorders with a significant RhoG with TS

to determine the unique contributions of ADHD and OCD to the RhoG between TS and each of these disorders (mood, anxiety, and disruptive behavior disorders). Blank cells represent nonsignificant correlations (ie,  $P > .05$ ).

<sup>b</sup> All analyses included sex, age, and sex by age as covariates.

<sup>c</sup> 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.

disorders (16.2%). We found relatively low rates of psychotic disorders and substance abuse disorders at the time of evaluation, although we do not have longitudinal data for the younger individuals as they age, when such disorders typically manifest.

To our knowledge, this study is the first to report the 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 5 years, 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<sup>13,40</sup>; ADHD generally appears 2 to 3 years earlier<sup>41</sup> and OCD 5 to 6 years later.<sup>42</sup> In this study, DBD and ADHD began at or before age 5 years, prior to tic onset. In contrast to the findings of population-based epidemiologic studies,<sup>43,44</sup> OCD and anxiety disorders also began early in the patients in our study, typically within 1 year of the onset of tics (with many cases beginning earlier); mood disorders had a more distributed age-at-onset pattern, beginning as early as age 5 years and becoming more frequent at approximately 7 to 8 years. These results, in combination with the high likelihood of developing a mood disorder, anxiety disorder, 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 have concomitant OCD or a parent with ADHD should be carefully evaluated over time for the development of mood disorder, anxiety disorder, and DBD. In addition, adolescents, particularly those with OCD and/or ADHD, should be monitored

for the development of a substance use disorder. In a similar manner, 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<sup>12</sup> demonstrating an association between tic severity and non-OCD anxiety disorders.

### Etiologic Relevance

The heritability estimates we observed confirm previous research<sup>26,35</sup> showing that TS, OCD, and ADHD are highly genetically related. However, for what we believe to be the first time, we also provide evidence of a strong genetic relationship between these TS-related phenotypes and mood disorders, anxiety disorders, and DBDs. 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 evidence<sup>45</sup> to support shared genetic variance between ADHD and DBD and some data<sup>46</sup> 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 those of a previous study that found no increased rates of ADHD<sup>47</sup> or other non-OCD disorders, such as anxiety, affective, substance abuse, and psychotic disorders,<sup>48</sup> among parents of probands with TS compared with 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 could not assess causation (eg, 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 siblings with previously undiagnosed TS, who were typically less severely affected. Third, although consistent with previous studies, the total psychiatric burden identified in the present study is likely an underestimate given that some disorders were not assessed (eg, pervasive developmental disorders) and not everyone had passed the age of risk for all disorders. Specifically, parents were not routinely assessed for certain childhood disorders (eg, elimination disorders) and children were not assessed for schizophrenia, although they were evaluated for psychosis. In addition, the lifetime rates of schizophrenia, bipolar disorder, and substance use disorders could be attenuated by an ascertainment bias (ie, 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 the recruitment methods (ie, Tourette Syndrome As-

sociation vs specialty clinics), and the characteristics of participants may vary by recruitment method. Sixth, pervasive developmental disorders were not systematically assessed or uniformly excluded; future studies should examine patterns of comorbidity between TS and pervasive developmental disorders.<sup>49</sup> Finally, because the parent genetic study focused on sibling pairs and parent-child trios, the heritabilities may be underestimated because the algorithm used by SOLAR is best suited to analysis of multigenerational families.

### Conclusions

This study provides important new data regarding the prevalence, predictors, and ages of the highest risk for psychiatric illness among individuals affected with TS, as well as what we believe to be the first formal evaluation of the etiologic relationships between disorders other than OCD and ADHD. The key clinical findings, that mood disorders, anxiety disorders, and DBDs 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 etiologic relationships between TS and other psychiatric disorders and provide a framework for future studies aimed at better understanding these complex, interrelated syndromes.

#### ARTICLE INFORMATION

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## REFERENCES

- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, text revision. Washington, DC: American Psychiatric Association; 2000.
- Swain JE, Scahill L, Lombroso PJ, King RA, Leckman JF. Tourette syndrome and tic disorders: a decade of progress. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):947-968.
- Coffey BJ, Miguel EC, Biederman J, et al. Tourette's disorder with and without obsessive-compulsive disorder in adults: are they different? *J Nerv Ment Dis*. 1998;186(4):201-206.
- Gorman DA, Thompson N, Plessen KJ, Robertson MM, Leckman JF, Peterson BS. Psychosocial outcome and psychiatric comorbidity

in older adolescents with Tourette syndrome: controlled study. *Br J Psychiatry*. 2010;197(1):36-44.

- Sukhodolsky DG, Scahill L, Zhang H, et al. Disruptive behavior in children with Tourette's syndrome: association with ADHD comorbidity, tic severity, and functional impairment. *J Am Acad Child Adolesc Psychiatry*. 2003;42(1):98-105.
- Bernard BA, Stebbins GT, Siegel S, et al. Determinants of quality of life in children with Gilles de la Tourette syndrome. *Mov Disord*. 2009;24(7):1070-1073.
- Bloch MH, Peterson BS, Scahill L, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. *Arch Pediatr Adolesc Med*. 2006;160(1):65-69.
- Peterson BS, Pine DS, Cohen P, Brook JS. Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample. *J Am Acad Child Adolesc Psychiatry*. 2001;40(6):685-695.
- Denckla MB. Attention deficit hyperactivity disorder: the childhood co-morbidity that most influences the disability burden in Tourette syndrome. *Adv Neurol*. 2006;99:17-21.
- Mathews CA, Waller J, Glidden D, et al. Self injurious behaviour in Tourette syndrome: correlates with impulsivity and impulse control. *J Neurol Neurosurg Psychiatry*. 2004;75(8):1149-1155.
- Robertson MM. The Gilles de la Tourette syndrome: the current status. *Arch Dis Child Educ Pract Ed*. 2012;97(5):166-175.
- Coffey BJ, Biederman J, Smoller JW, et al. Anxiety disorders and tic severity in juveniles with Tourette's disorder. *J Am Acad Child Adolesc Psychiatry*. 2000;39(5):562-568.
- Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Dev Med Child Neurol*. 2000;42(7):436-447.
- Ghanizadeh A, Mosallaei S. Psychiatric disorders and behavioral problems in children and adolescents with Tourette syndrome. *Brain Dev*. 2009;31(1):15-19.
- Mol Debes NM, Hjalgrim H, Skov L. Validation of the presence of comorbidities in a Danish clinical cohort of children with Tourette syndrome. *J Child Neurol*. 2008;23(9):1017-1027.
- Comings BG, Comings DE. A controlled study of Tourette syndrome, V: depression and mania. *Am J Hum Genet*. 1987;41(5):804-821.
- Comings DE, Comings BG. A controlled study of Tourette syndrome, II: conduct. *Am J Hum Genet*. 1987;41(5):742-760.
- Haddad AD, Umoh G, Bhatia V, Robertson MM. Adults with Tourette's syndrome with and without attention deficit hyperactivity disorder. *Acta Psychiatr Scand*. 2009;120(4):299-307.
- Berthier ML, Kulisevsky J, Campos VM. Bipolar disorder in adult patients with Tourette's syndrome: a clinical study. *Biol Psychiatry*. 1998;43(5):364-370.
- Bloch MH, Leckman JF, Zhu H, Peterson BS. Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. *Neurology*. 2005;65(8):1253-1258.

- Eapen V, Fox-Hiley P, Banerjee S, Robertson M. Clinical features and associated psychopathology in a Tourette syndrome cohort. *Acta Neurol Scand*. 2004;109(4):255-260.
- Wand RR, Matazov GS, Shady GA, Furer P, Staley D. Tourette syndrome: associated symptoms and most disabling features. *Neurosci Biobehav Rev*. 1993;17(3):271-275.
- Rickards H, Robertson M. A controlled study of psychopathology and associated symptoms in Tourette syndrome. *World J Biol Psychiatry*. 2003;4(2):64-68.
- Termine C, Balottin U, Rossi G, et al. Psychopathology in children and adolescents with Tourette's syndrome: a controlled study. *Brain Dev*. 2006;28(2):69-75.
- Grados MA, Mathews CA; Tourette Syndrome Association International Consortium for Genetics. Latent class analysis of Gilles de la Tourette syndrome using comorbidities: clinical and genetic implications. *Biol Psychiatry*. 2008;64(3):219-225.
- Mathews CA, Grados MA. Familiality of Tourette syndrome, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder: heritability analysis in a large sib-pair sample. *J Am Acad Child Adolesc Psychiatry*. 2011;50(1):46-54.
- Sheppard DM, Bradshaw JL, Purcell R, Pantelis C. Tourette's and comorbid syndromes: obsessive compulsive and attention deficit hyperactivity disorder: a common etiology? *Clin Psychol Rev*. 1999;19(5):531-552.
- Tourette Syndrome Association International Consortium for Genetics. Genome scan for Tourette disorder in affected-sibling-pair and multigenerational families. *Am J Hum Genet*. 2007;80(2):265-272.
- First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders-Non-Patient Edition (SCID-I/NP, version 2.0)*. New York: Biometrics Research Dept, New York State Psychiatric Institute; 1995.
- Fyer A, Endicott J, Mannuzza S, Klein DF. *Schedule for Affective Disorders and Schizophrenia-Lifetime Version, Modified for the Study of Anxiety Disorders (SADS-LA)*. New York: Anxiety Disorders Clinic, New York State Psychiatric Institute; 1985.
- Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980-988.
- Orvaschel H, Puig-Antich J, Chambers W, Tabrizi MA, Johnson R. Retrospective assessment of prepubertal major depression with the Kiddie-SADS-e. *J Am Acad Child Psychiatry*. 1982;21(4):392-397.
- Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM. Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch Gen Psychiatry*. 1982;39(8):879-883.
- Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet*. 1998;62(5):1198-1211.
- Grados MA, Mathews CA. Clinical phenomenology and phenotype variability in Tourette syndrome. *J Psychosom Res*. 2009;67(6):491-496.



36. Chee KY, Sachdev P. The clinical features of Tourette's disorder: an Australian study using a structured interview schedule. *Aust N Z J Psychiatry*. 1994;28(2):313-318.
37. Kurlan R, Como PG, Miller B, et al. The behavioral spectrum of tic disorders: a community-based study. *Neurology*. 2002;59(3):414-420.
38. Khalifa N, von Knorring AL. Psychopathology in a Swedish population of school children with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1346-1353.
39. Specht MW, Woods DW, Piacentini J, et al. Clinical characteristics of children and adolescents with a primary tic disorder. *J Dev Phys Disabil*. 2011;23(1):15-31.
40. Leckman JF, Zhang H, Vitale A, et al. Course of tic severity in Tourette syndrome: the first two decades. *Pediatrics*. 1998;102(1, pt 1):14-19.
41. Robertson MM. Attention deficit hyperactivity disorder, tics and Tourette's syndrome: the relationship and treatment implications: a commentary. *Eur Child Adolesc Psychiatry*. 2006;15(1):1-11.
42. Delorme R, Golmard JL, Chabane N, et al. Admixture analysis of age at onset in obsessive-compulsive disorder. *Psychol Med*. 2005;35(2):237-243.
43. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593-602.
44. Kessler RC, Angermeyer M, Anthony JC, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry*. 2007;6(3):168-176.
45. Nadder TS, Rutter M, Silberg JL, Maes HH, Eaves LJ. Genetic effects on the variation and covariation of attention deficit-hyperactivity disorder (ADHD) and oppositional-defiant disorder/conduct disorder (ODD/CD) symptomatologies across informant and occasion of measurement. *Psychol Med*. 2002;32(1):39-53.
46. Lee SH, Ripke S, Neale BM, et al; Cross-Disorder Group of the Psychiatric Genomics Consortium; International Inflammatory Bowel Disease Genetics Consortium (IIBDGC). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45(9):984-994.
47. Pauls DL, Hurst CR, Kruger SD, Leckman JF, Kidd KK, Cohen DJ. Gilles de la Tourette's syndrome and attention deficit disorder with hyperactivity: evidence against a genetic relationship. *Arch Gen Psychiatry*. 1986;43(12):1177-1179.
48. Pauls DL, Leckman JF, Cohen DJ. Evidence against a genetic relationship between Tourette's syndrome and anxiety, depression, panic and phobic disorders. *Br J Psychiatry*. 1994;164(2):215-221.
49. Clarke RA, Lee S, Eapen V. Pathogenetic model for Tourette syndrome delineates overlap with related neurodevelopmental disorders including autism. *Transl Psychiatry*. 2012;2:e158.