Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2011 July ; 156B(5): 553–560. doi:10.1002/ajmg.b.31195.

The Familial Association of Tourette's Disorder and ADHD: the impact of OCD Symptoms

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Abstract

Objective—Tourette's disorder (TD) frequently co-occurs with attention-deficit/hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). While the relationship between TD and OCD suggests that they share etiological factors, the exact relationship between TD and ADHD is less clear. The goal of the current analyses was to understand better the familial relationship between DSM-IV ADHD and TD.

Method—Direct interview diagnostic data from a case-control study of 692 relatives of 75 comorbid TD and ADHD (TD+ADHD), 74 TD without ADHD (TD Only), 41 ADHD without TD (ADHD Only) and 49 control probands were analyzed. Hierarchical loglinear modeling was used to explore association patterns between TD, ADHD, and OCD or sub-clinical OCD (OCD/OCDsub) diagnoses among the 190 affected probands and their 538 relatives.

Results—The increased risk of comorbid ADHD and TD among relatives of TD and/or ADHD probands is associated with the presence of an OCD/OCDsub diagnosis in the proband (OR = 7.8; $p < .0001$).

Conclusions—The presence of OCD or OCDsub diagnosis in a proband was associated with a significantly increased risk of comorbid TD+ADHD in his/her relatives. The finding of an association between TD, ADHD and a proband OCD/OCDsub diagnosis was unexpected. The current results suggest that TD, ADHD, and OCD symptoms have overlapping neurobiology when occurring in families of TD and/or ADHD probands.

Keywords

Tourette's Disorder; ADHD; OCD; comorbidity

Introduction

Tourette Disorder (TD) is a common childhood onset neuropsychiatric disorder characterized by recurrent motor and phonic tics that onset before the age of 18 and persist

for at least one year. The prevalence of TD has been estimated to be between 0.15% and 3.8% in school-aged children (Hornse et al., 2001; Kadesjo and Gillberg, 2000; Khalifa and von Knorring, 2003; Kurlan et al., 2001). It is well established that genetic factors are important for the manifestation of TD. (see Scharf and Pauls, 2007 for review.) However the precise genetic mechanisms are unknown.

Nearly 90% of individuals with TD who have been ascertained through clinics have at least one comorbid psychiatric condition; the most common being attention deficit hyperactivity disorder (ADHD) and/or obsessive compulsive disorder (OCD) (Freeman et al., 2000). Family and twin studies support the hypothesis that at least some forms of OCD are etiologically/genetically related to TD (Pauls et al., 1991; Pauls et al., 1986a). However, the findings for a genetic relationship between ADHD and TD are not as straightforward.

ADHD is one of the most common (Canino et al., 2004; Ford et al., 2003) childhood neuropsychiatric disorders, affecting 8–12% of children (Biederman and Faraone, 2005). Results from family, twin and adoption studies demonstrate that genetic factors contribute significantly to the manifestation of ADHD (Biederman and Faraone, 2005). Furthermore, as noted above, many studies of TD have reported a high prevalence of ADHD among individuals affected with TD who were ascertained through clinics (Freeman et al., 2000). These observations resulted in several investigators hypothesizing that ADHD and TD represented alternative expressions of the same underlying genetic factors; similar to what has been hypothesized for OCD. For example, Comings and Comings (Comings and Comings, 1984; Comings and Comings, 1987; Comings and Comings, 1990) proposed that a wide range of psychiatric and behavioral disorders, including ADHD, represented variant genetic forms of TD. This hypothesis was based on the observations that a large number of TD probands had comorbid ADHD, and that TD probands had siblings with ADHD without tics at a higher frequency than siblings of control probands. Pauls and colleagues (Pauls et al., 1986b; Pauls et al., 1993; Pauls et al., 1991) reported that the increased frequency of ADHD in relatives of TD probands occurred because there was a higher than expected rate of comorbid TD and ADHD in the relatives. In a subsequent family study, Knell and Comings (Knell and Comings, 1993) observed that the rates of ADHD were increased in relatives of TD probands regardless of proband ADHD status (17.5% in relatives of probands with TD+ADHD, 9.7% in relatives of probands with TD alone, and 4.7% in relatives of controls). Although the rates of ADHD among relatives of probands diagnosed with TD without ADHD (TD Only) and probands with both TS and ADHD (TD+ADHD) were significantly greater than the rates observed in the control group, these rates were also significantly different in the two different TD family types, suggesting that probands with TD Only and those with TD+ADHD might be distinct genetic subtypes of TD. Taken together, these results are inconclusive regarding the hypothesis that TD and all forms of ADHD are alternative expression of the same underlying genetic factors. However the patterns within the families suggest that it is likely that TD and some forms of ADHD share common pathways of expression.

All of the studies cited above that were designed to examine the relationship between TD and ADHD included only families of probands diagnosed with both TD and ADHD, and probands diagnosed with TD alone. A limitation of these studies was the absence of families where probands were diagnosed with ADHD without TD. Furthermore, the sample sizes were not adequate to fully examine the relation between TD and ADHD among relatives.

In the most recent family study of TD and ADHD, Stewart and colleagues (Stewart et al., 2006) examined families of probands diagnosed with TD Only, TD+ADHD, and an additional sample of families ascertained through probands with ADHD Only. Estimation of the rate of TD in the relatives of ADHD only probands allows further assessment of the

common genetic origin hypothesis: if ADHD is a variant expression of TD, the rate of TD among the relatives of ADHD probands should be increased. These investigators reported that the rate of ADHD Only was not significantly elevated among the relatives of TD Only probands, although the overall rate of ADHD (including individuals who were comorbid with TD) was significantly higher in relatives of the TD Only group. Similarly, the overall rate of TD was significantly higher among the relatives of ADHD Only probands, but that was due to a higher than expected occurrence of relatives who had both TD and ADHD. The rate of TD Only among relatives of ADHD Only probands was not significantly elevated when compared to controls. In fact, the rate of comorbid TD+ADHD was elevated among relatives of all case probands. Furthermore, the results of logistic regression analyses indicated that a diagnosis of TD in a relative predicted a diagnosis of ADHD in that relative and conversely that a diagnosis of ADHD in a relative predicted a diagnosis of TD. An unexpected finding from the logistic regression analyses was that a diagnosis of OCD in a relative predicted both ADHD and TD. Unfortunately, it was not possible to determine if OCD predicted the co-occurrence of TD and ADHD in the same relative.

The goal of the current study was to examine in more detail the relationship between TD, ADHD and OCD symptoms among the relatives of the case probands in the Stewart et al. (Stewart et al., 2006) family study sample.

Method

The methods for this study have been described in detail elsewhere (Stewart et al., 2006). Additional analyses of the data described in Stewart and Colleagues are presented in the paper.

Subjects

The sample included in this study consisted of 931 individuals (239 probands and 692 biological first degree relatives). Four different types of families were investigated: 1) 205 relatives of 75 probands with TD and ADHD (TD+ADHD); 2) 219 relatives of 74 probands with TD and no ADHD (TD Only); 3) 114 relatives of 41 probands with ADHD and no TD (ADHD Only); and 4) 154 relatives of 49 control individuals who did not have TD, ADHD or OCD. As described previously (Stewart et al., 2006), there were no significant age or sex differences when comparing the total case and control groups for either probands or relatives

Case probands and their families were recruited from the Connecticut and Massachusetts chapters of the Tourette Syndrome Association, the Children and Adults with Attention Deficit Disorder (CHADD) Association, child psychiatry clinics and the internet. Control participants were ascertained using a random-digit dialing procedure undertaken by a survey research contractor. Probands with diagnoses of mental retardation, psychosis, or pervasive development disorder were excluded.

Written informed consent was obtained for all adults in the study and written assent was obtained for children between the ages of 7 and 18 in the presence of their parents. Every available family member was directly assessed. Individuals 18 years of age and older were interviewed directly. For children under the age of 18, child and parent interviews and direct interviewer observations were obtained. Institutional review boards at each site where the study was conducted approved the research.

Assessments

Clinical information was obtained from each family member using interviews developed for a genetic linkage study of TD ((TSAICG), 1999). These interviews focus specifically on TD, OCD and ADHD symptoms and were based on the Yale Global Tic Severity Scale and

Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989a; Goodman et al., 1989b). They also include ADHD items derived from the Schedule for Affective Disorders and Schizophrenia for School-Age Children- Epidemiological-Version, the Conner's Parent Rating Scale Revised – Long Version and the Conner's Adult ADHD Rating Scale – Long Version (Conners et al., 1998). These interviews have been shown to have good validity and reliability when compared to expert clinician ratings of tic and obsessive compulsive symptomatology (Leckman et al., 1993; Pauls et al., 1995).

TD, ADHD and OCD diagnoses were assigned to individuals who met DSM-IV-TR criteria. Also, subjects were given a diagnosis of OCDsub or obsessive compulsive symptoms (OCsym). Diagnoses of subclinical OCD and OC symptoms were assigned for cases with OC features not severe enough to merit a full diagnosis of OCD using criteria developed by McMahon et al. (2003). Specifically, "subclinical OCD was defined as the presence of OC symptoms that occupied some time every day, but less than one hour, or were associated with mild interference or distress. The diagnosis of OC symptoms was assigned if symptoms that were developmentally unusual were present, but such symptoms were reported to take no time, cause no distress and cause no interference". A diagnosis of Chronic Tic (CT) was given when multiple tics were present for at least a year but diagnostic criteria for TD were not met. Participants were also screened for other major psychiatric disorders using the Structured Clinical Interview for DSM-IV-Non-Patient edition (First et al., 1996) for adults and the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (Kaufman et al., 1997) for children under the age of 18 years. Both interviews have established reliability. In addition, adult members from each family completed family histories on their adult first degree relatives with brief, semi-structured interviews (Pauls et al., 1995). DSM-IV-TR criteria were used for diagnoses.

Interviewers held at least a bachelor's degree and were trained to reliability for the conduct of structured interviews. Best-estimate diagnoses were made by two expert clinicians for the study participants (Leckman et al., 1982). Best estimates for the two raters were compared, and, in cases of disagreement, raters discussed the case until either consensus was reached or a third diagnostician was consulted to reach the final diagnosis. Consensus was reached between diagnosticians in all cases without the need for a third diagnostician.

Statistical Analyses

Categorical data were analyzed as indicated using χ^2 analysis or Fisher exact tests. Statistical significance was defined at the $p < 0.05$ level and tests were two tailed. SPSS 15.0 (SPSS Inc, SPSS 15) was used for this analysis.

Hierarchical loglinear modeling was performed to examine association patterns of seven variables without specifying a dependent variable. This analysis incorporates table frequencies and can be used to detect the most parsimonious explanation for the distribution within the contingency table. The model included the following seven variables for 538 relatives of affected probands: relative gender, relative ADHD diagnosis, relative TD diagnosis, relative OCD/OCDsub diagnosis, proband ADHD diagnosis, proband TD diagnosis, and proband OCD/OCDsub diagnosis. Because of the limited sample size ($n = 538$), it was not possible to investigate models with more than three interaction terms. Gender was included to account for potential gender effects. Additional model expanded TD diagnosis by also including individuals with CT. The CATMOD procedure in SAS 9.2 (SAS Institute Inc, SAS 9.2) was used to perform backward elimination, starting with the saturated model that included all possible third-order interactions. The goodness of fit was assessed by the likelihood ratio chi-square statistics $G^2 = 2 \sum n \log(n/m)$, where n and m correspond to the observed and fitted cell frequencies (Stokes et al., 2001). The likelihood ratio statistics G^2 was used in backward elimination procedure. This procedure compared two models M1 and

M2, where M2 was a nested model of M1 and contained a subset of modeling coefficients while maintaining the hierarchical structure of the model. The likelihood ratios at each step were compared and the M2 was selected when the difference between G2 statistics was not significant at the tested level of degrees of freedom (Stokes et al., 2001). The model was selected when the backward elimination showed the significant rise in likelihood ratio statistics.

Results

The rates of TD, CT, and ADHD in the relatives of the four proband groups (TD Only, ADHD Only, TD+ADHD, and controls) are presented in Table 1. As reported previously (Stewart et al., 2006), the rates of TD and ADHD are elevated in all three proband groups when compared to controls. However, the rate of CT is elevated only among relatives of TD probands. Of note, while the rate of ADHD is elevated among the relatives of all three proband groups, the increased rate of ADHD in the relatives of TD Only probands is due to the higher than expected rate of TD+ADHD comorbidity among the relatives. The rate of ADHD alone among the relatives of TD Only probands is not significantly higher than the rate among controls. This significant elevation of TD+ADHD comorbidity is also observed among relatives of TD+ADHD and ADHD Only probands. As noted above, the rate of TD is significantly increased among the relatives of ADHD Only probands. But, as can be seen in Table 1, this increase is due to the higher than expected rate of TD+ADHD comorbidity among the relatives of ADHD Only. The rate of TD alone among these relatives is not significantly different than the rate observed among controls.

The relationship between TD and ADHD when occurring in the same individual is complex. The results presented in Table 1 do not support the hypothesis that there exists a homogeneous TD+ADHD subtype. If TD+ADHD were a distinct subtype, one would expect an elevated rate of TD+ADHD only in the first degree relatives of TD+ADHD probands compared to the first degree relatives of other proband groups. But, as is apparent from the results presented in Table 1, the rates of comorbid TD+ADHD are elevated in the relatives of all proband groups. Furthermore, when examining the number of affected individuals in each mutually exclusive cell, it is clear that the number of affected individuals is much larger than the expected number. For example, the expected number of affected relatives with both TD and ADHD in the TD Only families is 5 but the observed number is 15 in the TD Only families. Similarly, the expected number of TD+ADHD relatives in the TD +ADHD families is 4 while the observed number is 10 and finally the expected number of TD+ADHD relatives in the ADHD Only families is 1 compared to 4 observed.. Further examination of these family data and inclusion of OCD/OCDsub diagnostic information for both probands and relatives reveals an interesting pattern of association. As seen in Table 2, the increased rates of TD+ADHD among the relatives appear to be related to the presence of an OCD/OCDsub diagnosis in the proband. For example, of the 15 relatives with TD +ADHD in the families where the proband did not have a diagnosis of ADHD, 13 were in families where the proband had comorbid TD+OCD/OCDsub. Furthermore, of the 10 TD +ADHD relatives in the TD+ADHD proband families, 6 occurred in the families where the proband also had a diagnosis of OCD/OCDsub. A similar pattern was observed in the families ascertained through probands with ADHD.

To understand better this relationship, loglinear analyses were undertaken to investigate associations between relative and proband diagnoses. As noted above, loglinear analyses are useful when attempting to understand the distribution of data within a contingency table. These analyses allow the examination of specific models of association.

The variables examined in the loglinear analyses included gender, TD, ADHD and OCD/OCDsub diagnoses of both the relatives and probands (Supplemental Table 1a). As expected a gender effect was observed showing that TD (OR=4.9, $p=0.0004$) and ADHD (OR=1.8, $p=0.01$) are more common in males and OCD/OCDsub (OR=0.5, $p=0.002$) is less common in males. Furthermore, since these conditions are familial, associations were observed for proband diagnoses and relative diagnoses for ADHD (OR=1.9, $p=0.007$) and OCD/OCDsub (OR=2.5, $p=0.0002$). Proband TD diagnosis did not show an association with the relative TD diagnosis, but showed an association with relative OCD/OCDsub diagnosis (OR=1.7, $p=0.02$). As expected, based on the previous analysis of this data set (Stewart et al., 2006), a strong association was observed between TD and OCD/OCDsub in the relatives (OR=6.1, $p<0.0001$) and ADHD and OCD/OCDsub in the relatives (OR=2.5, $p=0.0009$). Finally, the most interesting results and the one most salient to the goal of the study was the highly significant association between TD and ADHD in the relatives and OCD/OCDsub in the proband (OR=7.8, $p<0.0001$) suggesting that the comorbidity of TD and ADHD observed in this and previous studies is at least partially explained by the presence of OCD/OCDsub in the proband. Of note is that when the proband does not have OCD/OCDsub, the odds of observing comorbid TD and ADHD in the relative is not significantly different from 1 (OR=1.7, $p=0.3$).

Additional analyses were completed in which probands and relatives with either TD or CT were included as affected. The results are similar to those when only TD was included as affected with four notable exceptions. The association between TD/CT and ADHD is significantly weaker (OR 3.3 vs. 7.8) suggesting that there is not an association between CT and ADHD in the same person. Furthermore, the associations between relative ADHD diagnosis and probands OCD/OCDsub diagnosis (OR = 1.8, $p=0.03$) and relative OCD/OCDsub and proband TD diagnosis (OR = 1.7, $p=0.02$) were significant when only TD was included as affected, these two associations were not significant when TD/CT was included as affected. Finally, when TD/CT was included as affected, a significant association was observed between relative TD/CT and proband TD/CT (OR = 4.2, $p=0.0005$) which was not observed when only TD was included as affected. Detailed results of these analyses are presented in the Supplemental Table 1 available online.

Discussion

The goal of this study was to understand better the increased rates of co-morbid TD+ADHD in relatives of TD Only, TD+ADHD and ADHD Only probands that had been observed in a number of earlier studies (see Scharf and Pauls, 2007 for review.) The majority of previous studies have demonstrated that ADHD does not represent a variant expression of the same underlying etiological factors that are important for TD. However, it has been frequently reported that TD and ADHD co-occur much more often than expected by chance. While one explanation for this might be ascertainment bias (Pauls et al., 1993), since the vast majority of studies reporting this association have been done on clinical samples, this explanation cannot account for the increased rate of TD+ADHD among relatives of probands who do not have both conditions.

In an hierarchical logistic regression analysis of these same data, Stewart et al (Stewart et al., 2006) observed that sex (males), age (younger) and OCD diagnosis of the relative all were significantly associated with a diagnosis of either TD or ADHD in the relatives. Furthermore, as expected, those analyses demonstrated that a diagnosis of TD in the proband predicted a diagnosis of TD in the relative and a diagnosis of ADHD in the proband predicted a diagnosis of ADHD in the relatives. Reflecting the observed increased comorbidity of TD and ADHD in the relative, the results of logistic regression showed that a diagnosis of TD in the relatives predicted a diagnosis of ADHD in the same relatives and a

diagnosis of ADHD in the relative predicted a diagnosis of TD in the same relative. Stewart et al did not examine the effect of an OCD diagnosis in the proband.

In the current study, loglinear analyses were performed and OCD/OCDsub diagnosis of the proband was included. As noted, loglinear analyses allow a more general examination of association without specifying a dependent variable. Thus, it is possible to include all three case proband groups and the relative diagnoses in a single analysis. Furthermore, loglinear analysis is recommended with categorical response variables when there is no clear distinction between dependent and independent variables as it is in this case, where there is not a clear a priori relationship between the multiple diagnoses in the relatives themselves and their probands. Loglinear modeling performed in this study included the following seven variables and all possible second and third order interactions: relative's TD diagnosis, relative's ADHD diagnosis, relative's OCD/OCDsub diagnosis, relative's gender, proband's TD diagnosis, proband's ADHD diagnosis, and proband's OCD/OCDsub diagnosis. As expected, these analyses demonstrated that: 1) proband diagnoses were associated with the same disorder in the first degree relative; 2) ADHD and TD are more common in males; and 3) OCD/OCDsub is more common in females. This analysis also revealed an association between proband OCD/OCDsub diagnosis and increased rate of TD/ADHD comorbidity in the relatives, regardless of whether the proband had TD or ADHD or both. These results suggest that there may be a TD/OCD/ADHD familial subtype, which could represent a more severe form of TD (Spencer et al., 1998).

An increased genetic burden appears to influence the risk of TD and comorbid disorders. In a prospective study of children at risk for TD, children of two TD-affected parents had three times greater risk of developing ADHD compared to the children of one affected parent, and two times greater risk of developing either tics, ADHD, or OCD (McMahon et al., 2003). TD appearing in the context of ADHD is likely to represent a more severe form of TD than TD without ADHD (Spencer et al., 1998). Patients with comorbid TD and ADHD perform less on cognitive tasks than patients with TD alone (Brand et al., 2002; Ozonoff et al., 1998; Pennington and Ozonoff, 1996), have significantly increased rates of anger control problems (Budman et al., 2000; Freeman, 2007; Stephens and Sandor, 1999; Sukhodolsky et al., 2003) and tic severity (Mol Debes et al., 2008).

There is some evidence that comorbid TD/OCD/ADHD may be heritable. A latent class analysis of 952 individuals from 222 TD families was performed to identify TD subphenotypes based on diagnoses of TD, OCD, OC symptoms and ADHD (Grados and Mathews, 2008). The investigators identified five classes of categorical TD subphenotypes, of which only the comorbid TD/OCD/ADHD class was highly heritable (Grados and Mathews, 2008). Thirty four percent of all TD affected individuals had comorbid OCD and ADHD, while only 10% had comorbid ADHD without OCD (Grados and Mathews, 2008).

Individuals with comorbid conditions may exhibit a specific subset of symptoms. A recent principle components analysis of symptom data from 410 TD patients (Robertson et al., 2008) revealed five symptom factors characterized by: 1) socially inappropriate behaviors and other complex vocal tics; 2) complex motor tics; 3) simple tics; 4) compulsive behaviors; and 5) touching self. Individuals with comorbid TD and ADHD or comorbid TD and OCD had significantly higher scores on Factor 1, supporting the notion that these three conditions may represent a unique clustering of symptoms in individuals with TD.

Epidemiological data suggests that ADHD and OCD are more frequent in TD than in other less severe tic disorders (Khalifa and von Knorring, 2006; Saccomani et al., 2005). In a Swedish study of school-aged children, 66% of the TD cases had comorbid ADHD compared to 33% of children with chronic vocal tics, 12% of children with chronic motor

tics, and just 4% of children with transient motor tics (Khalifa and von Knorring, 2006). A similar gradient was observed in the rates of OCD (Khalifa and von Knorring, 2006). Another study found 44% of children with TD had comorbid ADHD, compared with 23% of children with chronic tics, and 54% of children with TD had comorbid OCD, compared with 8% of children with chronic tics (Saccomani et al., 2005). Furthermore, individuals with comorbid TD and ADHD are more likely to have additional comorbidities, compared with individuals with TD only. A large study of almost 6,000 TD affected individuals found a significant increase in OCD and other psychiatric disorders in individuals with comorbid TD and ADHD compared to individuals with TD without ADHD (Freeman, 2007).

In the current study, we did not observe a significant association between a diagnosis of OCD/OCDsub and TD+ADHD in the relative but inspection of Table 2 suggests that there is a trend in that direction. In fact, when analyses were repeated and diagnoses of OCD/OCDsub and OCSym were included, a significant association was observed between TD, ADHD and OCD/OCDsub/OCSym in the same individual (Supplemental Table 2). The inclusion of OCSym in the analyses is suggested by some reports (do Rosario-Campos et al., 2005) indicating that at least in families ascertained through probands with TD and/or OCD, the rate of OCSym is increased, suggesting that it might be part of the inherited OCD spectrum. Thus, this co-morbidity of TD and ADHD in the relatives may be in individuals who also have some aspects of OC symptomatology.

Brain imaging studies of TD, ADHD and childhood-onset OCD consistently point to involvement of cortico-striato-thalamo-cortico circuits in all three disorders (Albin and Mink, 2006; Friedlander and Desrocher, 2006; Sachdev and Malhi, 2005), suggesting that disturbances in these structures contribute to behavioral outcomes such as impulsivity, hyperactivity, compulsions and tics. The possibility of a common neurobiological origin of a combined TD, ADHD and OCD phenotype is supported an increased number of subcortical hyperintensities in children with TD, OCD, and ADHD (Amat et al., 2006). Primate studies also supports the suggestion that overlapping areas of the basal ganglia are responsible for TD, OCD and ADHD symptoms (Francois et al., 2004; Grabli et al., 2004).

Limitations of this study should be acknowledged. As is the case in all other studies, the sample collected here was ascertained through a specialty clinic for TD. Thus, the rates within families may be higher than in a population sample; however it is unlikely that this ascertainment would affect the patterns of co-occurrence within families. Loglinear analyses should also be considered as exploratory and hypothesis generating. It has been shown that when a large number of cells in the loglinear analysis have zero values, the theoretical chi-square distribution can not be used to evaluate model fit, and bootstrapping approach is recommended (Langeheine et al., 1996). Simulation studies found that when over 60% of cell have zero values there is a significant deviation from the chi-square distribution (Langeheine et al., 1996). In the current study, the sparsest model was the extended loglinear model shown in Supplemental Table 1 where the number of zero count cells approached 44%. Finally, to fully evaluate the relationship between proband OCD diagnosis and the prevalence(or presence) of comorbid TD+ADHD in the relatives, it will be important to repeat the study with an OCD-only proband group (Geller et al., 2007). Because of these limitations our findings should be treated as hypothesis generating, and must be repeated on a larger sample.

In conclusion, this is the first study to provide a possible mechanism to explain the increased rate of TD and ADHD in families ascertained through probands with TD, ADHD and OCD. The findings suggest a common underlying pathophysiology for at least some forms of tic disorder, particularly TD, ADHD and OCD and suggest that additional studies need to be

conducted to more fully understand the underlying biology of these common complex disorders of childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by NINDS NS-16648 (DLP), MH-49351 (JFL) and MH076273 (JFL) and the McIngvale Foundation (S.E.S. D.A.G. and D.L.P.).

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Table 1

Uncorrected Rates of TD, CT, and ADHD among First Degree Relatives of Affected Probands and Controls.

Relative Diagnosis	Proband Diagnosis										
	TD Only (N = 219)			TD+ADHD (N = 205)			ADHD Only (N = 114)			Controls (N = 154)	
	N	% ± SE		N	% ± SE		N	% ± SE		N	% ± SE
TD A, B, C, E, F *	32	14.6 ± 2.4		22	10.7 ± 2.2		6	5.3 ± 2.1		0	0
CT A, B, E, F	20	9.1 ± 1.9		19	9.3 ± 2.0		4	3.5 ± 1.7		3	1.9 ± 1.1
ADHD A, B, C, E *	32	14.6 ± 2.4		40	19.5 ± 2.8		25	21.9 ± 3.9		11	7.1 ± 2.1
TD Only A, B, E, F *	17	7.8 ± 1.9		12	5.9 ± 1.6		2	1.8 ± 1.2		0	0
TD+ADHD A, B, C	15	6.8 ± 1.7		10	4.9 ± 1.5		4	3.5 ± 1.7		0	0
CT Only A, B	17	7.8 ± 1.9		15	7.3 ± 1.8		3	2.6 ± 1.5		2	1.3 ± 0.9
CT+ADHD	3	1.4 ± 0.8		4	2.0 ± 1.0		1	0.9 ± 0.9		1	0.6 ± 0.6
ADHD Only B, C, D, E	14	6.4 ± 1.7		26	12.7 ± 2.3		20	17.5 ± 3.6		10	6.5 ± 2.0

Adapted from Stewart et al (Stewart et al., 2006) where age corrected rates are presented. TD = Tourette's Disorder, ADHD=Attention Deficit Hyperactivity Disorder, CT=Chronic Tic.

Superscript after relative diagnosis indicates significant differences between two groups. Values that reached statistical significance $p < 0.05$, two-tailed tests. Superscript followed by (*) indicates statistical significance $p < 0.1$, two-tailed tests:

A Relatives of TD only probands versus Controls;

B Relatives of TD+ADHD probands versus Controls;

C Relatives of ADHD only probands versus Controls;

D Relatives of TD only versus relatives of TD+ADHD probands;

E Relatives of TD only versus relatives of ADHD only probands;

F Relatives of TD+ADHD probands versus relatives of ADHD only probands;

Note: Comparisons were made either with the Fisher's Exact Test (for cell counts < 5) or Pearson Chi-Square Test.

Note: The TD and ADHD cells are not mutually exclusive. For example in the relatives of TD only probands, adding the number of individuals with TD Only (17) and those with TD+ADHD (15), the sum is 32, the same as in the TD cell in the first line of the table.

Uncorrected Rates of TD, CT, OCD/OCDsub and ADHD among First Degree Relatives of Affected Probands and Controls.

Table 2

Relative Diagnosis	TD ONLY Proband (N=219)						TD+ADHD Proband (N=205)						ADHD ONLY Proband (N=114)					
	- OCD/OCDsub (N=93)			+ OCD/OCDsub (N=126)			- OCD/OCDsub (N=95)			+ OCD/OCDsub (N=110)			- OCD/OCDsub (N=49)			+ OCD/OCDsub (N=65)		
	N	%±SE	N	%±SE	N	%±SE	N	%±SE	N	%±SE	N	%±SE	N	%±SE	N	%±SE	N	%±SE
TD	10	10.8±3.2	22	17.5±3.4	32	14.6±2.4	11	11.6±3.3	11	10.0±2.9	22	10.7±2.2	3	6.1±3.4	3	4.6±2.6	6	5.3±2.1
CT	10	10.8±3.2	10	7.9±2.4	20	9.1±1.9	7	7.4±2.7	12	10.9±3.0	19	9.3±2.0	2	4.1±2.8	2	3.1±2.1	4	3.5±1.7
ADHD	9	9.7±3.1	23	18.3±3.4	32	14.6±2.4	18	18.9±4	22	20.0±3.8	40	19.5±2.8	14	28.6±6.5	11	16.9±4.7	25	21.9±3.9
OCD/OCDsub	13	14.0±3.6	37	29.4±4.1	50	22.8±2.8	17	17.9±3.9	35	31.8±4.4	52	25.4±3.0	4	8.2±3.9	14	21.5±5.1	18	15.8±3.4
TD only	6	6.5±2.5	5	4.0±1.7	11	5.0±1.5	3	3.2±1.8	1	0.9±0.9	4	2.0±1.0	0	0	0	0	0	0
CT only	5	5.4±2.3	5	4.0±1.7	10	4.6±1.4	4	4.2±2.1	5	4.5±2.0	9	4.4±1.4	1	2.0±2.0	1	1.5±1.5	2	1.8±1.2
ADHD only	3	3.2±1.8	7	5.6±2.0	10	4.6±1.4	8	8.4±2.8	7	6.4±2.3	15	7.3±1.8	12	24.5±6.1	7	10.8±3.8	19	16.7±3.5
OCD/OCDsub only	5	5.4±2.3	17	13.5±3.0	22	10.0±2.0	5	5.3±2.3	13	11.8±3.1	18	8.8±2.0	1	2.0±2.0	10	15.4±4.5	11	9.6±2.8
ADHD+TD+ OCD/OCDsub	0	0	9	7.1±2.3	9	4.1±1.3	1	1.1±1.0	6	5.5±2.2	7	3.4±1.3	1	2.0±2.0	2	3.1±2.1	3	2.6±1.5
ADHD+TD- OCD/OCDsub	2	2.2±1.5	4	3.2±1.6	6	2.7±1.1	3	3.2±1.8	0	0	3	1.5±0.8	0	0	1	1.5±1.5	1	0.9±0.9
ADHD+TD +/- OCD/OCDsub	2	2.2±1.5	13	10.3±2.7	15	6.8±1.7	4	4.2±2.1	6	5.5±2.2	10	4.9±1.5	1	2.0±2.0	3	4.6±2.6	4	3.5±1.7
ADHD+CT+ OCD/OCDsub	1	1.1±1.1	1	0.8±0.8	2	0.9±0.6	0	0	2	1.8±1.3	2	1.0±0.7	0	0	0	0	0	0
ADHD+CT- OCD/OCDsub	1	1.1±1.1	0	0	1	0.5±0.5	1	1.1±1.0	1	0.9±0.9	2	1.0±0.7	1	2.0±2.0	0	0	1	0.9±0.9
ADHD+CT +/- OCD/OCDsub	2	2.2±1.5	1	0.8±0.8	3	1.4±0.8	1	1.1±1.0	3	2.7±1.6	4	2.0±1.0	1	2.0±2.0	0	0	1	0.9±0.9
ADHD+ OCD/OCDsub -TD/CT	2	2.2±1.5	2	1.6±1.1	4	1.8±0.9	5	5.3±2.3	6	5.5±2.2	11	5.4±1.6	0	0	1	1.5±1.5	1	0.9±0.9
TD+ OCD/OCDsub - ADHD	2	2.2±1.5	4	3.2±1.6	6	2.7±1.1	4	4.2±2.1	4	3.6±1.8	8	3.9±1.4	2	4.1±2.8	0	0	2	1.8±1.2
CT+ OCD/OCDsub - ADHD	3	3.2±1.8	4	3.2±1.6	7	3.2±1.2	2	2.1±1.5	4	3.6±1.8	6	2.9±1.2	0	0	1	1.5±1.5	1	0.9±0.9

Note: TD = Tourette's Disorder, ADHD=Attention Deficit Hyperactivity Disorder, CT=Chronic Tic, OCD/OCDsub =Obsessive Compulsive Disorder or Obsessive Compulsive Disorder Sub-clinical, TD/CT=Tourette's Disorder or Chronic Tic.

The difference in the rates of TD only, ADHD only and CT only between Table 1 and Table 2 is due the exclusion of individuals with OCD/OCDsub in Table 2. For example, in Table 1 in the relatives of TD only probands, the rate of TD only is 17, which in Table 2 corresponds to the sum of TD only (11 individuals) and TD+ OCD/OCDsub–ADHD (6 individuals).