

Supplementary Online Content

Hirschtritt ME, Lee PC, Pauls DL, et al; Tourette Syndrome Association International Consortium for Genetics. Lifetime prevalence, age of risk, and genetic relationships for comorbid psychiatric disorders in Tourette syndrome. *JAMA Psychiatry*. Published online February 11, 2015. doi:10.1001/jamapsychiatry.2014.2650.

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

eFigure. Algorithm for Heritability Testing

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.

References

1. Wechsler D. *Manual for the Wechsler Intelligence Scale for Children—Revised*. New York: Psychological Corporation; 1974.
2. Pauls DL, Alsobrook JP, 2nd, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. *Am J Psychiatry*. 1995;152(1):76-84.
3. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry*. 1989;28(4):566-573.
4. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46(11):1006-1011.
5. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. II. Validity. *Arch Gen Psychiatry*. 1989;46(11):1012-1016.
6. First M, Gibbon M, Williams J. *Structured Clinical Interview for DSM-IV Axis I Disorders*. Washington, DC: American Psychiatric Press; 1997.
7. 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. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(7):980-988.
8. Simon GE, VonKorff M. Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. *Epidemiol Rev*. 1995;17(1):221-227.

eTable 1. Demographic and Clinical Characteristics of the Sample

	Participants with TS (n = 1,374) ^a	First-degree relatives without TS (n = 1,142) ^a	All participants, including unaffected first-degree family members (n = 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 n/total with available data (%)	Sex		P value
		Male n/total with available data (%)	Female n/total with available data (%)	
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.

^aCumulative 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.

^bIncludes major depressive disorder with and without psychotic features

^cDoes 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>)			P 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
Bulimia nervosa	12/937 (1.3)	0/425 (0.0)	2/233 (0.9)	10/279 (3.6)	<.001

Comorbid disorder	All TS-affected participants <i>n/total with available data (%)</i>	Age (<i>n/total with available data [%]</i>)			P value
		6-12 y	13-17 y	≥ 18 y	
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)	.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)	.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					
Alcohol abuse/dependence	42/939 (4.5)	14/521 (2.7)	28/418 (6.7)	.38 (.20-.74)**	.88 (.41-1.92)

Comorbid disorder	Proband status				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>	OR (95% CI)	
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 ^b	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>)				P 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>)				P 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>)				p-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	0.72 (.09)	5.6×10^{-11}	0.31 (.13)	.03
ADHD with TS/CMVTD	3182	0.54 (.09)	6.6×10^{-7}	0.30 (.15)	.08
ADHD with OCD	3182	0.67 (.09)	1.0×10^{-11}	0.09 (.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)	Rho p-value	RhoE (SE)	Rho p-value	RhoG (SE)	Rho p-value	RhoE (SE)	Rho p-value	RhoG (SE)	RhoG p-value	RhoE (SE)	RhoE p-value
	No additional diagnostic covariates ^a				Covarying for ADHD ^a				Covarying for OCD ^a			
Mood	.47 (.17)	3.6E-3	-.14 (.17)	.40	.37 (.22)	.09	-.04 (.15)	.79	.16 (.25)	.53	-.07 (.14)	.63
Anxiety	.35 (.15)	.02	.24 (.16)	.15	.15 (.20)	.46	.29 (.14)	.04	.01 (.21)	.96	.24 (.14)	.10
Disruptive behavior	.40 (.18)	.02	-.20 (.38)	.59	.28 (.25)	.26	-.30 (.36)	.40	.23 (.22)	.30	-.06 (.37)	.87
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
Substance use	.22 (.32)	.48	-.17 (.26)	.52	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

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.

^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. Algorithm for Heritability Testing

