Familial Risks of Tourette Syndrome and Chronic Tic Disorders: A Population-Based Cohort Study

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IMPORTANCE Tic disorders, including Tourette syndrome (TS) and chronic tic disorders (CTDs), are assumed to be strongly familial and heritable. Although gene-searching efforts are well under way, precise estimates of familial risk and heritability are lacking. Previous controlled family studies were small and typically conducted within specialist clinics, resulting in potential ascertainment biases. They were also underpowered to disentangle genetic from environmental factors that contribute to the observed familiality. Twin studies have been either very small or based on parent-reported tics in population-based (nonclinical) twin samples.

OBJECTIVE To provide unbiased estimates of familial risk and heritability of tic disorders at the population level.

DESIGN, SETTING, AND PARTICIPANTS In this population cohort, multigenerational family study, we used a validated algorithm to identify 4826 individuals diagnosed as having TS or CTDs (76.2% male) in the Swedish National Patient Register from January 1, 1969, through December 31, 2009.

MAIN OUTCOMES AND MEASURES We studied risks for TS or CTDs in all biological relatives of probands compared with relatives of unaffected individuals (matched on a 1:10 ratio) from the general population. Structural equation modeling was used to estimate the heritability of tic disorders.

RESULTS The risk for tic disorders among relatives of probands with tic disorders increased proportionally to the degree of genetic relatedness. The risks for first-degree relatives (odds ratio [OR], 18.69; 95% CI, 14.53-24.05) were significantly higher than for second-degree relatives (OR, 4.58; 95% CI, 3.22-6.52) and third-degree relatives (OR, 3.07; 95% CI, 2.08-4.51). First-degree relatives at similar genetic distances (eg, parents, siblings, and offspring) had similar risks for tic disorders despite different degrees of shared environment. The risks for full siblings (50% genetic similarity; OR, 17.68; 95% CI, 12.90-24.23) were significantly higher than those for maternal half siblings (25% genetic similarity; OR, 4.41; 95% CI, 2.24-8.67) despite similar environmental exposures. The heritability of tic disorders was estimated to be 0.77 (95% CI, 0.70-0.85). There were no differences in familial risk or heritability between male and female patients.

CONCLUSIONS AND RELEVANCE Tic disorders, including TS and CTDs, cluster in families primarily because of genetic factors and appear to be among the most heritable neuropsychiatric conditions.
Tourette syndrome (TS) is thought to be a strongly familial and heritable neuropsychiatric disorder.1 Controlled family studies2-6 have reported a 10- to 100-fold increase in the rates of TS in first-degree relatives of affected individuals compared with control relatives. Furthermore, chronic tic disorders (CTDs) also occur more frequently among first-degree relatives of TS probands compared with relatives of controls (7- to 22-fold increase), suggesting that TS and CTDs share common etiologic factors.1 These previous family studies were carefully conducted but also had important limitations. First, the estimates of family risk have varied broadly, suggesting that previous studies may have been underpowered to provide precise estimates of familial transmission. Second, families were primarily recruited from specialist clinics, potentially resulting in the inclusion of more severe and impaired cases. Families with several affected members may have been more likely to volunteer for participation, thus inflating the familial risk. These possible biases can optimally be addressed by examining the familial structure of tic disorders at the population level,7 recruiting patients from nonspecialist clinics, and randomly selecting control families from the general population. Third, studies conducted to date were underpowered to calculate risks for relatives with different degrees of genetic relatedness to the proband and different degrees of shared environmental exposures. Consequently, these studies could not disentangle genetic from environmental factors that contribute to the observed familiality of tic disorders. Fourth, previous family studies were too small to examine possible sex differences in familiality and heritability, which is of critical importance given that tic disorders are much more common in males than females.8-12

Twin studies are ideal to disentangle these etiologic factors based on the different genetic resemblance of twins. To our knowledge, only 2 small twin studies13,14 of diagnosed TS or CTD cases have been published to date. Price and colleagues13 recruited 30 identical (monozygotic) and 13 same-sex nonidentical (dizygotic) twin pairs (mean age, 18 years) from the Tourette Syndrome Association and found that 77% of monozygotic twins and 23% of dizygotic twins were concordant for tic disorders (TS or CTDs). The monozygotic concordance rate reached 100% for TS or CTDs when direct observational interviews were conducted on the same twin sample.14 In another study15 of 16 pairs of monozygotic twins (mean age, 13 years), 56% were concordant for TS and 94% were concordant for tic disorders; however, because dizygotic twins were not included, no conclusions could be made about heritability. Although the higher monozygotic concordance rates have been interpreted as implicating genetic factors as strongly contributing to the cause and familial transmission of tic disorders and gene-searching efforts are well under way,16-18 this evidence comes from small samples that may not represent broader populations with tic disorders.

Three population-based studies19-21 have examined the heritability of parent-rated tics in children, resulting in modest heritability estimates. A Japanese study19 of 1896 twin pairs aged 3 to 15 years (mean, 11 years) reported modest heritability estimates (approximately 30%) for parent-rated tics. A British study,20 including 854 pairs of 6-year-old twins, found evidence of strong familial effects on parent-rated tics (61%) but was unable to separate genetic from shared environmental sources of familial aggregation because of power issues. A large, nationally representative sample of more than 10 000 Swedish twins aged 9 to 12 years reported heritability estimates for parent-rated tics of 56% (95% CIs, 37%-68%), with the remaining variance due to nonshared environmental factors.21 Although the assessment instrument varied across these studies, collectively, they suggest moderate heritability of parent-rated tics in young people, but it is unclear to what extent these findings can be extrapolated to clinically diagnosed tic disorders.

In an attempt to overcome some of these limitations and provide unbiased estimates of familial clustering and heritability of tic disorders at the population level, we linked and analyzed data from 2 Swedish population-based registers and tested 3 hypotheses: (1) tic disorders will cluster in families at the population level, (2) the risk of tic disorders will increase proportionally to the degree of genetic relatedness to the proband, and (3) shared environment effects will be negligible. In exploratory analyses, we also examined possible sex differences in the patterns of familial clustering of tic disorders.

Methods

Swedish Registers

This study was approved by the Regional Ethics Committee in Stockholm, Sweden. No informed consent is required for this type of study. We linked 2 Swedish national registers by using the individual national registration numbers assigned at birth. The Multi-Generation Register contains information about the identity of biological and adoptive parents of each individual born in Sweden since 1932 (with the mother as informant) or who immigrated to Sweden together with one or both parents before the age of 18 years and lived in Sweden at any time since 1961. Unless the biological or adoptive parents have actually lived in Sweden since 1947, when the national personal identification number was introduced, it is not possible to identify them. The father was defined as the mother’s husband at the time of birth or the man acknowledged as the father by unmarried mothers. With information on parents, it is possible to create family pedigrees for all individuals with relatives at increasing genetic and environmental distances from each index person.

The National Patient Register contains diagnostic information about patients treated in Sweden since 1969, with each consultation as a unique record in the register. Initially, it contained information on all inpatient care. From 2001, however, it also includes individuals with outpatient visits to specialist physicians (other than general practitioners) that resulted in one or more diagnoses according to the International Statistical Classification of Diseases, 10th Revision (ICD-10).22
ICD Diagnostic Codes

The ICD codes for TS and CTDs have been validated in Sweden.23 Briefly, we obtained a random sample of 73 records from patients with TS or CTDs from 3 Swedish counties, of which 64 contained sufficient information for analysis. Each file was carefully reviewed and rated by 2 masked, independent physicians (C.R. and K.J.L.). There was 100% agreement between the 2 raters regarding the presence or absence of a tic disorder (κ = 1, P < .001). Overall, the ICD codes had excellent validity, with a positive predictive value of 92% for both raters. The positive predictive values for ICD-8, ICD-9, and ICD-10 codes were 0.89, 0.86, and 0.97, respectively.

Further examination of specific ICD-10 subcodes revealed that most patients who had F95.1 (CTD) codes in the register were diagnosed as having TS (F95.2) by the raters (both motor and vocal tics were identified in the clinical histories). Unspecified tic disorder (F95.9) cases were diagnosed by the raters as TS (F95.2), CTD (F95.1), unspecified tic disorder (F95.9), or transient tics (F95.0), suggesting that code F95.9 is used more freely by health care professionals. Consequently, we developed an algorithm to ensure that individuals who had transient tics as their only or final diagnostic code within the same year of the initial diagnosis were excluded from the analyses. Furthermore, individuals who received an initial diagnosis of transient, other, or unspecified tics were only included if they received at least an additional diagnosis of a tic disorder except if the last available diagnosis was of transient tic disorder given within the same year of the initial diagnosis.21 We did not exclude any participants based on comorbidities because we preferred not to make assumptions about the hierarchical structure of mental disorders.

Statistical Analysis

The risk of tic disorders in relatives of probands with TS or CTDs were compared with the risk in relatives of 10 randomly selected, unaffected control individuals matched by sex, birth year, and county of residence at the time of the first recorded TS or CTD diagnosis of the proband. Relatives were also matched by sex and birth year. For instance, for each proband, we detected all possible proband–full sibling pairs and randomly selected 10 control–full sibling pairs matched to proband–sibling pairs by sex and birth year. Because each proband may appear multiple times in different categories (eg, parent, sibling, and cousin) depending on family structure, the matching was done separately for each proband–relative pair to ensure adequate control of cohort and period effects and allow for equal time at risk for proband–relative pairs and control–relative pairs. The matching procedure was used for all available first-, second-, and third-degree relatives of each proband. We also examined potential sex effects by separately analyzing respective pairs of male-male, male-female, female-female, and female-male probands and relatives.

Because the data were matched and the outcome was dichotomous, we used a conditional logistic regression model with the PROC PHREG procedure in SAS statistical software, version 9.3.24 Because several possibly correlated pairs of relatives from every family could be included in the analysis, we adjusted for the non-independence of family members (eg, several sibling pairs, which share the same parents) by computing corrected (less narrow) CIs with a robust sandwich estimator (cowsandwich option in PHREG).

By assuming that a continuous, normally distributed liability underlies the observed dichotomous diagnosis of tic disorders, the tetrachoric correlations of tic disorders among family members can be estimated. These correlations are often used in twin and family studies to obtain approximate heritability estimates using structural equation modeling. We fitted liability-threshold models using full siblings and maternal half siblings to decompose the variance in liability of tic disorders into additive genetic effects (A), shared environmental effects (C), and nonshared environmental effects (E) (ACE). Age and sex were adjusted for in the threshold of TS or CTDs. The genetic correlation was fixed to 0.5 for full siblings (sharing a mean of 50% of their segregating genes) and to 0.25 for maternal half siblings (sharing 25% of their genes), and we assumed that the family environment is shared between full siblings and maternal half siblings (eMaterial in the Supplement). We began our model fitting with a full ACE model and allowing sex difference for the estimates of ACE. We then sought to simplify the model by equating the ACE estimates between males and females and then dropping the shared environmental effects. Goodness of fit among the different models was assessed by a likelihood ratio test. Maximum likelihood estimation and univariate model fitting were performed using the structural equation modeling package OpenMx in R (http://openmx.psyc.virginia.edu).

Results

Sample Characteristics

Our algorithm resulted in the identification of 4826 individuals diagnosed as having a tic disorder (TS or CTDs) (3678 male [76.2%; mode age, 10 years) from January 1, 1969, through December 31, 2009. Of the patients with tic disorders, 72.8% had at least one lifetime psychiatric comorbidity (attention-deficit/hyperactivity disorder, 37.5%; obsessive-compulsive disorder, 14.9%; pervasive developmental disorders, 20.3%; intellectual disability, 21.1%; depression, 15.9%; anxiety disorders, 12.1%; other neurotic, stress-related, and somatoform disorders, 14.4%; and substance use, 9.9%).

Familial Risk of Tic Disorders

First-degree relatives of individuals with tic disorders had significantly higher risk of having TS or CTDs than second- and third-degree relatives. In turn, the odds ratios (ORs) for second-degree relatives were higher than for third-degree relatives, although the CIs overlapped (Table 1 and Figure). The pattern of results did not change substantially when cases with pervasive developmental disorders or intellec-
tual disability were excluded from the analyses (eFigure 1 in the Supplement).

Shared environmental influences on tic disorders appeared to be considerably less important. Full siblings, parents, and children of TS or CTD probands (all with 50% genetic similarity but with siblings assumed to have more shared environment because they grew up together in the same family during approximately the same period) had comparable risks. In addition, the risks for full siblings (50% genetic similarity) were significantly higher than those for maternal half siblings (25% genetic similarity) despite similar shared environmental exposures. Furthermore, the risks did not differ significantly between maternal and paternal half siblings (both with 25% genetic similarity but with maternal half siblings sharing more environment because most Swedish children [90%] continue to live with their mother after parental divorce or separation; eMaterial in the Supplement).25 Finally, first cousins (12.5% genetic similarity) had a 3-fold higher risk of having TS or CTDs compared with controls despite no or marginal shared environmental exposures with the TS or CTD proband.

**Sex Effects**

Analyses by sex of the proband and relative revealed a higher number of male-male dyads, but the risks and tetrachoric correlations (which are not affected by sample size) were approximately similar for male-male, male-female, female-female, and female-male dyads (Table 2).

**Heritability Estimates**

Tetrachoric correlations were approximately double for full siblings than for maternal half siblings (Table 1). There was no evidence of quantitative sex differences in the liability to TS or CTDs. In the full ACE model, the variance in liability of TS or CTDs was largely attributable to additive genetic factors (0.72; 95% CI, 0.42-1.00), with a negligible effect of shared environment (0.03; 95% CI, 0.00-0.16). The remaining variance was attributable to nonshared environmental influences and measurement error (0.25; 95% CI, 0.08-0.43). The best-fitting model included additive genetic factors (0.77; 95% CI, 0.70-0.85) and nonshared environmental factors (0.23; 95% CI, 0.15-0.30). The shared environment component could be dropped without any significant loss of fit (Table 3).

**Discussion**

Extending previous, much smaller family studies primarily conducted in specialist clinical settings, tic disorders, including TS and CTDs, were significantly more prevalent among biological relatives of probands with tic disorders than in relatives of matched population controls. Furthermore, the risk of tic disorders in relatives increased signifi-
Table 2. Sex Effects on the Risks of the Presence of Tourette Syndrome (TS) or Chronic Tic Disorders (CTDs) in Relatives of Probands Diagnosed as Having TS or CTDs

<table>
<thead>
<tr>
<th>Relation to Proband</th>
<th>Male-Male Pairs</th>
<th>Male-Female Pairs</th>
<th>Female-Male Pairs</th>
<th>Female-Female Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Observed</td>
<td>Matched OR (95% CI)</td>
<td>Tetrachoric Correlation (SE)</td>
<td>Matched OR (95% CI)</td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>84</td>
<td>16.75 (11.95-23.50)</td>
<td>0.34 (0.01)</td>
<td>31</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>35</td>
<td>4.78 (3.00-7.64)</td>
<td>0.12 (0.02)</td>
<td>9</td>
</tr>
<tr>
<td>Third-degree relatives</td>
<td>32</td>
<td>2.69 (1.71-4.24)</td>
<td>0.11 (0.02)</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable. OR, odds ratio.

Table 3. Model-Fitting Results Based on the Family Data

<table>
<thead>
<tr>
<th>Model</th>
<th>−2LL</th>
<th>χ² Test</th>
<th>Δ df</th>
<th>P Value</th>
<th>AIC</th>
<th>Comparison Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ACE model with sex difference</td>
<td>142638.2</td>
<td></td>
<td></td>
<td></td>
<td>-30358610</td>
<td>Reference</td>
</tr>
<tr>
<td>2. ACE model without sex difference</td>
<td>142642.5</td>
<td>4.3</td>
<td>2</td>
<td>.12</td>
<td>-30358610</td>
<td>Model 1</td>
</tr>
<tr>
<td>3. AE model without sex difference</td>
<td>142642.6</td>
<td>0.1</td>
<td>1</td>
<td>.70</td>
<td>-30358611</td>
<td>Model 2</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, additive genetic effects (A), shared environmental effects (C), and nonshared environmental effects (E); AIC, Akaike information criterion; LL, log likelihood.

cantly with increasing genetic relatedness to the proband. The pattern of results was similar in male and female patients. The heritability of tic disorders was estimated to be approximately 77%, with the remaining variance being attributable to nonshared environmental influences and measurement error.

Together with the previous family and twin literature, largely derived from clinical samples of European origin, our data confirm that tic disorders run in families primarily because of genetic factors. Previous twin studies of strictly diagnosed tic disorders were too small to provide robust heritability estimates, whereas population-based (nonclinical) studies of parent-rated tics estimated the genetic contribution to range from 30% to 60% but were limited by the lack of health care professional–based diagnostic assessments. Recent efforts to estimate the heritability of TS from genotyped data using genome-wide complex trait analysis methods have also estimated the heritability of TS to be approximately 60%. Our estimates suggest that tic disorders may be even more heritable than previously thought.

Although we cannot conclusively rule out shared environmental factors, these factors appear to make a much smaller contribution to the etiology of the disorder. Instead, unique or nonshared environmental influences may confer increased risk to developing tic disorders. A range of environmental risk factors for tic disorders has been tentatively identified, including older paternal age and a number of perinatal adversities (eg, severe maternal stress, severe nausea and vomiting during the pregnancy, low birth weight, delivery complications, and low Apgar scores at birth). However, longitudinal, genetically informed studies are still rare; such studies should be prioritized alongside gene-searching efforts. The identification of genetic differences in susceptibility to particular environments (gene by environment interactions) in tic disorders will be an important challenge for the future. Finally, the possibility of gene-environment correlations should also be investigated because it is plausible that genetic factors could influence the specific environmental experiences of children vulnerable to developing tic disorders.

Although tic disorders are clearly more prevalent in males, both in clinical and epidemiologic samples, our results suggest that the familial risk for tic disorders is comparable in male and female probands regardless of the sex of the relative. The implication for molecular genetic research would be that, when specific genes associated with tic disorders are identified, they will be associated with tic disorders in both sexes and that they will have similar effect sizes in males and females. However, these findings do not preclude the role of sex-specific factors during embryonic and fetal development in the causation of the disorder. Female sex may be a protective factor against tic disorders; whether females require a greater familial etiologic load to manifest the phenotype, as has been suggested in autism spectrum disorder, is an interesting question for the future.
Strengths of the present study include the large population-based sample of patients with tic disorder diagnosed in Sweden during 40 years, all their relatives, and carefully matched, randomly selected controls. This large sample ensured minimal risk of selection, recall, and report biases for the population with tic disorders and the control families. Furthermore, this is the first study, to our knowledge, to have sufficient power to examine the familial risk of tic disorders across relatives at varying genetic and environmental distances from the probands. Another important strength was careful selection of probands based on our validation of the ICD codes in the Swedish National Patient Register, which resulted in an algorithm designed to minimize the risk of false-positive diagnoses.

Registers also have limitations. Individuals diagnosed as having TS or CTDs in the National Patient Register probably represent only a fraction of all cases in the Swedish population. Many individuals with mild tics may not seek help; thus, their conditions may never be diagnosed or treated. Furthermore, the National Patient Register only includes patients seen by specialist physicians (eg, pediatricians, neurologists, or psychiatrists); those whose conditions are diagnosed in primary care by general practitioners or other professionals (eg, nurses) are not included. Finally, outpatients were only included in the register from 2001. Thus, the register may only include the more severe and complex forms of TS and CTDs (in our cohort, more than 70% of patients had at least one lifetime psychiatric comorbidity), and our results may not generalize to milder forms of the disorder. However, the incomplete coverage of tic disorder cases in the register should be constant across the families of probands and the families of comparison individuals, thus not influencing our estimates. It is theoretically possible that having a relative with a tic disorder increases the chance of seeking help or receiving a diagnosis, although our findings suggest small or negligible shared environmental effects, which would argue against this possibility. Another limitation is that longitudinal registers are subject to left truncation or missing data before the date the register started, which may result in a greater prevalence of tic disorders in younger generations. However, because we matched for birth year and time at risk, such losses would be similar for both case and control dyads and not affect family risks. Despite the very large sample size, our study could not distinguish between TS and CTDs because our validation study suggested that health care professionals in Sweden often use these diagnostic codes indiscriminately. Finally, our results may not generalize to non-European populations; it has been suggested that ethnic differences in allelic frequencies may explain the low prevalence of tic disorders in non-European populations.

**Conclusions**

With these caveats in mind, our results indicate that tic disorders, including TS and CTDs, are strongly familial disorders within the Swedish population, and the observed pattern of familiality is consistent with a likely genetic cause. Our heritability estimates place tic disorders among the most heritable neuropsychiatric conditions.


