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Evidence Against a Genetic Relationship between Tourette's Syndrome and Anxiety, Depression, Panic and Phobic Disorders

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Analyses were undertaken to examine whether a wide range of psychiatric disorders, including anxiety, affective, substance abuse and psychotic disorders, represent variant manifestations of Tourette's syndrome (TS). Previous studies have suggested that chronic tics (CT) and obsessive–compulsive disorder (OCD) are variant expressions of TS since both CT and OCD are elevated among relatives of TS probands. In the current study, no other psychiatric disorder was significantly elevated among the relatives who did not have TS, CT or OCD when compared with a control sample. These findings are not consistent with the hypothesis that a wide range of psychiatric and behavioural disorders are variant expressions of TS.

Tourette's syndrome (TS) is a childhood-onset neuropsychiatric disorder characterised by recurrent, waxing and waning motor and phonic tics. The average age at onset of symptoms is approximately seven years. The syndrome is familial, with some chronic tics (CT) (either motor or phonic) apparently representing a less severe but more prevalent form of the illness (Shapiro *et al*, 1978; Kidd *et al*, 1980; Pauls *et al*, 1981, 1984, 1991; Shapiro *et al*, 1988; Cohen *et al*, 1988).

While the tic symptoms represent the hallmark features necessary for a diagnosis of TS, patients with the disorder have a wide range of other difficulties. In his original description, Gilles de la Tourette reported an association with obsessive–compulsive symptoms in several of the cases he described. Subsequent studies have documented that obsessive–compulsive symptoms are experienced by a substantial number of TS patients (Robertson *et al*, 1988). Furthermore, a large percentage of TS patients also have sufficient difficulties with attention, impulsiveness and hyperactivity to satisfy diagnostic criteria for attention-deficit hyperactivity disorder (ADHD) (Comings & Comings, 1985).

A wide range of other psychiatric and behavioural disorders have been observed in TS patients seen in clinics (Comings & Comings, 1985; Cohen *et al*, 1988). Comings & Comings (1987*a–f*, 1990*a–c*) have proposed that these other psychiatric disorders also represent variant expressions of a hypothetical gene(s) for TS. In addition to obsessive–compulsive disorder (OCD) and chronic tics, they have concluded that ADHD, conduct disorder, specific learning disorders, specific reading disability, specific language disorders, stuttering, speech disorders (non-stuttering), phobic disorders, panic disorder, schizoid behaviour, major depressive disorder, bipolar affective disorder, alcoholism, drug abuse, and obesity are all variant manifestations of the 'TS gene(s)'.

The purpose of the present study was to examine some of the hypotheses proposed by Comings & Comings with data collected from a sample of families in which the majority of first-degree relatives were personally interviewed. If any of these disorders are genetically related to TS, then the rate of that illness should be significantly elevated among the relatives of TS probands when compared with a control sample or population prevalence estimates. In previous publications, we have reported (a) that OCD appears to be a variant expression of TS (Pauls *et al*, 1986*b*, 1991) and (b) that ADHD is most likely not related to TS in the same way as OCD (Pauls *et al*, 1986*a*, 1993). In this paper, we present results of analyses designed to determine whether major depressive disorder, generalised anxiety disorder, panic disorder and phobic disorders are genetically related to the TS spectrum.

Method

The sample for this study consists of 338 biological first-degree relatives of 85 GTS probands, 92 biological first-degree relatives of 27 unaffected control probands and 21 non-biological first-degree relatives of 6 adopted TS probands. The relatives of the unaffected probands and the adopted TS probands serve as a control sample for the total data set.

All available individuals were interviewed using a precoded structured interview developed specifically for this study (Pauls & Hurst, 1981). Two versions of the interview were used. The adult version included the Diagnostic Interview Schedule (DIS; Robins *et al*, 1981), which enables assessment of any psychiatric disorder during an individual's lifetime. The children's version of the interview, administered to a parent about his/her child, included the Schedule for

Affective Disorders and Schizophrenia for School Age Children (K-SADS-E; Puig-Antich *et al*, 1980).

The TS probands for the present study were randomly selected from membership of the Connecticut Chapter of the Tourette's Syndrome Association (TSA). Because there were comparatively few female members, a greater percentage of them were invited to participate to ensure that a sufficient number of families of female probands would be available for data analyses. After ascertainment, interviews were conducted to determine if the individual met DSM-III criteria (American Psychiatric Association, 1980) for TS. All probands 18 years of age and older were interviewed directly. If the proband was under the age of 18, the parent(s) were interviewed about the child; whenever possible, the child was interviewed regarding specific symptoms and an attempt was made to observe directly any symptoms that the child might manifest. After the diagnosis of TS had been established for the proband, a history concerning each adult first-degree relative was obtained and permission to contact all first-degree relatives was requested.

Controls

Some of the controls for this study were ascertained through adopted TS probands. These probands came from the roster of the Connecticut TSA Chapter and were assessed blind to their adoptive status. The additional control individuals were ascertained through unaffected volunteers. To determine whether or not the volunteers were affected, they were interviewed with the complete battery of instruments designed for this study. At the time of the interview, permission was obtained to contact first-degree relatives. The relatives were contacted only after it was determined that the volunteer did not meet criteria for any psychiatric diagnosis. Those relatives who agreed to be in the study were included in the control sample. Non-interviewed relatives were included in the control sample only if there were at least two family members who provided family history information about that relative.

Relatives

Once permission was granted to contact relatives, they were invited to participate in the study. After informed consent was obtained, each relative over the age of 18 was interviewed in person about himself/herself. Then family history data were collected from each informant about all of his/her adult first-degree relatives. A parent interview was obtained for each relative under the age of 18; whenever possible, the individual under 18 was also interviewed in person. Family history information was not collected about individuals under age 18.

The family history information solicited about each adult relative was obtained with a semi-structured interview. It was designed to elicit information necessary for diagnosis of TS, OCD, substance abuse, major depression, bipolar disorder, panic disorder and other anxiety disorders. This instrument included questions about the presence or absence of motor and phonic tics and symptoms of other neuropsychiatric disorders; it also elicited general descriptive information, which was collected via an open-ended question in which the informant was asked to describe the relative in general terms. Thus, two types of information were obtained about all participating individuals: (a) information from a direct structured interview, and (b) personal history information from each of his/her adult relatives and/or spouses. For those individuals who were not interviewed in person, only family histories were available.

Diagnostic procedure

After completion of all interviews within a given family, all available materials (personal interview and/or family history descriptions) for each individual were collated. All identifying information was removed so that diagnostic ratings could be completed by raters blind to the diagnosis of the proband. The diagnosticians were never given a complete family to evaluate at one time and all diagnostic evaluations of probands were done separately from those of the relatives.

Best estimate diagnoses were made independently by two investigators using DSM-III criteria. Several levels of diagnostic certainty were used. When an individual had sufficient symptoms to meet all criteria, a 'definite' diagnosis was assigned. If one symptom or symptom cluster was missing or there was lack of supporting information from family reports, a 'probable' diagnosis was assigned. If some symptoms were present but not enough to satisfy either a probable or definite diagnosis, a 'possible' diagnosis was given. Only definite and probable diagnoses were used in the analyses reported here. Where major disagreements occurred between the two diagnosticians, consensus diagnoses were reached following established procedures developed for other neuropsychiatric disorders (Leckman *et al*, 1982).

Diagnostic estimates were made for 451 first-degree relatives of 85 TS and 33 control probands. All 118 probands were interviewed in person, as well as 309 of 451 (69%) first-degree relatives. In all cases, direct interview data were collected from at least two individuals per family.

Data analyses

All analyses were done using the Statistical Analysis System (SAS) (SAS Institute, 1985). Survival analyses, as described by Thompson & Weissman (1979), were performed as implemented by the SAS's LIFETEST procedure to obtain Kaplan-Meier estimates of the time to onset of illness. These age-corrected morbidity risks were then compared for relatives of TS probands and controls. Logistic regression analyses were performed as implemented by the SAS's CATMOD procedure.

Results

The rates of major depressive disorder, OCD, panic disorder, and simple phobia were significantly elevated among the TS probands (Table 1). The rates of generalised anxiety disorder and social phobia were also higher among the TS probands than among the controls but the differences were not statistically significant. There were no significant differences between TS probands and controls for any other psychiatric diagnoses examined.

Table 1
Rates of diagnosis among the TS probands and the controls (relatives of control probands)

Diagnoses	TS probands ($n=86$)		Controls ($n=113$)	
	Number	%	Number	%
Generalised anxiety disorder	14	16.3	9	8.0
Major depressive disorder	35	40.7	16	14.2**
Obsessive-compulsive disorder	31	36.0	2	1.8***
Panic disorder	11	12.8	3	2.7*
Simple phobia	16	18.6	5	4.4**
Social phobia	5	5.8	1	0.9

*$P<0.05$; **$P<0.01$; ***$P<0.001$.

This elevation in rates among TS probands does not by itself demonstrate that these disorders are genetically related to TS. If any disorder is genetically related to TS, then the rate of that disorder should be increased among the relatives of TS probands. We have proposed that OCD is genetically related to TS (Pauls *et al*, 1986*b*, 1991; Pauls & Leckman, 1986) because the rate of OCD among the relatives of TS probands is significantly elevated regardless of whether or not the proband has a concomitant diagnosis of OCD.

As can be seen in Table 2, the frequencies of diagnoses of generalised anxiety disorder, major depressive disorder, panic disorder and simple phobia were significantly elevated among the first-degree relatives of TS probands. However, these estimates included relatives who themselves had diagnoses of TS, CT and OCD. While this was consistent with the hypothesis that these disorders are genetically related to TS, it was necessary to examine whether the rate of each disorder was elevated among relatives who did not have TS, CT or OCD. It is possible that the frequency of a disorder could be significantly increased among relatives because it occurred more frequently among individuals with TS, CT or OCD. In such a situation, the disorder could be secondary to the TS spectrum and would not necessarily represent a variant expression of the syndrome when it occurred in the absence of TS, CT or OCD. If a disorder is genetically related to TS and represents a variant expression of the syndrome, then the rate of that disorder should be elevated among the relatives who do not have TS, CT or OCD.

To test this prediction, rates of generalised anxiety disorder, major depressive disorder, panic disorder, simple phobia and social phobia were estimated among relatives and controls not affected with TS, CT or OCD. Two estimates of morbidity risk were obtained. The first included all relatives and controls without TS, CT or OCD and the second included only those who were interviewed (Table 3). For interviewed individuals, the rates of generalised anxiety disorder, panic disorder, simple phobia and social phobia were not significantly different between relatives of TS probands and controls. The rate of simple phobia was significantly higher when non-interviewed individuals were included. This is most likely due to the fact that the family history instrument used to collect information about non-interviewed family members did not include specific questions about phobias. Thus, rates estimated using family history data would be underestimates of the true rate of phobias. Since there were proportionately fewer controls interviewed than biological relatives of TS probands, the rates for phobias could be substantially underestimated. For all of the other conditions, adequate information was collected with the family history interview to assign diagnoses and there was not the same discrepancy observed for interviewed and non-interviewed relatives and controls.

Only major depressive disorder (MDD) was significantly increased among the relatives of TS probands. To examine whether MDD might represent a variant expression of the TS spectrum, the relatives without TS, CT or OCD were divided into two samples according to whether or not the TS proband had MDD. If MDD represents a variant expression of TS, the rates of MDD should be equal across these two samples. The two samples were compared with the controls not affected with TS, CT or OCD. The age-corrected rate of MDD among the relatives of those TS probands who did not have MDD (21.1 (4.5)) was not significantly different from the rate among the controls (19.5 (4.5)); however, the rate of MDD among the relatives of the TS probands who had MDD (38.7 (5.8)) was significantly higher than the rate among controls ($\chi^2=10.65$, $P<0.001$). Thus, the increased rate of MDD among relatives of TS probands appears to be due to the increased rate among relatives of the probands with MDD. This is expected since MDD is a familial disorder.

Table 2
Age-corrected % rates (s.e.) of diagnosis among first-degree relatives

	Relatives of TS probands ($n=338$)		Relatives of control probands ($n=113$)	
	Number	Rate	Number	Rate
Generalised anxiety disorder	55	17.7 (2.3)	9	10.2 (3.2)*
Major depressive disorder	94	38.1 (3.3)	16	20.7 (4.6)*
Panic disorder	36	14.2 (2.3)	3	3.5 (2.0)**
Simple phobia	45	15.0 (2.1)	5	5.9 (2.5)*
Social phobia	15	4.7 (1.2)	1	1.2 (1.2)*

*$P<0.05$; **$P<0.01$.

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Table 3
Age-corrected % rates (s.e.) of diagnosis among first-degree relatives without TS, CT or OCD

Diagnoses	Relatives of TS probands ($n=223$)	Relatives of control probands ($n=110$)	Interviewed relatives of TS probands ($n=155$)	Interviewed relatives of control probands ($n=66$)
Generalised anxiety disorder	12.7 (2.5)	9.2 (3.1)	18.7 (3.8)	18.5 (6.3)
Major depressive disorder	28.5 (3.6)	19.5 (4.5)*	31.6 (3.9)	21.1 (5.0)*
Panic disorder	8.6 (2.2)	4.0 (2.2)	10.2 (3.0)	9.7 (5.3)
Simple phobia	10.6 (2.2)	4.9 (2.1)*	12.2 (2.7)	10.9 (4.6)
Social phobia	2.3 (1.0)	1.0 (1.0)	3.4 (1.5)	2.0 (2.0)

*$P<0.05$.

Similar analyses for generalised anxiety disorder, panic disorder, simple phobia and social phobia showed no significant differences between relatives of probands with or without each diagnosis and controls. None of the results suggested that any of the disorders were phenotypic variants of TS.

Further analyses were undertaken to understand why the rates of anxiety, depression, panic disorder and phobias were significantly higher among all relatives of TS probands. Mutually exclusive classes of relatives were examined to determine whether a higher than expected rate of anxiety, depression, panic disorder or phobia occurred among family members with diagnoses of TS, CT or OCD.

The findings for generalised anxiety disorder (GAD) are presented in Table 4. The increased rate of GAD among all relatives of TS probands appears to be due to the increased frequency of GAD among relatives who have a diagnosis of OCD. Of the 40 relatives who meet diagnostic criteria for OCD, 19 (47.5%) also have GAD.

Logistic regression analyses were undertaken to examine more rigorously the relationship between GAD, TS, CT and OCD. The initial full model predicted the occurrence of GAD and included (a) age as a covariate; (b) sex of the individual; (c) anxiety diagnosis of the proband; (d) TS, CT or OCD diagnosis of the relative; (e) whether the individual was a relative of a TS proband or control; and (f) all possible interactions. Stepwise selection by simple deletion of effects produced the most parsimonious model that included age ($P<0.0003$), sex ($P<0.0034$) and diagnosis of OCD ($P<0.0001$). There were no statistically significant interactions. This reduced model had a likelihood ratio ($\chi^2=152.34$, d.f. $=167$, $P<0.79$) indicating a good fit between observed frequencies and expected frequencies generated by the model. The results of these analyses confirm that GAD occurred most often in those individuals who had a diagnosis of OCD. Furthermore, once that relationship was accounted for, there was no difference in the rate of GAD between relatives of TS probands and controls. This finding is not unexpected, since many OCD individuals also report significant symptoms of anxiety (Rasmussen & Eisen, 1991).

The data for major depressive disorder (MDD) are shown in Table 5. Of note is that the overall frequency of MDD is equal in families of TS probands with and without MDD (25.7% v. 30.3%), but the rate of MDD alone is twice as high among the relatives of probands with MDD. Examination of the occurrence of MDD in the families of TS probands without MDD suggests that most of the MDD occurs in conjunction with TS, CT and OCD: 28 (59.6%) of the 47 depressed relatives have at least one of these diagnoses. In the families of depressed TS probands,

Table 4
Rates of mutually exclusive diagnostic categories among relatives of those TS probands with and without generalised anxiety disorder

Diagnosis	Relatives of those TS probands without GAD ($n=258$)		Relatives of those TS probands with GAD ($n=80$)		Total ($n=338$)	
	Number	%	Number	%	Number	%
TS	13	5.0	2	2.5	15	4.4
CT	29	11.2	13	16.3	42	12.4
OCD	15	5.8	2	2.5	17	5.0
TS + OCD	6	2.3	1	1.3	7	2.1
CT + OCD	4	1.6	0	0	4	1.2
TS + GAD	3	1.2	1	1.3	4	1.2
CT + GAD	1	0.4	0	0	1	0.3
TS + OCD + GAD	2	0.8	0	0	2	0.6
CT + OCD + GAD	7	2.7	1	1.3	8	2.4
OCD + GAD	10	3.9	5	6.3	15	4.4
GAD	21	8.1	4	5.0	25	7.4

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Table 5
Rates of mutually exclusive diagnostic categories among relatives of those TS probands with and without depression

Diagnosis	Relatives of those TS probands without MDD ($n=183$)		Relatives of those TS probands with MDD ($n=155$)		Total ($n=338$)	
	Number	%	Number	%	Number	%
TS	6	3.3	9	5.8	15	4.4
CT	14	7.7	20	12.9	34	10.1
OCD	8	4.4	6	3.9	14	4.1
TS + OCD	1	0.5	3	1.9	4	1.2
CT + OCD	1	0.5	3	1.9	4	1.2
TS + MDD	1	0.5	3	1.9	4	1.2
CT + MDD	8	4.4	5	3.2	13	3.8
TS + OCD + MDD	4	2.2	1	0.6	5	1.5
CT + OCD + MDD	3	1.6	1	0.6	4	1.2
OCD + MDD	12	6.6	6	3.9	18	5.3
MDD	19	10.4	31	20.0	50	14.8

only 16 (34.0%) of the 47 depressed relatives have TS, CT or OCD.

As in the case of GAD, logistic regression analyses were undertaken to examine more rigorously the relationship between MDD, TS, CT and OCD. The initial full model predicted the occurrence of MDD and included (a) age as a covariate; (b) sex of the individual; (c) MDD diagnosis of the proband; (d) TS, CT or OCD diagnosis of the relative; (e) whether the individual was a relative of a TS proband or control; and (f) all possible interactions. Stepwise selection by simple deletion of effects produced the most parsimonious model which included age ($P<0.008$), sex ($P<0.002$), the relative's diagnosis of OCD ($P<0.0001$) and the proband's diagnosis of MDD ($P<0.01$). No interactions reached statistical significance. This reduced model had a likelihood ratio ($\chi^2=178.54$, d.f. $=227$, $P<0.95$) indicating a good fit between observed frequencies and expected frequencies generated by the model. Similar to the findings with GAD, the results with MDD confirm that it was diagnosed most often in those individuals who had OCD. However, in contrast to GAD, MDD was also significantly elevated among relatives of probands who themselves had a diagnosis of MDD. In the case of relatives who had both MDD and OCD, the onset of the MDD almost always followed the onset of the OCD (data not shown). This was particularly true for the relatives of those TS probands who did not have MDD. Thus, much of the depression occurring in these families was chronologically secondary to OCD.

The findings for panic disorder and simple phobia are quite similar to those for GAD and MDD. In general, the rates of panic disorder and simple phobias alone are not elevated among the relatives, but the rates of both disorders are considerably higher than expected by chance among relatives with OCD. Logistic regression analyses gave results almost identical to those obtained for GAD. The significant predictors for the presence of either panic disorder or simple phobias among the relatives were age, sex and OCD diagnosis of the relative. Thus, the significant increase of GAD, MDD, panic disorder and simple phobias among relatives of TS probands appears to be due primarily to the presence of OCD. The rates of these disorders are considerably higher among relatives who also have a diagnosis of OCD. As with GAD, these findings are consistent with reports in the literature that suggest that phobic and panic disorders occur more frequently among OCD patients (Rasmussen & Eisen, 1991).

Discussion

Previous analyses have shown (Pauls *et al*, 1991; Eapen *et al*, 1993) that there is an increased rate of OCD among the relatives of TS probands and that the rate does not depend on the OCD diagnosis of the TS proband. No such patterns were observed for any other psychiatric illness in this study. While it appears that TS patients seen in clinics have a high rate of other difficulties (Table 1), this increased rate is not observed among the non-TS, non-CT, non-OCD relatives of TS probands.

The reasons for the increased rates of some psychiatric illnesses among TS probands are not entirely clear. One possible explanation is that individuals with TS are more likely to experience anxiety and mood disorders secondary to having a chronic disorder. If that were true, then an increased rate of these disorders should be observed among the relatives affected with TS. This was not the case in the families ascertained for this study. Rates of generalised anxiety disorder, major depressive disorder, panic disorder, simple phobia and social phobia were not significantly elevated among relatives with TS. These disorders did, however, occur much more frequently among relatives with OCD.

Another explanation for the increase of these disorders among clinic patients is that TS patients with a second disorder may be more likely to seek help from a physician than those with no other difficulties.

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This type of ascertainment bias was first described by Berkson (1946) and could account for the higher than expected rate of illnesses among TS patients observed by a number of investigators. However, this high rate is not seen by all researchers (Robertson *et al*, 1988). As TS becomes more widely recognised, it is possible that the early observations may prove to be false.

Rates of affective, anxiety and phobic disorders have been shown to be elevated among OCD patients (Rasmussen & Eisen, 1991). Thus, since the rate of OCD is elevated among first-degree relatives of TS probands, it is expected that the rates of these diagnoses would be increased among relatives of TS probands. However, accounting for the presence of OCD should result in a reduction of the rates of these other illnesses. The fact that none of these conditions was significantly elevated among the relatives without TS, CT or OCD suggests that these disorders are not genetically related to TS.

While our conclusions differ from those of Comings & Comings, examination of their data suggests that the results in both studies may be quite similar. In the Comings & Comings study (1990*c*), the rates of affective, anxiety and phobic disorders among first-degree relatives are not significantly higher than among controls. Only when these investigators combine all illnesses across all first-, second- and third-degree relatives do they find a significant increase among relatives of TS probands.

Recent family studies in psychiatry suggest that the underlying familial factors for the major psychiatric disorders are distinct (Tsuang, 1991). Furthermore, the evidence from family studies of anxiety disorders indicates that panic disorder and generalised anxiety disorder are not genetically related (Noyes *et al*, 1987) and that simple phobia is a highly familial disorder that does not transmit increased risk for other phobic or anxiety disorders (Fyer *et al*, 1990). Thus, there appears to be no justification for combining all disorders to estimate rates of illness. There is also no justification for combining the data from a genetic standpoint. First-, second- and third-degree relatives represent different genetic relationships. Combining them into a single category to estimate rates is not appropriate. Since the significantly increased rates among relatives reported by Comings & Comings appear to be an artefact of sample size obtained from combining all diagnostic categories across all relatives, it is not clear whether the data they present provide any evidence that other psychiatric disorders are variant expressions of TS.

The finding that other psychiatric disorders are not genetic variants of TS does not refute the clinical observation that many TS patients seen by physicians have significant psychiatric and behavioural difficulties. Chronic medical illness whether psychiatric or non-psychiatric can have major emotional and behavioural sequelae. Clearly, having one illness does not protect an individual from developing another. In fact, having one illness may increase the chance of having another. This does not imply that the two are genetically related. It simply implies that one illness can act as a risk factor for another. As stated earlier, if two conditions, A and B, are genetically related, then the rate of condition A should be elevated among the relatives of the probands with condition B. Furthermore, this increase should be observed among the relatives who do not have condition B. The data presented here are not consistent with that prediction. It is unlikely that disorders of anxiety and mood are variant expressions of the inherited TS spectrum. However, it is to be expected that patients with a chronic condition such as TS or OCD may experience depression and/or anxiety as a result of having a lifelong disorder. It is important that clinicians responsible for the care of TS patients be aware that these other conditions may be causing considerable distress for the TS sufferer.

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