Social disinhibition is a heritable subphenotype of tics in Tourette syndrome

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ABSTRACT

Objective: To identify heritable symptom-based subtypes of Tourette syndrome (TS).

Methods: Forty-nine motor and phonic tics were examined in 3,494 individuals (1,191 TS probands and 2,303 first-degree relatives). Item-level exploratory factor and latent class analyses (LCA) were used to identify tic-based subtypes. Heritabilities of the subtypes were estimated, and associations with clinical characteristics were examined.

Results: A 6-factor exploratory factor analysis model provided the best fit, which paralleled the somatotopic representation of the basal ganglia, distinguished simple from complex tics, and separated out socially disinhibited and compulsive tics. The 5-class LCA model best distinguished among the following groups: unaffected, simple tics, intermediate tics without social disinhibition, intermediate with social disinhibition, and high rates of all tic types. Across models, a phenotype characterized by high rates of social disinhibition emerged. This phenotype was associated with increased odds of comorbid psychiatric disorders, in particular, obsessive-compulsive disorder and attention-deficit/hyperactivity disorder, earlier age at TS onset, and increased tic severity. The heritability estimate for this phenotype based on the LCA was 0.53 (SE 0.08, $p = 1.7 \times 10^{-18}$).

Conclusions: Expanding on previous modeling approaches, a series of TS-related phenotypes, including one characterized by high rates of social disinhibition, were identified. These phenotypes were highly heritable and may reflect underlying biological networks more accurately than traditional diagnoses, thus potentially aiding future genetic, imaging, and treatment studies.

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GLOSSARY

ADHD = attention-deficit/hyperactivity disorder; **BIC** = Bayesian information criterion; **EFA** = exploratory factor analysis; **LCA** = latent class analysis; **OCD** = obsessive-compulsive disorder; **TS** = Tourette syndrome.

Tourette syndrome (TS) is a highly heritable neurodevelopmental disorder, yet it is also etiologically and phenotypically heterogeneous.¹ Identifying TS-related subphenotypes may decrease this heterogeneity, aiding efforts to clarify its pathophysiology and genetic architecture.²

Previous studies using data modeling techniques such as hierarchical cluster analysis, exploratory factor analysis (EFA), and latent class analysis (LCA) to explore TS symptom patterns have been hampered by small sample sizes and divergent techniques. Although the number of TS subtypes has varied (2 to 5) across studies, one pattern has emerged: a subtype with predominantly simple tics separating from one containing both simple and complex tics.³⁻⁸ Otherwise,

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however, the current studies have not converged on a unified model to date. Refinement of the emerging patterns of TS subphenotypes can only arise from analyses of larger sample sizes.

Our primary goal in conducting phenotypic subtyping was to develop a clearer understanding of the genetic architecture of TS. Although previous studies suggest that some TS-related subphenotypes may be more heritable than others,^{3,4,6,8–10} no detailed information exists about the heritability of specific TS symptom subtypes.

The aims of this study were to (1) analyze tic symptom data using EFA and LCA in a large sample of TS-affected families, (2) characterize the resulting phenotypes according to sex, age, symptom severity, and comorbid psychiatric diagnoses, and (3) determine their utility for genetic studies. Moreover, any identified phenotypes may also be useful for other investigations into TS pathophysiology (e.g., for neuroimaging and treatment studies).

METHODS Sample. The sample included 3,850 individuals from 1,365 families collected by the Tourette Syndrome Association International Consortium for Genetics between April 1, 1992, and August 16, 2011. Patients diagnosed with TS were referred from TS specialty clinics in the United States, Canada, Great Britain, and the Netherlands, and from the US Tourette Syndrome Association. Probands were excluded from analysis if they were missing all responses for tic symptom items. Family members were excluded if they were missing all responses regarding tics. In addition, cases were excluded when data were missing on family status (e.g., unknown whether individual was proband, sibling, child, or parent) or when symptom data were not verified by clinicians. See supplemental data on the *Neurology*[®] Web site at Neurology.org for inclusion and exclusion criteria for the parent genetic study.

Standard protocol approvals, registrations, and patient consents. All participants provided written informed consent (parental consent and written assent was obtained for individuals younger than 18 years). This study was approved by the institutional review boards of all participating sites.

Procedure. Research staff administered clinical assessments using a standardized protocol. Demographic data, tic, obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder (ADHD) symptoms were assessed using a comprehensive assessment, the TICS Inventory,^{11,12} including 49 motor and phonic tics that were verified by the staff when possible. Psychiatric diagnoses were validated using a best-estimate process (appendices e-1 to e-3).

Statistical analyses. Descriptive statistical analyses and latent variable modeling were performed using SPSS version 19 (IBM Corp., Armonk, NY) and MPlus version 7.1,¹³ respectively.

Exploratory factor analysis. EFA, a technique that groups items that frequently co-occur in a sample (in contrast to LCA,

which groups participants with similar response patterns), was conducted on tic data using robust weighted least squares estimation, as recommended for dichotomous variables,¹⁴ and oblique rotation (geomin). Unlike in previous TS factor analyses,⁶ we chose not to first create clusters of variables because our sample size was sufficiently large to use the individual tic variables in the factor analysis. Data were limited to probands to examine independent cases. The best factor solution was chosen using a stepwise approach based on widely accepted criteria¹⁵: first, we examined the eigenvalues and excluded models containing eigenvalues <1. Second, we examined the scree plot to identify potential “elbows.” Third, we compared the root mean square error of approximation^{16,17} and χ^2 difference test¹⁸ values among competing models to provide quantitative measures of fit. Fourth, we examined the number of variables that “cross-loaded” (i.e., loaded on ≥ 1 factor at ≥ 0.40), and finally, we assessed the clinical applicability and interpretability of the models. Within each factor model, items were retained if factor loadings (the degree to which a factor explains or affects a variable) were ≥ 0.40 ; items that loaded ≥ 0.40 on more than one factor were retained on the factor with the highest loading. Items with loadings <0.40 were excluded from the final model. Cronbach α was calculated for each factor to examine internal consistency. Mean sum scores were calculated for each participant by dividing the number of items the individual endorsed by the total number of items answered for each factor, allowing for generalization of the data.¹⁹ Logistic and linear regression models were used to examine relationships between clinical characteristics (comorbid psychiatric diagnoses, sex, age at TS onset, TS severity, age at OCD onset, OCD severity) as outcome variables, and all 6 tic factor sum scores and age at interview (to control for differential onset of tics based on age) as predictors. Significance for regression models was set at $p < 0.005$ by Bonferroni correction to account for multiple testing.

Latent class analysis. The least Bayesian information criterion (BIC)²⁰ and results of the Lo, Mendel, and Rubin likelihood ratio test²¹ were used to determine the number of classes to retain. Specifically, the least BIC and a significant likelihood ratio test ($p < 0.05$) were used to indicate good fit. If these criteria left the model choice unclear, the clinical interpretability of the solutions was examined (i.e., if clinically relevant patterns distinguished the classes in one solution but not another). Classes were labeled according to the group of symptoms that individuals in the class endorsed with a high frequency. Latent class models with 2 to 6 classes were first fit in probands and then replicated with probands plus family members to facilitate heritability analyses. We compared the rates of psychiatric comorbidity between classes using the auxiliary variable function of MPlus, which is similar to a χ^2 test while accounting for uncertainty inherent in classifying individuals. Significance level was $p < 0.05$. This test was also used to compare the rates of mothers and fathers in different classes.

Heritability analyses. Last, heritability estimates were calculated for factor sum scores and class membership. The Sequential Oligogenic Linkage Analysis Routine statistical package²² uses a variance component approach and calculates kinship coefficients using information from all available family members across generations. Families were included only if a proband was present. Age, sex, and sex-by-age were used as covariates in all analyses. For factor sum scores, we inversed normalized all mean sum scores because of the skewed distribution of the raw data. For class membership, because the probability distributions from the LCA (i.e., probabilities that an individual will belong to each class from 0 [no probability] to 1 [100% probability]) approximated

a binary distribution, we assigned each individual to his or her most likely class. For heritability analyses, class membership was binary and mutually exclusive.

RESULTS Sample characteristics. The final sample included 3,494 participants: 1,191 probands and 2,303 first-degree family members (table 1). Missing data patterns did not differ by site.

Tic symptom factors. Eigenvalues were ≥ 1.0 for models containing up to 12 factors, and the scree plot showed elbows at 2 and 3 factors, with a small elbow at 8 factors (figure e-1). We thus examined the fit statistics of the 1- to 8-factor models. All models had root mean square error of approximation values < 0.05 , and the χ^2 difference tests were significant for all comparisons up to the 8-factor model. Of these, the 7- and 8-factor models were discarded, since each had one factor without any items with significant factor loadings. Of the remaining models, the 3- and 6-factor models had the fewest items that did not load at ≥ 0.40 and the fewest variables that cross-loaded. Although the scree plot showed an elbow at 3 factors, and examination of the factor loadings also indicated that this model was a reasonable fit, we decided to retain the 6-factor model because it provided more clinical information than the 3-factor model, and because the fit statistics indicated that it was a good fit for the data.

The first 3 factors in this solution paralleled the rostral to caudal somatotopic maps in the cortex and basal ganglia²³: F1 = eye tics, F2 = head and

facial tics, and F3 = body/trunk tics. F4 included complex vocal and socially disinhibited or inappropriate tics (e.g., copropraxia, palilalia). F5 included touching tics (e.g., tapping) and F6 included simple vocal tics (e.g., coughing). These 6 factors demonstrated good internal consistency (Cronbach α for subscales was 0.61–0.73) (table e-1). Estimated heritabilities of the tic factors ranged from 0.10 to 0.25 (all p values $\leq 5 \times 10^{-6}$); the highest heritability estimate was for head and facial tics ($h^2r = 0.25$). The socially disinhibited tic factor had the next highest heritability estimate ($h^2r = 0.19$) (table 2).

Regression models yielded several notable findings (table 3). Higher scores on F2 (head and facial tics) were associated with the presence of a mood disorder (depression or bipolar disorder). F4 (socially disinhibited tics) and F5 (touching) were associated with comorbid OCD and higher OC severity; F4 was also associated with comorbid ADHD, earlier TS age at onset, and higher tic severity. F1 (eye tics) and F3 (body tics) were associated with higher tic severity; F1 was additionally associated with earlier TS age at onset.

Tic symptom classes. Latent class models were fit to the 49 tic symptoms. The 4-class model for probands demonstrated the best fit based on the BIC and Lo, Mendel, and Rubin test (table e-2). Posterior probabilities for class assignment ranged from 0.86 (LC4) to 0.94 (LC3), indicating that a categorical assignment to a specific class membership was appropriate. The classes primarily differentiated individuals regarding symptom endorsement rates,

Table 1 Sample characteristics

	Patients only (n = 1,191)			Patients and family members (n = 3,494)		
	No.	M	SD	No.	M	SD
Age	1,191	15.3	10.0	3,494	30.6	17.2
TS age at onset	1,131	5.8	2.5	1,692	6.1	2.7
TS severity	1,181	11.4	2.6	3,490	4.1	4.6
OCD age at onset	442	7.1	4.0	712	8.2	5.3
OCD severity	694	4.3	3.4	2,442	3.0	3.3
		<i>f</i>	%		<i>f</i>	%
Male	1,191	944	79.3	3,494	2,140	61.2
Parental history of TS/CMVTD	864	385	44.6	—	—	—
OCD	1,135	570	50.2	3,286	1,125	34.2
ADHD	1,116	628	56.3	3,220	1,013	31.5
Mood disorders	498	132	26.5	1,603	487	30.4
Anxiety disorders	507	176	34.7	1,620	515	31.8
Disruptive behavior disorders	390	121	31.0	662	192	29.0

Abbreviations: ADHD = attention-deficit/hyperactive disorder; CMVTD = chronic motor or vocal tic disorder; *f* = frequency; M = mean; OCD = obsessive-compulsive disorder; TS = Tourette syndrome. Tic severity total possible = 30.

Table 2 Heritability estimates for tic symptom factors and symptom-based classes of patients and family members

	h^2r	SE	p Value
Tic symptom classes			
LC1: High on all symptoms	0.43	0.15	0.002
LC2: Intermediate without disinhibited tics	0.19	0.09	0.012
LC3: Intermediate with disinhibited tics	0.29	0.10	0.002
LC4: Simple tics	0.04	0.06	0.25
LC5: Unaffected	—	—	—
Tic symptom factors			
F1: Eye tics	0.16	0.03	1.00×10^{-7}
F2: Head/facial tics	0.25	0.03	1.47×10^{-16}
F3: Body tics	0.10	0.02	4.90×10^{-6}
F4: Socially disinhibited tics	0.19	0.02	6.67×10^{-16}
F5: Touching tics	0.11	0.02	2.00×10^{-7}
F6: Simple vocal tics	0.18	0.03	1.00×10^{-7}

Abbreviations: h^2r = heritability estimate; SE = standard error.
All analyses included sex, age, and sex $\times$ age as covariates.

with some important exceptions. LC1 probands endorsed all tic symptoms at a high frequency. LC4 probands endorsed the fewest tics; >50% of individuals in LC4 endorsed only a few simple tics and <20% endorsed any complex tics. LC2 and LC3 had intermediate rates of tic endorsement and were differentiated by the number of individuals endorsing socially disinhibited tics (i.e., coprolalia, copropraxia,

echolalia, complex words, palilalia, animal noises, syllables, rotating, bending, or gyrating). Specifically, LC3 probands endorsed these disinhibited tics as frequently as LC1 (the class with high rates of endorsement overall), while most LC2 probands reported few or no disinhibited tics. The same solution arose when incorporating family members into the analysis, with an additional “unaffected” class, LC5 (figure 1). Posterior probabilities for the 5-class solution ranged from 0.86 (LC3) to 0.97 (LC5).

Classes with higher rates of tic endorsement (i.e., LC1 and LC3) also had higher rates of comorbidity than those with lower rates of endorsement (OCD, ADHD, anxiety disorders, disruptive behavior disorders, $p < 0.001$ for all; figure 2). Similarly, among the 2 intermediate classes, a higher proportion of the class endorsing socially disinhibited tics (LC3) had comorbid OCD and ADHD compared to the class who did not endorse these tics (LC2) ($\chi^2 = 8.84$, $p = 0.003$, and $\chi^2 = 28.46$, $p < 0.001$, respectively). The unaffected and simple tic classes were the most represented among mothers (51% and 22%, respectively) and fathers (43% and 24%, respectively) of probands. Heritability analyses were conducted for 4 of the 5 classes in the LCA solution that included data from family members (excluding the “unaffected” class; table 2). Heritability estimates were higher for the 2 tic classes in which members endorsed disinhibited tics (LC1, $h^2r = 0.43$, and LC3, $h^2r = 0.29$;

Table 3 Association of tic factor sum scores with clinical characteristics among patients (n = 1,191)

Clinical characteristic	F1: Eye tics	F2: Head/facial tics	F3: Body tics	F4: Socially disinhibited tics	F5: Touching tics	F6: Simple vocal tics
Psychiatric comorbidity ^a						
OCD	0.9 (0.5, 1.5)	1.1 (0.6, 1.2)	1.9 (0.9, 3.9)	2.7 (1.6, 4.6) ^b	4.0 (2.5, 6.4) ^c	0.8 (0.5, 1.2)
ADHD	1.1 (0.6, 1.9)	0.5 (0.3, 1.0)	0.9 (0.4, 1.8)	4.6 (2.6, 8.1) ^c	1.2 (0.8, 2.0)	1.5 (1.0, 2.2)
Anxiety	2.0 (0.9, 4.5)	0.4 (0.1, 1.0)	0.6 (0.2, 1.8)	1.9 (0.9, 4.0)	1.2 (0.6, 2.4)	0.7 (0.4, 1.3)
Mood	1.0 (0.4, 2.7)	8.0 (2.4, 26.7) ^b	0.9 (0.3, 3.0)	0.5 (0.2, 1.3)	1.6 (0.7, 3.5)	0.7 (0.4, 1.5)
Disruptive behavior	3.2 (1.2, 8.6)	1.7 (0.5, 6.1)	0.2 (0.1, 0.9)	1.7 (0.7, 4.3)	1.5 (0.7, 3.4)	1.3 (0.6, 2.7)
Sex ^{a,d}	0.8 (0.4, 1.6)	2.3 (1.1, 4.8)	1.3 (0.6, 2.8)	0.5 (0.3, 1.0)	0.9 (0.5, 1.6)	1.4 (0.9, 2.2)
TS age at onset ^e	0.4 (0.2, 0.7) ^f	1.5 (0.7, 3.0)	1.1 (0.5, 2.4)	0.4 (0.2, 0.7) ^f	1.2 (0.7, 1.9)	0.6 (0.4, 0.9)
Tic severity ^e	3.9 (2.0, 7.5) ^c	2.1 (1.0, 4.4)	3.9 (1.8, 8.5) ^b	4.4 (2.5, 8.0) ^c	1.2 (0.7, 2.0)	1.8 (1.2, 2.9)
OCD age at onset ^e	0.2 (0.0, 0.8)	0.2 (0.0, 1.1)	1.7 (0.3, 8.4)	0.4 (0.1, 1.3)	0.8 (0.3, 2.2)	0.6 (0.2, 1.8)
OC severity ^e	1.2 (0.4, 3.4)	1.7 (0.4, 6.3)	2.0 (0.5, 8.0)	10.2 (3.8, 27.6) ^c	7.5 (3.0, 18.8) ^c	0.7 (0.3, 1.6)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; OC(D) = obsessive-compulsive (disorder).

Regression models simultaneously covary for all 6 factors, age at interview, and tic severity (except in the model in which tic severity is the outcome) and define each clinical characteristic as the outcome variable in separate models.

^aValues represent odds ratio (95% confidence interval).

^b $p < 0.001$.

^c $p < 0.0001$.

^dOdds ratios >1 indicate higher odds of female sex.

^eValues represent standardized β coefficient (95% confidence interval).

^f $p < 0.005$.

Figure 1 Endorsement rates of individual tic symptoms among classes of patients and family members

Lines represent members of each of the 5 latent classes. The tic symptoms are divided into 2 sections. The first section contains the items that members of LC3 (intermediate, high disinhibited tics) endorsed 15% or more of the time compared to LC2 (intermediate, low disinhibited tics). The second section of the graph contains all other tics and is sorted by decreasing frequency of endorsement by members of LC1.

$p = 0.002$ for both) than classes who did not endorse these symptoms (LC2, $h^2r = 0.19$, $p = 0.01$; LC4, $h^2r = 0.04$, $p = 0.25$). As we identified an unexpected pattern of symptom endorsement that might be useful for future studies of TS pathophysiology (socially disinhibited tics), we conducted additional post hoc heritability analyses combining the classes endorsing these symptoms at high rates (i.e., LC1 and LC3). Six hundred fifty-five individuals (19% of the sample) endorsed socially disinhibited tics at high rates; the heritability estimate for this phenotype was 0.53 (SE = 0.08, $p = 1.7 \times 10^{-18}$).

DISCUSSION This study extends previous work using latent variable modeling by examining the phenotypic and genetic structure of tics in TS using multiple modeling approaches on symptom-level data in a large sample of TS-affected individuals and family members. The use of EFA and LCA in the same dataset provides an opportunity to thoroughly examine the phenotypes of complex disorders by investigating clustering patterns for symptoms and individuals. The complementary findings across

these 2 approaches are notable. While LCA identifies subgroups of individuals based on their phenotype, EFA identifies groups of symptoms that co-occur across all individuals, allowing for the creation of quantitative phenotypes that may be more powerful than categorical phenotypes, or may tap into different pathophysiologic mechanisms. The large sample size used in the current study allowed for analysis of individual tics, which may provide a more precise delineation of groups of tics and individuals than in previous studies that first created clusters of symptoms, on which EFA or LCA was then performed.

One notable finding arising from this work is the identification, using both modeling approaches, of socially disinhibited tics as a separate tic subtype. Of note, the factor identified in our EFA is similar to the aggressive tic factor found in a previous TS factor analytic study, which included the following symptoms: coprolalia, mental coprolalia, coprophagia, palipraxis, hitting, kicking, echolalia, echopraxia, palilalia, spitting, random words, forced touching, and self-injurious behavior.⁴ In both the LCA and EFA,

Figure 2 Adjusted rates of comorbid diagnoses for 5 tic classes of patients and family members

Rates were adjusted by uncertainty of classifying individuals into separate classes. Letters above bars indicate pairwise comparisons with significant difference at $p < 0.05$ (LC1 = a, LC2 = b, LC3 = c, LC4 = d, LC5 = e); bars indicate SEM. Overall, there were significant differences in rates of OCD ($\chi^2 = 540.95$, $df = 4$, $p \leq 0.001$), ADHD ($\chi^2 = 928.3$, $df = 4$, $p \leq 0.001$), anxiety disorders ($\chi^2 = 28.18$, $df = 4$, $p \leq 0.001$), and disruptive behavior disorders ($\chi^2 = 31.82$, $df = 4$, $p \leq 0.001$) among the 5 LCs. *In contrast, no significant differences were found for presence of comorbid mood disorders among the classes ($\chi^2 = 4.43$, $df = 4$, $p = 0.35$). ADHD = attention-deficit/hyperactivity disorder; LC = latent class; OCD = obsessive-compulsive disorder.

the socially disinhibited phenotype was associated with increased tic severity and psychiatric comorbidity. In the EFA, it should be noted that associations between factors and clinical characteristics represent a spectrum; for example, a greater diversity of different eye tics (not just the presence of eye tics) is associated with elevated tic severity. This is an important concept given that most individuals with TS experience isolated eye tics and many have low overall tic severity. Individuals with intermediate rates of tics in general, but high rates of socially disinhibited tics (LC3), had higher rates of comorbid OCD and ADHD and slightly more severe tic and OC symptoms compared to those without socially disinhibited tics (LC2). This finding suggests that individuals with higher rates of socially disinhibited tics tend to have more severe psychopathology in general compared to those with lower rates of socially disinhibited tics.

The heritability estimates for the socially disinhibited phenotype (LC1 and LC3 combined; $h^2r = 0.53$) exceeds the estimated heritability of TS as a categorical phenotype ($h^2r = 0.32$, $SE = 0.16$) calculated in a subset of the current sample,²⁴ suggesting that this phenotype may be of particular interest for future studies aimed at elucidating the genetic architecture and underlying genetic susceptibility of TS and related disorders. This unexpected finding may

be attributed to a reduction in heterogeneity and/or concentration of heritability for this TS subtype. In addition, the relatively low (and nonsignificant) heritability of LC4 (simple tics) may be a result of the inherent phenotypic heterogeneity of this latent class, which likely includes isolated tic-like behaviors that are not as strongly heritable as, for example, complex motor tics.

Our analyses also build on and extend previous TS research. The 6-factor model of tic symptoms more finely parses tics, beyond the simple vs complex distinction found in other studies,²⁵ and parallels the somatotopic map of the basal ganglia in humans and primates, with disproportionate representation of the head, face, and hands relative to the rest of the body.²³ Furthermore, the socially inappropriate tic factor may represent a severe phenotype that integrally and diffusely affects multiple aspects of frontostriatal circuitry. The convergence between observed tic symptoms and neuroanatomical organization suggests that these factors may represent direct correlates of distinct frontostriatal circuits whose functions are thought to be dysregulated in TS and OCD.^{26,27} As such, future neuroimaging and neurophysiologic studies of TS may benefit from classifying patients and their families based on these symptom-based subtypes.^{2,28} Similarly, the identification of these

subphenotypes may one day aid treatment studies. Although currently speculative, individuals with complex tics, for example, may respond differently to particular forms of treatment, both pharmacologic and other, than those with primarily simple tics. Additional future research might explore whether individuals endorsing these symptoms differ clinically (e.g., regarding tic persistence or prognosis), pathophysiologically (location or severity of frontostriatal circuit disruption), or in treatment response.

The primary limitation of this work reflects the fact that the data were collected over an extended time period at many different sites. This limitation may paradoxically also represent an advantage: the heterogeneity of the sample is likely to increase the generalizability of the findings. Similarly, data on comorbid psychiatric disorders, age at onset, and severity of tic symptoms were only available for a subset of individuals, limiting the power of these analyses. Finally, the

heritability analyses may underestimate the heritability of the classes because of the exclusion of bilinear sib-pair families and the decision to use binary class membership, potentially resulting in a loss of power. While we ignore the uncertainty of class membership in these analyses, the loss of information is likely minimal because of the quality of the model.

Our analyses suggest that among individuals with TS, there are several subphenotypes that may have relevance for future etiologic, pathophysiologic, and treatment outcome studies, as well as for individual clinical outcomes. In particular, the identification of a subgroup of individuals with high rates of socially disinhibited tics and correspondingly higher psychiatric comorbidity and tic severity has potential clinical implications for these individuals and their families. Similarly, utilization of the tic phenotypes described in ongoing etiologic studies may help to clarify the genetic architecture of this complex disorder and to identify additional TS genetic susceptibility loci that serve as risk factors for TS.

Comment: **Dissecting the genetic architecture of Tourette syndrome into subphenotypes**

Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder marked by multiple motor and vocal tics and a waxing and waning course. Although the genetic basis of TS remains elusive, multiple genes and interacting environmental factors are likely involved.¹ Our search for the TS genetic component is hampered by its phenotypic complexity; TS is characterized by a broad spectrum of simple to complex tics, and up to 90% of patients also exhibit psychiatric comorbidities such as obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorders.² This great phenotypic heterogeneity may also be accompanied by etiologic heterogeneity.

Although TS is not a unitary condition, heritable TS subtypes have not been clearly defined. Hirschtritt et al.³ present the largest study to date, attempting to dissect the phenotypic and corresponding genetic structure of TS using complementary modeling approaches and symptom-level data. TS can be viewed as an excellent model disorder for the development of a framework for the study of complex neuropsychiatric phenotypes. The combined use of exploratory factor analysis to identify heritable subtypes of TS, and latent class analysis to determine the number of heritable classes, is an interesting approach to analyze symptom-level data in large samples. A future direction could be the exploration of nonlinear models, with the hope of capturing nonlinear correlations between the underlying variables, as well as the use of classification algorithms and cross-validation techniques to evaluate different models.

The approach and TS subphenotypes described by Hirschtritt et al.³ will undoubtedly become the focus of the multiple large-scale TS genetics studies currently under way. Such approaches set the basis for the definition of quantitative TS phenotypes that may more accurately represent distinct pathophysiologic mechanisms and may be envisaged as a starting point for personalized therapies in TS.

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AUTHOR CONTRIBUTIONS

Drs. Hirschtritt and Darrow had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Drs. Hirschtritt, Darrow, Delucchi, Scharf, and Mathews. Acquisition, analysis, or interpretation of data: all authors. Critical revision of the manuscript for important intellectual content: all authors. Drafting of the manuscript: Drs. Hirschtritt, Darrow, Scharf, and Mathews.

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