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A Family Study of Gilles de la Tourette Syndrome

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Summary

Previous studies have demonstrated that Gilles de la Tourette syndrome (TS) is a familial disorder and that chronic tics (CT) and obsessive compulsive disorder (OCD) appear to be etiologically related to the syndrome. In the present study we report the results from a study of 338 biological relatives of 86 TS probands, 21 biologically unrelated relatives of adopted TS probands, and 22 relatives of normal subjects. The 43 first-degree relatives of the adopted TS and normal probands constituted a control sample. The rates of TS, CT, and OCD in the total sample of biological relatives of TS probands were significantly greater than in the relatives of controls. In addition, the morbid risks of TS, OCD, and CT were not significantly different in families of probands with OCD when compared to relatives of probands without OCD. These findings provide further evidence that OCD is etiologically related to TS.

Introduction

Gilles de la Tourette syndrome (TS) is a neuropsychiatric disorder with onset in childhood. There has been a renewed interest in the disorder over the last two decades, as evidenced by the publication of two recent volumes devoted entirely to research on TS (Cohen et al. 1988; Shapiro et al. 1988). In the original description (Gilles de la Tourette 1885), the syndrome was thought of as a familial disorder in which chronic tics (CT) represented a less severe but more prevalent form of the illness. However it was not until the late 1970's that several studies provided evidence for a positive family history of tics in families of TS probands (Eldridge et al. 1977; Golden 1978; Shapiro et al. 1978; Nee et al. 1980). All of these studies reported only frequencies of positive family history; no attempt was made to estimate the recurrence risk for either TS or CT in specific classes of relatives. Kidd and co-workers (1980) did attempt to estimate rates among relatives and demonstrated that the frequencies of TS and CT obtained by family history report were significantly elevated in families ascertained through a TS proband when compared to the prevalence in the general population. Furthermore, Pauls and co-workers (1981) found that the patterns of transmission of TS and CT within the families of TS probands were similar. These investigators also found that the rates of TS among siblings of TS probands were increased in those families where at least one parent had either TS or CT. These results suggested that CT (at least in the families of TS probands) was etiologically related to TS.

In all of the above studies, the investigators observed sex differences both in the frequency of TS (males being more frequently affected than females) and in the pattern of recurrence within families (the relatives of female probands being at greater risk for TS or CT than the relatives of males). Baron et al. (1981) incorporated this apparent sex differences into family analyses and reported that the transmission of TS and CT was consistent with a single-locus genetic model. However, the genetic parameters of this model predicted a very high rate of phenocopies. Thus, although the statistical evidence was significant, the predictions of the model suggested that the overwhelming majority of the affected relatives did not have the hypothetical susceptibility gene.

Kidd and Pauls (1982) incorporated both sex and severity differences into genetic analyses of the families studied by Pauls et al. (1981). They demonstrated that the pattern of transmission was consistent with genetic inheritance, but they were unable to distinguish between

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the hypotheses of polygenic and single-locus inheritance. Additional support for the hypothesis of genetic transmission and for a single-major-gene hypothesis has been reported by Comings et al. (1984), Devor (1984), and Price et al. (1988). All of these studies were done with family history data, which has been shown to underestimate the true rates of illness within families (Orvaschel et al. 1982; Pauls et al. 1984). Therefore, the estimates of the genetic model parameters obtained by these analyses may be inaccurate.

Only one family study has been reported in which all first-degree relatives were personally interviewed. Results from that study, which included first-degree relatives of 32 TS probands, suggest that (1) the rates of TS and CT are significantly elevated in the families of TS probands, (2) the rate of obsessive compulsive disorder (OCD) is significantly increased in relatives of TS probands regardless of whether the proband has OCD (Pauls et al. 1986*b*), and (3) the pattern of transmission in families of TS probands is consistent with an autosomal dominant hypothesis of inheritance and that a particularly good statistical fit of the predicted values from the model with observed family data is obtained when relatives with OCD are included in the analyses (Pauls and Leckman 1986).

The purpose of the present study was to extend the above findings from the first 32 families ascertained and interviewed (Pauls et al. 1984; Pauls et al. 1986*b*) by analyzing data from a larger sample of families. This paper will report the rates of TS, CT, and OCD in these families and examine hypotheses regarding the familial relationship of these diagnoses and the effect of gender on the rates of illness. Subsequent papers will report the results of analyses done to examine the relationship between Tourette syndrome and other neuropsychiatric diagnoses and whether the patterns of illness within these families are consistent with specific hypotheses of genetic transmission.

Subjects and Methods

The data presented in this report represent the total data set collected in a large family study of TS. As indicated above, several earlier reports (Pauls et al. 1984; Pauls et al. 1986*a;* Pauls et al. 1986*b;* Pauls and Leckman 1986) presented data on the 103 biological first-degree relatives of 27 TS probands and 19 nonbiological first-degree relatives of five adopted TS probands. The relatives of the adopted probands served as a control sample. This report includes data from 70 additional families. Of these 70 new families, 60 were ascertained through an individual with TS; the remaining 10 families were relatives of unaffected normal controls. The normal control probands were individuals who had been interviewed with a structured psychiatric interview as part of an epidemiological study and were determined to be free of any psychiatric illness. Their available first-degree relatives were included as part of the control sample. Among the 60 newly ascertained TS probands, one was adopted. Thus, the total sample (both the 32 families included in the earlier reports and the 70 newly ascertained families included in this report) consists of 360 biological first-degree relatives of 86 TS and 10 unaffected control probands and 21 nonbiological first-degree relatives of six adopted TS probands. The relatives of the unaffected probands and the adopted TS probands served as a control sample for the total data set. It should be noted that for six of the unaffected probands only one first-degree relative was interviewed. These relatives were chosen because of their availability.

All available relatives were interviewed using a precoded structured interview developed specifically for this study (Pauls and Hurst 1981). This interview grew out of a questionnaire first developed for an epidemiological study (Jagger et al. 1982). The most informative and reliable items from that questionnaire were combined with items from rating scales developed for clinical assessment of TS and related disorders (Harcherick et al. 1984). Over the 8 years of this study, the OCD section of the interview has become more detailed. Specifically, items which elicited information regarding the presence of obsessions and compulsions, the senselessness or repugnance of those symptoms, and resistance to the thoughts and behaviors were integrated. Two versions of the interview were developed. 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 child version of the interview for this study, 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 members of the Connecticut chapter of the Tourette Syndrome Association (TSA). Because there were comparatively few female members, a greater percentage of them were invited to participate to insure that a sufficient number of families of female probands would be available for data analyses. After ascertain-

ment, interviews were conducted to determine if the individual met DSM-III-R criteria 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 symptoms of TS, attention-deficient hyperactivity disorder (ADHD) and OCD, and an attempt was made to observe directly any symptoms that the child might manifest) and permission was obtained for medical records pertinent to the diagnosis of TS. After the diagnosis of TS had been established for the proband, a history on each adult first-degree relative was obtained and permission to contact all first-degree relatives was requested.

Once permission was granted to contact relatives, they were invited to participate in the study. After informed consent was obtained, all relatives over the age of 18 were interviewed directly about themselves. Following completion of the direct interview, family history data were collected from all informants about their adult first-degree relatives. A parent interview was obtained for each relative under the age of 18. Again, whenever, possible, the individual under 18 was interviewed directly regarding symptoms of TS, ADHD, and OCD. Family history information was not collected about individuals under age 18.

The family history information solicited about each adult relative was collected with a semistructured interview. This instrument included questions about the presence or absence of motor and phonic tics, questions about symptoms of other neuropsychiatric disorders, and items eliciting general descriptive information. Thus, two types of information were obtained about all participating individuals: (1) a direct structured interview and (2) personal history information from each of his or her adult relatives and/or spouses. For those individuals who were not interviewed directly, only personal histories were obtained.

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 (i.e., all assessments of the proband were done separately from the relatives). Best-estimate diagnoses were made independently by two investigators using DSM-III-R 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. Finally, 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 by following established procedures developed for other neuropsychiatric disorders (Leckman et al. 1982).

Diagnostic estimates were made for 381 first-degree relatives. There were 338 biological relatives of 86 TS probands, 21 nonbiological relatives of six adopted TS probands, and 22 biological relatives of 10 unaffected control probands. All of the 102 probands were interviewed directly, as well as 297 of 381 (78%) first-degree relatives. In all cases, direct interview data were collected from at least two individuals per family. For each noninterviewed adult relative, an average of two family history reports was obtained.

All analyses were done using the Statistical Analysis System (SAS) (SAS Institute 1985). Lifetable/survival analyses, as described by Thompson and Weissman (1979), were performed as implemented by the SAS's LIFETEST procedure (SAS Institute 1985) to compute age-corrected rates of illness and to make statistical comparisons of age-corrected distributions.

Results

The results from the two independent collection stages of the total sample are presented in table 1. Findings from the first stage, consisting of 27 nuclear biological families, were reported previously (Pauls et al. 1984; Pauls et al. 1986*a;* Pauls et al. 1986*b;* Pauls and Leckman 1986). In the second stage, 59 additional nuclear biological families were ascertained and interviewed. To determine whether the families collected in the two separate stages gave similar results, analyses were performed comparing the rates of TS, CT, and OCD in each sample with the rates of those diagnoses in the control relatives. As seen in table 1, the rate of TS in the first-stage sample is 10.7% compared to 0% in the control sample (Fisher's exact test, $P = .02$). For the category of CT it is important to note that in the first reports (Pauls et al. 1984; 1986*a;* 1986*b;* Pauls and Leckman 1986) only relatives with chronic multiple tics were included to obtain a rate of 18.5%. For the present report, all relatives with CT (those individuals with chronic single tics as well as those with chronic multi-

Table 1

Rates of TS, CT, and OCD among First-Degree Relatives: Comparison of Sample 1 and Sample 2

Diagnosis	Sample 1 (N = 103)	Sample 2 (N = 235)	Control (N = 43)
TS:			
Number affected	11	17	0
Uncorrected rates	.107	.071	0
Age-corrected rates	.112 ± .032	.076 ± .018	0
CT:			
Number affected	22	33	1
Uncorrected rates	.213	.140	.023
Age-corrected rates	.225 ± .043	.150 ± .024	.027 ± .027
OCD:			
Number affected	23	26	1
Uncorrected rates	.223	.111	.023
Age-corrected rates	.228 ± .047	.164 ± .025	.025 ± .025

ple tics) have been included. When relatives were chronic single tics are added to the first sample, the rate of CT increases to 21.3% compared to 2.3% in the control sample (Fisher's exact test, P = .002). The rate of OCD among the relatives in the first sample was 22.3% compared to only 2.3% in the control sample (Fisher's exact test, P = .001).

The results for the second-stage sample were remarkably similar to those just reported for the first-stage sample. When compared to the rates among the control relatives, the rates of TS (7.2%, Fisher's exact test, P = .05), CT (14.0%, Fisher's exact test, P = .02), and OCD (11.1%, Fisher's exact test, P = .05) were all significantly elevated. Thus, the overall results were the same for the two stages of data collection. In both samples the rates of TS, CT, and OCD are significantly higher than the rates of those diagnoses among the control relatives.

Comparing the rates of illness between the two samples of biological relatives of TS probands resulted in one apparent difference. While the rates of TS (10.7% vs. 7.1%, χ^2 = 0.71, P = .40) and CT (21.4% vs. 14.0%, χ^2 = 2.30, P = .129) were not significantly different, the rate of OCD in the first sample (22.3%) was significantly higher than the rate of OCD in the second-stage sample (11.1%) (χ^2 = 6.45, P = .011). Examination of the age distribution of the two samples reveals that the average age of first-degree relatives is lower in the second-stage sample. The mean age of relatives in the first-stage sample was 34.2 ± 15.8, whereas the mean age for relatives in the second-stage sample was 31.7 ± 18.9. Thus, age-corrected rates of illness were calculated for TS, CT, and OCD. As seen in table 1, the rates for TS and CT do not change appreciably after age correction. However, for OCD, the differences between samples are no longer as large and, furthermore, they are no longer significantly different. Thus, age-corrected rates of TS, CT, and OCD are presented in the remaining tables. Even though the rates for each diagnostic category were no longer significantly different, examination of table 1 suggests that the overall rate of TS, CT, and OCD combined may be significantly higher in sample 1 than in sample 2. To determine if this was true, age-corrected rates were calculated for individuals who had TS, CT, and/or OCD. This differs from the way the estimation was done in table 1 since the rates included there are rates of diagnosis and individuals may be included more than once if, for example, they have both TS and OCD. To determine if there were differences in the rates of ill relatives, analyses were done using affected relatives only once in the estimation of age-corrected rates. The rate of TS, CT, or OCD obtained in that way for sample 1 was .474 ± .052. The rate for sample 2 was .333 ± .034. These two rates are not significantly different. Since there were no significant differences between the age-corrected rates for two samples, the data have been combined for the remaining analyses reported.

The total sample contains 338 biological first-degree relatives of 86 TS probands, 22 biological relatives of 10 unaffected control probands, and 21 nonbiological relatives of six adopted TS probands. As indicated ear-

Table 2

Rates of TS, CT, and OCD among First-Degree Relatives in the Total Sample

A. Uncorrected Rates

	Biological Relatives of TS Probands		Relatives of Control Probands		
Diagnosis	Number Affected/Total	Rate	Number Affected/Total	Rate	*P*
TS	28/338	.083	0/43	0	.03
CT	55/338	.163	1/43	.023	.007
OCD	32/338	.095	1/43	.023	.09

B. Age-corrected Rates

Diagnosis	Biological Relatives of TS Probands	Relatives of Control Probands	*P*
TS	.087 ± .016	0	.02
CT	.173 ± .021	.027 ± .027	.004
OCD	.115 ± .019	.025 ± .025	.05

lier, all relatives of unaffected probands and adopted TS probands have been combined for the control sample. Of the 86 TS probands, 64 were male and 22 were female. The average age of male probands was 18.6 ± 10.8; female proband's average age was 27.1 ± 14.6. The 338 biological first-degree relatives of the 86 TS probands included 84 fathers (mean age = 47.8 ± 13.8), 85 mothers (mean age = 44.1 ± 12.3), 61 brothers (mean age = 19.5 ± 12.9), 83 sisters (mean age = 20.6 ± 15.3), 13 sons (mean age 14.3 ± 9.8) and 12 daughters (mean age 14.6 ± 9.5). The average age for all biological relatives was 32.6 ± 17.1. For the control relatives the mean age was 32.5 ± 19.0.

For the remaining analyses all relatives were grouped into mutually exclusive diagnostic categories. Rather than the number of diagnoses—a figure that would have been obtained by including relatives in more than one diagnostic category—the actual number of affected individuals is given. The following diagnostic hierarchy was used to assign affected status. If people met criteria for TS, they received that diagnosis regardless of whether they had concomitant OCD. Similarly for CT, if people met criteria for CT then they were given that diagnosis even if they had concomitant OCD. Thus, a person who was included in the OCD category had only OCD. This hierarchy can be represented graphically as TS > CT > OCD. Using this hierarchy results in a reduction in the number of individuals reported as having OCD since, of the 49 relatives with a diagnosis of OCD, 17 also have either TS or CT.

Table 2 presents the rates of TS, CT, and OCD without tics in the first-degree relatives of TS probands compared to the rates in the control relatives. All of the rates are higher in the biological relatives of TS probands than in the relatives of controls. The uncorrected rates of TS and CT are significantly greater in the biological relatives (Fisher's exact tests, $P = .03$ and $P = .007$), whereas the rate of OCD without tics among the biological relatives is marginally significant (Fisher's exact test, $P = .09$). After age correction, all differences are again statistically significant (see table 2). Since all diagnoses were assigned by raters blind to the diagnosis of the probands, these results support the hypothesis that TS, CT, and OCD are related and familial.

In a previous study (Pauls et al. 1986*b*), data were presented which were consistent with the hypothesis that at least some form of OCD was part of the TS spectrum. This conclusion was reached because the rate of OCD was higher among the biological relatives of TS probands when compared to a control sample and the general population and because the rates of OCD among first-degree relatives were not significantly different among relatives of probands with OCD (TS + OCD probands) and relatives of probands without OCD (TS − OCD probands). Table 3 presents the data from the current study separated with respect to the OCD diagnosis of the proband. Once again, there are no significant differences between relatives of TS + OCD and TS − OCD probands. Moreover, the overall rates of OCD (i.e., the rate of OCD regardless of whether the

Table 3

Recurrence Risks among First-Degree Relatives

Diagnosis	TS − OCD Probands		TS + OCD Probands	
	Number of Affected Relatives	Age-corrected Rate	Number of Affected Relatives	Age-corrected Rate
TS	19	.090 ± .020	9	.081 ± .026
CT	36	.176 ± .027	19	.170 ± .036
OCD	19	.104 ± .023	13	.136 ± .036
Total	74	.363 ± .034	41	.382 ± .048

NOTE.—There were 55 TS − OCD probands and 223 relatives; there were 31 TS + OCD probands and 115 relatives.

individual also has TS or CT) among the relatives of both types of probands are significantly greater than among the relatives of controls. The overall age-corrected rate of OCD is .157 ± .027 among relatives of TS − OCD probands and .200 ± .041 among relatives of TS + OCD probands. Both rates are significantly higher than the rate (.025 ± .025) among relatives of controls. Thus, the results give additional support to the hypothesis that some forms of OCD are etiologically related to the TS spectrum.

Early studies (Shapiro et al. 1978; Kidd et al. 1980; Pauls et al. 1981) reported a sex difference in the pattern of transmission within families such that relatives of females were at greater risk for TS and CT than relatives of males. To examine whether that sex effect was present in this sample, the data were separated on the basis of the sex of the proband. The results are presented in table 4. There are no significant differences in the rates of TS, CT, or OCD in the relatives of male and female probands.

Although there is no apparent effect of the sex of the proband, there is a sex difference in the frequency of TS, CT, and OCD among the relatives. Table 5 presents the actual numbers of affected male and female relatives. Male relatives are significantly more likely ($P < .0003$) to have TS than female relatives, while female relatives are more likely ($P < .04$) to have OCD without tics than male relatives. Although the rate of CT is higher among males than females, the difference is not significant ($P < .11$). Examining the specific types of relatives by sex reveals the same pattern. For example, the uncorrected rate of TS or CT among fathers is 38.1% compared to only 17.7% of mothers. On the other hand, the rate of OCD among fathers is only 6.0% compared to 15.3% for mothers. For siblings, 24.6% of brothers and 14.5% of sisters have TS or CT, while 6.6% of brothers and 12.1% of sisters have OCD.

Discussion

Results from our previous small family study of TS (Pauls et al. 1984; Pauls et al. 1986*b*) were supported

Table 4

Recurrence Risks among First-Degree Relatives

Diagnosis	Male Probands		Female Probands	
	Number of Affected Relatives	Age-corrected Rate	Number of Affected Relatives	Age-corrected Rate
TS	15	.069 ± .017	13	.123 ± .032
CT	37	.176 ± .026	18	.168 ± .036
OCD	22	.120 ± .024	10	.105 ± .032
Total	74	.358 ± .034	41	.392 ± .048

NOTE.—There were 55 male probands and 226 relatives; there were 31 female probands and 112 relatives.

Table 5

Recurrence Risks among First-Degree Relatives

Diagnosis	Number of Affected Males (Rate [%])			Age-corrected Rate for All Males	Number of Affected Females (Rate [%])			Age-corrected Rate for All Females
	Fathers (N = 84)	Brothers (N = 61)	Sons (N = 13)	(N = 158)	Mothers (N = 85)	Sisters (N = 83)	Daughters (N = 12)	(N = 180)
TS	10 (11.9)	7 (11.5)	5 (38.5)	.150 ± .030	1 (1.2)	4 (4.8)	1 (8.3)	.034 ± .014
CT	22 (26.2)	8 (13.1)	1 (7.7)	.215 ± .034	14 (16.5)	8 (9.6)	2 (16.7)	.138 ± .024
OCD	5 (6.0)	4 (6.6)	0	.072 ± .023	13 (15.3)	10 (12.1)	0	.152 ± .030
Total	37 (44.0)	19 (31.1)	6 (46.2)	.430 ± .042	28 (32.9)	22 (26.5)	3 (25.0)	.318 ± .037

with a larger series of families ascertained through TS probands. The patterns in the two samples were remarkably similar. The rates of TS, CT, and OCD were significantly increased in both samples when compared to a control sample, and the age-corrected rates of illness were not different between the two independent samples. Because the rates of TS, CT, and OCD did not differ significantly between the two samples, they were combined. The total sample should give more precise estimates of the morbid risks of TS, CT, and OCD. Furthermore, the total sample was used to examine more rigorously several hypotheses regarding familial patterns of the disorder and relationships between TS, CT, and OCD.

Our current findings support results of our earlier study using similar data collection methods. First, the rates of TS and CT are significantly elevated in biological families of TS probands when compared to relatives of controls; second, OCD appears to be related to the TS spectrum since the morbid risk of OCD among relatives of TS probands is also significantly higher than the rate in controls. Moreover, the sex differences reported earlier (Pauls and Leckman 1986), with male relatives showing higher rates of TS and female relatives showing higher rates of OCD without tics, are still observed. These findings have been supported by results from another study. Green and Pitman (1986) studied 16 (eight male and eight female) individuals with OCD. They interviewed all probands to confirm the diagnosis of OCD and in the course of that interview obtained family history data for the presence of OCD and tics among the relatives. Eight of 16 OCD probands reported a positive family history for tics. It is striking that six of those eight probands were females. Thus, a female with primary OCD was more likely to have a positive family history of tics. This pattern is consistent with our findings in that a female relative of a TS proband is more likely to have OCD without tics. Results from both studies suggest that there may be a sex-specific expression of the TS/CT/OCD spectrum. Certainly, these findings warrant further study of both TS and OCD families so that it will be possible to examine more rigorously the hypotheses related to these apparent sex differences.

The results from the data presented here could be spurious if the families of individuals who join the TSA are in some way different from families of randomly selected TS probands. However, it is unlikely that this is the case. First, the profile of patients selected from the TSA membership for inclusion in a study by Jagger et al. (1982) did not differ significantly from clinic sam-

ples (Shapiro et al. 1978). Second, the analyses reported by Pauls et al. (1981) demonstrated that the familial patterns in families of clinic patients were not significantly different from patterns observed in the families of patients ascertained through the TSA. Of course, these results do not demonstrate that the families of clinic patients or the families of TSA members are representative of randomly selected TS families from the general population. It may very well be possible that those individuals who seek help or join an organization such as the TSA are more likely to be from families where the condition is familial. It would be better to obtain families from the general population. In order to obtain such a randomly selected sample of families, given the current estimate of the population prevalence of TS, over 200,000 individuals would have to be screened to determine if they met criteria for TS. While such a sample would be preferable to a sample obtained through a clinic or a membership organization, it is not economically feasible to collect such a sample. Thus, the sample of patients studied here represents the best alternative.

In subsequent studies of TS and OCD it may be important to consider different diagnostic hierarchies for relatives in families of TS and OCD probands. Given the symptomatology, it would seem reasonable to consider OCD a more severe disorder than CT alone. Of course, not all relatives with OCD are severely affected, and the difference in severity between CT and some obsessions and compulsions is difficult to quantify.

It is of interest that when only individuals with TS or OCD were included as affected in the estimation of morbid risk (individuals with CT were included as unaffected), the overall rates of illness among male and female relatives were virtually identical, albeit the rate of TS was higher in males and the rate of OCD was higher in females. These results suggest that the predominant symptoms of the syndrome in males might be motor and phonic tics, whereas the most important clinical features for females might be obsessions and compulsions.

Although there are sex differences in the rates of illness among the relatives, the sex of the proband appears to have no effect on the rates of illness in first-degree relatives. In several early studies (Shapiro et al. 1978; Kidd et al. 1980; Pauls et al. 1981) it was proposed that the sex differences observed for the frequency of TS and CT in the general population were related to the transmission of the trait. These studies reported higher rates of TS and CT among relatives of females than among relatives of males. Our current data do not support this hypothesis. There are no significant differences in rates of illness observed between the relatives of male and female probands. It may be that the difference between our current study and the earlier ones is due to the different data collection methodologies employed. All of the previous results were based on family history data. That is, all information about a family was collected from one or two informants. In the present study most of the first degree relatives were directly interviewed. It has been shown that direct interview information is more reliable than family history data (Orvaschel et al. 1982; Pauls et al. 1984); hence, the sex differences observed among the relatives of males and females in the early studies could have been due to biased reporting of symptoms in relatives.

A caveat is in order in the interpretation of the overall results presented here. In general, the diagnosis of OCD is complicated and is often difficult to make from responses to items in a structured interview. Much work has recently been done to develop more valid and reliable measures for the assessment of OCD (Goodman et al. 1986; Kim and Dysken 1988). These measures, together with information from other sources (family informants and medical records) should result in more valid and reliable diagnoses.

The diagnostic data collected in this study used early versions of some of the recently developed measures and collected information from multiple sources. In addition, control families were included in the study so that all diagnoses of relatives were made by clinicians blind to the diagnosis of the proband. This combination of methods, the use of direct structured interviews, family history data, and blind clinical assessment increases the validity of the diagnoses for the relatives. An advantage of this approach over self-administered scales or structured interviews alone is that family members can corroborate the level of impairment crucial in determining the diagnosis of OCD. In this respect, the best-estimate method provides some protection against inflated frequencies by providing information useful in assessing the duration and degree of role impairment. In addition, by having a control sample and including data from these control relatives in such a way as to keep the diagnostician blind to the diagnosis of the proband and to the type of family (whether adopted or biological) from which the relative came, it is possible to determine what the rate of a specific diagnosis is among the relatives of TS and control probands and to compare directly the two types of families.

The data presented in this study strongly suggest a relationship between TS and OCD. However, this does

not imply that all of OCD is etiologically related to TS. Results from a small family study of OCD (Pauls et al. 1988*b;* Pauls 1989) show that not all families of OCD probands have relatives with tics. In fact, only 20%–30% of patients have a positive family history of tics. Thus, it seems quite possible that OCD is etiologically heterogeneous. These findings should prompt a reevaluation of some of the previous findings with respect to the underlying pathophysiology of both OCD and TS.

Our current results also suggest additional studies designed to examine the spectrum of behaviors which might be related to TS and/or OCD. What is evident from the work presented here is that TS family members do have sufficient symptoms to meet criteria for OCD. However, it is not clear if they have the same disorder as individuals seen for OCD in psychiatric clinics. Additional work is needed to evaluate carefully the spectrum of behaviors which may represent variable expression of TS, OCD, or both. It is necessary to evaluate the pattern of relationship of other diagnoses to this spectrum. Preliminary analyses suggest that the rates of other psychiatric diagnoses are not significantly increased among the relatives of the TS probands in this study (Pauls et al. 1988*a*). However, as illustrated in our earlier work with TS and ADHD (Pauls et al. 1986*a*), overall rates can be misleading, and more thorough analyses are required to examine specific patterns of illness within families and the possible cooccurrence of a specific diagnosis and the TS spectrum. In our previous analyses, the rate of ADHD was not significantly increased in the families of all TS probands. However, in the families of probands with TS and ADHD the rate of ADHD was increased. Furthermore, it was necessary to examine the cooccurrence of ADHD, TS, and CT to determine if ADHD was also part of the TS spectrum. Additional analyses examining specific patterns of relationships of other psychiatric illness to the TS spectrum are underway and will be reported in subsequent manuscripts.

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