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Familiality of Tourette Syndrome, Obsessive-Compulsive Disorder, and Attention-Deficit/Hyperactivity Disorder: Heritability Analysis in a Large Sib-Pair Sample

Carol A. Mathews, M.D. and

University of California, San Francisco, San Francisco, California

Marco A. Grados, M.D., M.P.H.

Johns Hopkins University School of Medicine

Abstract

Objective—Tourette Syndrome (TS) is a neuropsychiatric disorder with a genetic component that is highly comorbid with obsessive-compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD). However, the genetic relationships between these disorders have not been clearly elucidated. In this study we examine the familial relationships between TS, OCD, and ADHD in a large sample of TS families.

Method—Parent-offspring concordance of TS, OCD, and ADHD was examined in 952 individuals from 222 TS-affected sib pair families originally collected for genetic studies using logistic regression with generalized estimating equations (GEE) to control for correlated data. Variance components methods were used to estimate the heritability and genetic and environmental correlations between TS, OCD, and ADHD. Bilineal families where both parents had either TS or OCD were excluded.

Results—OCD and ADHD were highly heritable in these TS families. We found significant genetic correlations between TS and OCD and between OCD and ADHD, but not between TS and

Corresponding author: Carol A. Mathews M.D. Department of Psychiatry, University of California, San Francisco, 401 Parnassus Ave, San Francisco, CA 94143-0984, (415) 476-7702, fax: (415) 476-7389. cmathews@lppi.ucsf.edu.
Drs. Mathews and Grados contributed equally to this work.

This work was conducted under the auspices of the Tourette Syndrome Association International Consortium for Genetics (TSAICG). Members of the TSAICG are listed alphabetically by city: D. Cath and P. Heutink are with the Free University Medical Center Amsterdam, Amsterdam, the Netherlands; M. Grados, H.S. Singer, and J.T. Walkup are with Johns Hopkins University School of Medicine, Baltimore, MD; C. Illmann, S. Santangelo, S. E. Stewart, J. Scharf, and D.L. Pauls are with the Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital Harvard Medical School, Boston, MA; N.J. Cox, is with the University of Chicago, Chicago, IL; S. Service, D. Keen-Kim, C. Sabatti, and N. Freimer are with University of California – Los Angeles Medical School, Los Angeles, CA; M.M. Robertson is with the University College London Institute of Neurology, National Hospital for Neurology and Neurosurgery Queen Square London; G.A. Rouleau, J.-B. Riviere, S. Chouinard, F. Richer, P. Lesperance, Y. Dion University of Montreal, Montreal, Quebec, Canada; R.A. King, J.R. Kidd, A.J. Pakstis, J.F. Leckman, K.K. Kidd are with the Child Study Center and Department of Genetics, Yale University School of Medicine, New Haven, CT; G. Gericke is with Tshwane University of Technology, Pretoria, South Africa; R. Kurlan, P. Como, and D. Palumbo are with the University of Rochester School of Medicine, Rochester, NY; A. Verkerk, and B.A. Oostra are with Erasmus University, Rotterdam, The Netherlands; W. McMahon, M. Leppert, and H. Coon, are with the University of Utah School of Medicine, Salt Lake City, UT; C.A. Mathews is with the University of California, San Francisco, San Francisco, CA; P. Sandor and C.L. Barr are with The Toronto Hospital and University of Toronto, Toronto, Ontario, Canada.

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ADHD. We also found significant environmental correlations between TS and ADHD and between OCD and ADHD. Parental OCD+ADHD was associated with offspring OCD+ADHD.

Conclusions—This study provides further evidence for a genetic relationship between TS and OCD, and suggests that the observed relationship between TS and ADHD may in part be due to a genetic association between OCD and ADHD and in part due to shared environmental factors.

Keywords

heritability; bilineality; familiarity; obsessive-compulsive disorder; attention deficit hyperactivity disorder

Introduction

Tourette Syndrome (TS) is a childhood-onset neurodevelopmental disorder affecting between 1:300 and 1:400 individuals^{1–3}. TS has a complex etiology, with both genetic and environmental factors contributing to its expression^{4–12}. Although multiple motor and vocal tics form the core of the diagnosis, individuals with TS often present with a variety of additional symptoms and comorbid disorders, most commonly obsessive-compulsive disorder (OCD), subclinical obsessive-compulsive behaviors or symptoms (OCB), and attention-deficit hyperactivity disorder (ADHD)¹³. Despite genetic epidemiological studies showing strong evidence of familiarity, definitive susceptibility genes for TS have not yet been identified. One question that has not yet been satisfactorily answered is whether TS, OCD, and ADHD share susceptibility genes. OCD and/or ADHD are present in up to 50% of individuals with TS, and are enriched in TS families^{14–17}. While segregation analyses and family studies provide strong support for a genetic relationship between TS and OCD, the data are less clear with regard to the relationships between TS and ADHD and between OCD and ADHD^{4–6, 12, 18–31}. For example, family studies have shown that ADHD alone is not increased in TS families; when present, it is usually as a co-occurring condition with TS, suggesting that these disorders do not share genetic susceptibility factors (see O’Roarke, et al for review)³². Similarly, there is some evidence for an increased rate of ADHD in individuals and families with OCD but without tics^{30, 31, 33}. Familial risk studies have suggested that rather than TS and OCD being genetically related, OCD and ADHD may share susceptibility genes, and that the increased rates of ADHD in TS-affected individuals may be mediated via OCD^{26, 30, 31, 34, 35}. Similarly, the relationship of OCB to TS is unclear. Some studies have reported a prevalence of up to 80% in TS-affected individuals, suggesting that OCB may actually represent an integral part of the TS phenotype, and as such may be more akin to complex tics than to true obsessive/compulsive phenomena^{36–38}.

Partly because of the lack of success in current efforts to identify TS susceptibility genes, and partly in order to further define and understand this heterogeneous disorder, investigators have begun to re-examine the assumptions underlying the standard study designs, including phenotype definition, mode of transmission, and degree of bilineality. There is renewed interest in examining the heritability of potential alternate phenotypes for TS, including chronic motor or vocal tics (CMVT), OCD or OCB, and ADHD^{36, 39–41}. Additionally, studies have suggested that for TS and related disorders, the mode of transmission is not straightforward, and bilineality may be more common than previously thought^{8, 22, 42}.

We have previously examined the heritability of TS comorbid classes derived from latent class analysis (LCA), finding a highly comorbid (TS+OCD+ADHD) class that was highly heritable. The LCA approach, while useful for identifying groups of similar individuals (e.g., the TS+OCD+ADHD class), cannot be used for the identification of specific genetic

and environmental relationships between the individual disorders of TS, OCD, and ADHD³⁵. Thus, in this paper, we expand on those findings to examine the familiarity of TS, ADHD and OCD independently in TS-affected families and explore the genetic and environmental relationships between them. Based on our previous findings and on the earlier family studies, we hypothesize that: 1) there will be high rates of parental TS, OCD, OCB and ADHD in the sample compared to the population rates, and that parental diagnoses will be associated with offspring OCD, OCB and ADHD; 2) there will be evidence of non-random mating for ADHD with TS and OCD, partly accounting for the increased prevalence of ADHD in TS-affected offspring; and 3) TS and OCB/OCD will share genetic factors, OCD and ADHD will share genetic factors, but TS and ADHD will share both genetic and environmental factors.

METHOD

Sample

The sample consisted of 952 individuals from 222 affected sibling-pair (ASP) families collected by the Tourette Syndrome Association International Consortium on Genetics (TSAICG) for genetic linkage studies of TS^{35, 43, 44}. Families were included if at least two biological siblings had TS and if both siblings and at least one parent were willing to participate in the genetic studies. Sixty-six percent of families had two siblings, 27% had three siblings, 5.3% had four siblings, and 1.6% had five siblings. Four families included half siblings. Families that were known to be bilineal, i.e. both parents had a known diagnosis of TS, CMVT or OCD, were not recruited for inclusion into the study because the original study design aimed at minimizing genetic heterogeneity. However, families found to be bilineal at the time of the best estimate were not excluded. Families were not routinely excluded based on parental diagnoses of ADHD or subclinical obsessive-compulsive symptoms (OCB), or if only one parent had TS, CMVT, or OCD. Parents and all siblings thought to have a tic disorder were assessed for TS and related tic disorders, OCD, OCB, and ADHD. Siblings thought to be unaffected were not routinely recruited into the study, although siblings who were recruited into the study and later were determined not to have TS (N=14) were included. Eighty-six percent of probands and siblings were age 18 or under: their mean age was 14 years (SD=5.6 years). The mean age of the parents was 43 years (SD=5.7 years). Of the 589 individuals with TS (including parents and offspring), 203 (34.5%) were over age 18. Adults with TS were more likely to be female (44% vs. 25%, $X^2=22.6$, $p<0.0001$). There were no significant differences between adults and children with TS in the rates of OCD or ADHD. The study was approved by the Institutional Review Boards of the respective institutions and written informed consent was obtained. Assent was obtained for subjects younger than 13 years.

Clinical Assessments

All subjects were directly interviewed using a battery of structured interviews assessing tics, obsessive-compulsive symptoms, and ADHD symptoms using a clinician-reviewed self-report instrument developed by the TSAICG⁴³. Present and worst-ever lifetime tic severity was assessed using the Yale Global Tic Severity Scale (YGTSS)⁴⁵. Additional diagnostic instruments included the Yale Brown Obsessive Compulsive Inventory (YBOCS), adult or child version, as appropriate, the Diagnostic Confidence Index (DCI) to assess the confidence of the tic diagnoses, the Kiddie- Schedule for Affective Disorders and Schizophrenia (K-SADS) for children and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) for adults^{46, 47}. Diagnoses of TS, CMVT, OCD, and ADHD were made by two or more independent clinicians using a best-estimate/consensus approach and following DSM-IV criteria^{13, 48}. A diagnosis of OCB was made when symptoms were

present but time and severity criteria were not met (i.e., the subject had at least mild distress and interference, but the symptoms took up less than one hour a day).

Statistical Analyses

Maternal and paternal TS and related diagnoses were examined in relation to offspring diagnoses of OCD and ADHD using logistic regressions with generalized estimating equations (GEE), controlling for the correlation between individuals within families. Parallel logistic regression analyses were also conducted to obtain odds ratios. Gender was included in all analyses as a potential confounder. The percentage of mothers and fathers and the percentage of both parents with TS, CMVT, OCD, OCB, and ADHD were calculated. The presence of nonrandom mating for ADHD and TS or OCD/OCB was assessed by examining the frequency and concordance of maternal/paternal diagnoses of ADHD/ADHD, ADHD/TS or CMVT, and ADHD/OCD or OCB using chi square analyses.

Heritability estimates and the corresponding confidence and significance levels were calculated using the Sequential Oligogenic Linkage Analysis Routine (SOLAR) statistical package⁴⁹. SOLAR employs a variance components approach to provide an estimate of additive genetic variance (VA) and the remaining genetic variance (VE) using information from all available family members. The resultant heritability (h^2 , defined by $VA/(VA+VE)$) is based on a maximum-likelihood-based variance decomposition approach and does not assume an inheritance model. Because the disorders of interest vary with respect to gender ratios and age, (the sample consisted of individuals ranging in age from 4 to 77), age at interview and gender were controlled for in the heritability analyses. Note that proband status is automatically incorporated into the heritability estimates. Heritability estimates for TS, TS or CMVT, OCD, OCB, OCD or OCB, and ADHD were conducted. To further elucidate the genetic and environmental contributions of each disorder to the phenotype, bivariate analyses were conducted for pairwise combinations of these disorders, and the RhoE and RhoG, corresponding to the environmental and genetic correlations between the traits were calculated. It should be noted that we are not able to separate shared environment from some types of genetic effects (i.e., additive genetic variance) for single traits (such as TS), and do not attempt to do so in these heritability analyses given the opportunistic nature of this genetic study sample. However, this is not the case for the bivariate analyses, where this approach does allow for the separation of shared genetic and shared environmental factors between two traits.

RESULTS

Parental Diagnoses and Nonrandom Mating

Table 1 shows the percentages of parents with TS, CMVT, OCD, and ADHD. In general, fathers had slightly higher rates of TS and CMVT than mothers, mothers had higher rates of OCD and OCB, and rates of ADHD were similar between mothers and fathers. Mothers were more likely to have multiple comorbidities; 18.6% of mothers had OCD + ADHD (regardless of TS diagnosis), compared to 8.3% of fathers, and 7.8% of mothers had TS +OCD+ADHD, compared to 5.5% in fathers, although these differences were not statistically significant. Approximately 58% of mothers had either a tic or an OCD/OCB diagnosis, compared to 48% of fathers. Although bilineality for tics and/or OCD was an exclusion criterion for recruitment into the original genetic study, we did not exclude families who were found on best estimate to be bilineal, and in fact, we found low levels of bilineality for TS, CMVT, and OCD (Table 1). The proportion of concordant mating pairs were assessed for ADHD, as well as for ADHD in one parent and TS/CMVT or OCD/OCB in the other parent. There was no evidence of nonrandom mating for ADHD, or for ADHD in one parent and TS or OCD in the other parent in this sample.

Predictors of TS-related diagnoses in the offspring

As can be seen in Table 2, which shows rates of mothers, fathers, and offspring with no diagnoses, with simple phenotypes (TS alone, OCD alone, or ADHD alone) and with complex phenotypes (TS+OCD, TS+ADHD, OCD+ADHD, or TS+OCD+ADHD), offspring were more likely to have complex phenotypes than were parents, and mothers were more likely than fathers to have complex phenotypes. Of the parents, mothers were more likely to have OCD alone than were fathers, and fathers were more likely than mothers to have ADHD alone, while both had similar rates of TS alone.

To examine parental predictors of offspring diagnoses, we conducted GEE analyses, including paternal and maternal TS, OCD, and ADHD diagnoses as predictor variables. Gender was included as a covariate in all analyses. Maternal OCD (OR=2.10, $p=0.003$) and paternal OCD (OR=1.97, $p=0.018$) were associated with offspring diagnoses of OCD, as was maternal ADHD (OR=1.82, $p=0.023$), although maternal or paternal TS and paternal ADHD were not (overall model: $X^2=32.5$, $p<0.00001$). Paternal ADHD (OR=3.35, $p<0.0001$), maternal ADHD (OR=2.26, $p=0.006$), and male gender (OR=0.35, $p<0.0001$), but not parental TS or OCD, were associated with offspring ADHD (overall model: $X^2=54.4$, $p<0.00001$). Results of analyses using all parental tic (TS or CMVT) and OCD/OCB diagnoses gave similar results.

We then examined the relationship between offspring OCD+ADHD and parental diagnoses. Parental OCD+ADHD, in particular, maternal OCD+ADHD, was independently associated with offspring OCD+ADHD (OR=5.45, $p<0.0001$ for maternal; OR=3.0, $p=0.009$ for paternal; overall model: $X^2=30.8$, $p<0.00001$). This model was very similar to the model that incorporated parental diagnoses of OCD and ADHD independently. Parental triple diagnoses (i.e., TS+OCD+ADHD) showed a similar pattern, with even stronger associations. Maternal TS+OCD+ADHD increased the risk of offspring OCD+ADHD by over 6-fold (OR=6.6, $p<0.0001$), while paternal TS+OCD+ADHD increased the risk of offspring OCD+ADHD by approximately 3-fold (OR=2.8, $p=0.019$; overall model: $X^2=21.9$, $p<0.00001$). Note that that vast majority of the offspring had TS diagnoses (89%), while an additional 4% had CMVT, so that offspring OCD+ADHD was essentially equivalent to TS+OCD+ADHD.

Heritability analyses

Heritability analyses were initially conducted for TS, OCD, OCB, and ADHD independently. TS, OCD, ADHD, and ADHD+OCD were all highly heritable in this TS-enriched sample, although OCB was not (Table 3). Adding the less severe diagnoses (CMVT and OCB) to the phenotype generally decreased rather than increased the heritability estimates (Table 3).

To further elucidate the genetic and environmental contributions of each disorder to the phenotype, bivariate analyses were conducted for TS combined with OCD and ADHD, and the RhoE and RhoG, corresponding to the environmental and genetic correlations between the traits, were calculated. As hypothesized, there was a strong genetic correlation between TS and OCD, between OCD and ADHD, and between TS and OCD+ADHD, but not between TS and ADHD (Table 4). Instead, there was a significant environmental correlation between TS and ADHD. Contrary to our expectations, there were no significant genetic or environmental correlation between TS and OCB.

DISCUSSION

This study attempts to further elucidate the familial relationships between TS, OCD, and ADHD in a large sample of TS-affected sib pair families. Our results demonstrate not only

the independent familiarity and heritability patterns of the two main TS-associated disorders, OCD and ADHD, but also further elucidate the genetic and environmental relationships between these disorders and TS.

We found high rates of complex phenotypes (i.e., TS+OCD or TS+OCD+ADHD), in both parents and offspring, and unexpectedly high rates of TS (with or without comorbidities) among mothers. The reasons for this are unclear. While we originally hypothesized that we would find evidence of bilineal mating in our sample, at least for ADHD, and that this might account for the high rates of ADHD in offspring, we did not find evidence for this. One possible explanation for the high rates of maternal TS and also perhaps for the high rates of complex phenotypes is that mothers with TS may be more likely to transmit TS and related phenotypes to their offspring than are TS-affected fathers. Examination of this hypothesis is outside the scope of the current analysis, requiring the inclusion of additional families, including bilineal families and those with offspring who are unaffected with TS.

We found that, consistent with previous studies, and as expected, TS and OCD were heritable in our TS families^{11, 50, 51}. TS had a somewhat lower heritability estimate than either OCD or ADHD; this is most likely an artifact caused by the decreased variation in the sample (i.e., the vast majority of sibs were TS-affected). TS and OCD had an extremely strong genetic correlation of over 90%, and no significant environmental correlation, suggesting that, in multiply-affected families at least, TS and OCD are likely to be due to the same underlying genetic factors. One possibility is that TS+OCD in offspring may represent a more severe expression of the TS phenotype, perhaps resulting from a greater genetic loading. Another is that OCD represents an alternative phenotypic expression of TS-susceptibility genes, a hypothesis that has been put forward in previous family studies⁵². Unfortunately we are unable in the current study to distinguish between these hypotheses, which could be best tested in multi-generational families.

These results have potential relevance both for genetic studies of TS and related disorders and for clinicians. The high ρ_{G} between TS and OCD suggests that OCD could either be considered as a potentially relevant phenotype in genetic studies of TS, for example including OCD (particularly OCD-affected individuals who also have tics) together with TS in genome-wide association studies, or alternatively, as a constraint on TS genetic studies, limiting such studies to the potentially more genetically homogenous subgroup of individuals with TS+OCD. Another possibility would be to use individuals with one disorder as a replication sample for the other, for example, examining genetic variants associated with TS in a sample of OCD-affected individuals. For clinicians, our findings suggest that TS-affected families may need to be counseled that TS and OCD share genetic susceptibility factors, and thus that offspring of TS families may be at increased risk for either TS or OCD or for the combination of the two.

We also found that ADHD was highly heritable in our TS families, although, in contrast to OCD, there was no significant genetic correlation between TS and ADHD. In our parent-offspring analyses, the primary predictor of ADHD among TS-affected offspring was a parental diagnosis of ADHD rather than parental diagnoses of TS or OCD. Together with the heritability analyses, these results suggest that TS and ADHD are most likely genetically separate disorders, with the high rates of ADHD among TS-affected individuals resulting partly from increased but separate parental transmission of TS and ADHD susceptibility. These findings also have implications for genetic studies, suggesting that the presence or absence of ADHD is not of direct relevance for genetic studies of TS and should not be considered either as an inclusion or exclusion factor for such studies. Note that this does not necessarily extend to the more complex phenotype of TS+OCD+ADHD, which is highly heritable, and may in fact be an appropriate alternate phenotype for genetic studies. On the

clinical side, the association between maternal ADHD and offspring ADHD and/or OCD is of particular interest, particularly when counseling TS-affected families about potential risks to offspring. However, these results are preliminary, and the complex relationship between these disorders requires further investigation to have clear clinical relevance.

We initially hypothesized that the increased rates of ADHD found in TS families would be due to bilineal mating between individuals with ADHD and individuals with TS or OCD. However, we did not find evidence of non-random mating for ADHD, or for ADHD with either TS or OCD. Thus, we cannot easily explain the strong environmental correlation and lack of genetic correlation between TS and ADHD. It is possible that the observed association is related to specific environmental exposures (such as prenatal maternal smoking) that predispose an individual to both TS and ADHD, either alone or in combination with additional environmental or genetic environmental influences^{53, 54}.

It is also possible that the observed relationship between TS and ADHD is partly mediated through OCD, as has been previously suggested^{26, 30, 31}. For example, Geller and colleagues have suggested that, based on their studies of ADHD families and pediatric OCD families, ADHD+OCD exists as a distinct familial subtype rather than being alternative expressions of the same underlying genetic susceptibility^{30, 31}. We found some evidence to support this hypothesis in our TS families as well. First, although a TS+ADHD phenotype (without comorbid OCD) does exist in our families, it is not a large proportion, comprising only 11.8% of the sample, whereas the proportion of individuals with TS+OCD+ADHD is much higher (34%)³⁵. Second, we found strong genetic correlations between OCD and ADHD, and between TS and OCD+ADHD, although not between TS and ADHD. Third, we found that maternal ADHD was associated with offspring OCD, with an odds ratio of 1.8 (CI 1.1–3.1), in addition to being associated with offspring ADHD.

The hypothesis that the observed association between TS and ADHD is mediated through the genetic relationships between ADHD and OCD and OCD and TS could in future be tested through formal mediation analyses. Such analyses, which are outside of the scope of this paper, are of particular interest in genetic epidemiological studies of complex traits such as TS, where the relationships between commonly co-occurring phenotypes are difficult to define.

Finally, and somewhat surprisingly, and in contrast to previous family studies, we did not find evidence for increased heritability of the less severe phenotypes of CMVT and OCB in combination with the more severe phenotypes of TS and OCD. This may be due to the fact that the sample consists of nuclear families rather than multigenerational pedigrees, where the co-segregation of these phenotypes has been more clearly established^{11, 24}. However, it does suggest that the inclusion of CMVT and/or OCB would not provide a significant advantage, and may in fact be a disadvantage, at least in genetic studies of nuclear families or other samples (such as case-control studies) where there is not clearly a strong genetic loading.

There are some limitations to our study, most of which relate to the sample composition. Because the sample consists of nuclear families ascertained for having at least two siblings with TS, generally excluding families who were bilineal for tics or OCD, there is little phenotypic variability with regard to tic diagnoses (only 14 sibs were unaffected for TS), and there are only a small number of families where both parents have either a tic disorder or OCD. Additionally, although some information is provided by the few half-siblings, the vast majority of families in this study were biological full siblings. Because we do not have diagnostic information on second and third degree family members, the heritability estimates are just that, estimates, as the VA component is not able to distinguish some

genetic effects from environmental effects present within the family structure, potentially resulting in an over-estimate of the heritability if the shared environmental effects are substantial. Conversely, the decrease in variability for the TS phenotype may falsely decrease heritability estimates for TS and perhaps also for CMVT. Similarly, the fact our sample was specifically ascertained for genetic studies rather than being a population-based sample may also affect the heritability estimates, in this case, leading to a potential under-estimate of the heritabilities. In addition, we do not have data on putative environmental contributors to TS, OCD, and ADHD, which are ostensibly accounting for variance not explained by the genetic variance (h^2). Despite these limitations, the large sample size and the completeness of the clinical data make it possible to maximize the information available from such a sample in useful and previously unexplored ways.

In summary, while comorbidities are often seen clinically and are the most common management currency for clinicians, they have not been consistently considered in phenomenology and etiology studies. Taken together, our results extend the previously reported heritability analyses based on latent classes in TS families, now examining parent-offspring concordance for OCD and ADHD and genetic and environmental correlations between individual diagnoses³⁵. While further research is clearly needed into the complex relationships, both genetic and environmental, between TS, OCD, and ADHD, for the present, our studies suggest that in genetic studies of TS, OCD could also be appropriately considered as a relevant phenotype, (either as an alternate phenotype or as a more genetically homogenous subgroup within the TS phenotype) while ADHD should not. Similarly, clinicians should be aware that TS and OCD share genetic susceptibility factors, and thus that offspring of TS families may be at increased risk for either TS or OCD or for the combination.

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Table 1

Percentage of parents affected with Tourette Syndrome (TS) and related diagnoses.

	TS	CMVT	TS or CMVT	OCD	OCB	OCD or OCB	ADHD	Tics/OCB	TS+ OCD+ ADHD	OCD + ADHD
Mother	53 (26.4%)	22 (11.0%)	75 (37.3%)	62 (30.9%)	37 (18.4%)	99 (49.2%)	44 (21.9%)	117 (58.2%)	17 (7.8%)	29 (18.6%)
Father	64 (31.8%)	23 (11.4%)	87 (43.8%)	29 (14.4%)	25 (12.4%)	54 (26.9%)	53 (26.4%)	97 (48.3%)	11 (5.5%)	13 (8.3%)
Both	6 (3.0%)	3 (1.5%)	21 (10.4%)	5 (2.5%)	7 (3.5%)	24 (11.9%)	14 (7.0%)	48 (23.9%)	0 (0%)	1 (0.6%)

Note: Rates of parental diagnoses. N=201. ADHD=Attention deficit hyperactivity disorder, Both= both parents were given best estimate diagnoses of the condition; CMVT= Chronic Motor or Vocal Tic Disorder; OCB=Obsessive Compulsive Behaviors; OCD=Obsessive-Compulsive Disorder; Tics/OCB = TS or CMVT or OCD or OCB.

Rates of simple and complex phenotypes in parents and offspring of Tourette Syndrome (TS) affected sib pair families.

Table 2

	No diagnosis	TS alone	OCD alone	ADHD alone	TS +OCD	TS +ADHD	OCD +ADHD	TS +OCD +ADHD
Mother	53.4%	9.0%	11.7%	3.1%	8.1%	1.8%	4.9%	7.8%
Father	54.6%	16.1%	2.9%	9.3%	5.8%	5.8%	1.0%	5.5%
Offspring	7.4%	27.5%	1.9%	1.1%	15.8%	18.4%	0.4%	27.5%

Note: Note that rows total to 100%. $\chi^2 = 415.5$, $p < 0.0001$. ADHD= Attention deficit hyperactivity disorder; No diagnosis = no tic, obsessive compulsive disorder (OCD)/obsessive compulsive behavior (OCB) or ADHD diagnosis; OCD=Obsessive-Compulsive Disorder.

Table 3

Heritabilities for Tourette Syndrome (TS), chronic motor/vocal tic disorder (CMVT), obsessive-compulsive disorder (OCD), obsessive compulsive behavior (OCB), and attention deficit hyperactivity disorder (ADHD).

	Heritability (SE)	<i>p</i> -value	Sex	Age At Interview
TS	0.32 (0.16)	0.015	0.0003	$9.0 \times e^{-43}$
TS+CMVT	0.29 (0.21)	0.06	0.002	$3.9 \times e^{-39}$
OCD	0.56 (0.13)	$6.0 \times e^{-9}$	0.01	$4.2 \times e^{-11}$
OCB	0.15 (0.13)	0.11	NS	0.03
OCD+OCB	0.34 (0.09)	0.0001	0.0009	$1.8 \times e^{-14}$
ADHD	0.68 (0.10)	$3.3 \times e^{-11}$	0.00009	$1.0 \times e^{-13}$
OCD+ADHD	0.62 (0.12)	$1.5 \times e^{-8}$	NS	$1.1 \times e^{-10}$

Note: SE=standard error.

Table 4

Genetic and environmental correlations between Tourette Syndrome (TS), obsessive compulsive syndrome (OCD), and attention deficit hyperactivity disorder (ADHD), controlling for age and gender.

Phenotype 1	Phenotype 2	RhoG	SE	p value	RhoE	SE	p value
TS	OCD	0.92	0.40	0.00002	0.22	0.23	NS
TS	ADHD	0.26	0.21	NS	0.66	0.20	0.002
OCD	ADHD	0.63	0.12	0.0001	0.32	0.18	NS
TS	OCD+ADHD	0.64	0.20	0.005	0.38	0.10	0.08
TS	OCD/OCB	0.90	0.18	0.0007	0.35	0.13	0.01
TS/CMVT	OCD/OCB	1.0	NC	0.55	0.66	0.38	$3.1 \times e-16$
OCD/OCB	ADHD	0.57	0.13	0.0004	0.33	0.09	0.0006

Note: NC=not computable; NS= not significant; RhoE= environmental correlation; RhoG= genetic correlation; SE=standard error.