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Brief Communication

Complex Segregation Analysis of Gilles de la Tourette Syndrome: Further Evidence for a Major Locus Mode of Transmission

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SUMMARY

A sample of 35 published pedigrees of Gilles de la Tourette syndrome is studied using complex segregation analysis with pointers. Results indicate the presence of a rare, semidominant, incompletely penetrant allele leading to affection. This result is consistent with that previously reported by Comings et al. on a larger, independent sample.

INTRODUCTION

From its first full description in 1885 [1], Gilles de la Tourette syndrome of multiple motor and vocal tics has generated great interest among psychiatrists and human geneticists. Although initially thought to be an inherited disorder, a psychodynamic interpretation of Tourette syndrome was favored until the discovery, only 2 decades ago, of the effectiveness of haloperidol in treating a majority of affected individuals [2–4]. As a result of this discovery, the possibility of an inherited defect in Tourette syndrome has again been entertained. Numerous recent family studies have served to confirm this interpretation [5–7]. However, these studies have been consistently frustrated in attempts to define a precise mode of transmission of the defect.

Comings et al. [8] recently proposed a consistent model for the transmission of Tourette syndrome and etiologically related multiple tics. Using complex segregation analysis with "pointers," they suggest that a single major autosomal locus modified by a small multifactorial background effect accounts for the majority

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of observed family resemblance. The locus is characterized by the presence of a rare, semidominant, incompletely penetrant allele (termed *Ts* by Comings et al.) leading to affection. In the present paper, a sample of 35 published pedigrees of Gilles de la Tourette syndrome is evaluated via complex segregation analysis with pointers. This evaluation is carried out under the same ascertainment and prevalence conditions employed by Comings et al. The results of my study confirm those previously reported in implicating the presence of a rare, semidominant, incompletely penetrant allele in Tourette syndrome.

MATERIALS AND METHODS

Eldridge et al. [9] and Wassman et al. [10] reported on a total of 35 pedigrees of Tourette syndrome. The nuclear families of the probands in their pedigrees were coded for use by the FORTRAN segregation analysis program POINTER [11]. An additional 32 nuclear families were selected for analysis using "pointers" according to the Edinburgh Cytogenetics Registry sequential sampling scheme [12]. Under this scheme, the nuclear family of any first-degree relative of a proband is selected provided that that relative is also affected. Families meeting this criterion are included regardless of the affection status of any other family member. Conversely, families are excluded regardless of the affection status of any other family members if the eligible first-degree relative of the proband is unaffected. Subsequent extensions to second- and third-degree vertical and collateral relatives of the proband are made under the same conditions.

To avoid introducing an ascertainment bias as a result of the extension rule, the "pointee," who must be affected by definition, is designated as a secondary proband (J. M. Lalouel, personal communication, 1983). Further, criteria specified by Eldridge et al. [9] for the inclusion of a family in their study necessitated designation of secondary probands in those pedigrees at the outset. Thus, some of their 21 pedigrees contained three or more probands if extended. Since Tourette syndrome is known to be rare, the ascertainment probability for the primary probands was taken to be $\pi = .001$. An ascertainment probability of $\pi = 1.000$ was assigned to secondary (pointee) probands when pedigrees were extended. However, as noted by Comings et al., the values assigned to the ascertainment probability of the secondary probands had little effect on either parameter estimation or hypothesis testing.

Segregation analysis was carried out under the general mixed model of transmission of Morton et al. [13, 14], which allows for the simultaneous effects of a major autosomal locus and a multifactorial background. The full mixed model is specified by six parameters, namely, u, the mean value of the trait; V, the variance of the trait; d, the degree of dominance at the major locus, if present; t, displacement between major locus homozygotes in standard deviation units; q, the frequency of the allele leading to affection; and H, the multifactorial background effect. Lalouel et al. [15] showed that this model is applicable to a dichotomous trait like Tourette syndrome when u and V are restricted to the values zero and one, respectively.

Tests of hypotheses regarding alternative modes of transmission are performed against the general mixed model using likelihood ratio criteria.

RESULTS

Hypothesis tests of alternative transmission models and their associated parameter estimates are presented in table 1 for both nuclear families of probands and pedigrees extended via pointers. When only nuclear families of probands are considered, the hypothesis that there is no familial transmission of Tourette syndrome may be rejected against the general mixed model ($\chi^2_4 = 13.658$, $P < .01$). However, neither the hypothesis of multifactorial inheritance with no major

TABLE 1

PARAMETER ESTIMATES AND HYPOTHESIS TESTS FROM SEGREGATION ANALYSIS OF NUCLEAR FAMILIES AND EXTENDED PEDIGREES OF 35 PROBANDS WITH TOURETTE SYNDROME

COMPONENT OF TRANSMISSION		NUCLEAR FAMILIES					EXTENDED PEDIGREES				
		MODEL PARAMETERS*				Likelihood	MODEL PARAMETERS*				Likelihood
Major locus	Multifactorial	d	t	q	H	$-2\ln(L)+c$	d	t	q	H	$-2\ln(L)+c$
No	No	...	...	...	...	13.658†	...	...	...	...	137.215‡
No	Yes	...	...	...	.9943	4.005	...	...	...	.9802	9.860§
Yes	No	1.00	3.1993	.0153	...	0.026	.3037	7.0953	.0422	...	0.007
Yes	Yes	.8498	3.8739	.0149	.0021	0	.3167	6.4062	.0422	.0503	0

* All parameters estimated with $u = 0$ and $V = 1.0$ at an assumed lifetime risk of $K_p = 0.75\%$ (1.2% in men and 0.3% in women).
† $P < .01$.
‡ $P < .001$.
§ $P < .05$.

TABLE 2

ESTIMATED GENOTYPE PENETRANCES (A) AND CONDITIONAL AFFECTION PROBABILITIES (B) FOR TOURETTE SYNDROME BASED UPON THE GENERAL MIXED MODEL VALUES

SEX	GENOTYPE*		
	Ts/Ts	*Ts/ts*	*ts/ts*
A. Probability of affection given the genotype			
Male	.999	.125	.001
Female	.999	.015	.000
B. Probability of the genotype given affection			
Male	.148	.844	.008
Female	.592	.407	.000
Total	.237	.757	.006

* Genotype designations following Comings et al. [8].

locus effect ($d = t = q = 0$) nor the hypothesis that there is a major locus with no multifactorial background ($H = 0$) can be rejected.

When the pedigree extensions using pointers are included in the analysis, rejection of the hypothesis that there is no familial transmission becomes stronger against the general mixed model ($\chi^2_4 = 137.215$, $P < .001$). In addition, the alternative hypothesis that there is multifactorial transmission with no major gene effect is also rejected ($\chi^2_3 = 9.860$, $P < .05$). Conversely, accepting that there is a major gene effect but with no contribution from the multifactorial background cannot be rejected. This result is not surprising given the small estimated contribution from the multifactorial background in the general mixed-model solution shown in table 1.

As a consequence of hypothesis testing procedures under the unified model of segregation analysis, the possibility of ascertainment bias due to the pedigree extension rule may be examined by reestimating the major locus parameters plus the "tau" transmission probabilities [16]. Such a test is a sensitive indicator of ascertainment bias since there will be a significant distortion of the segregation probabilities if such bias exists [17]. The sufficient test is against the heterozygote segregation probability $\tau_2 = .50$ [17, 18]. An estimated value of $\tau_2 = .3272$ from the extended pedigree data was found not to be significantly different from the expected value ($\chi^2_1 = 3.188$, not significant). Thus, the present evidence favors a model for the transmission of Gilles de la Tourette syndrome in which the primary source of familial resemblance is a major autosomal locus with a rare ($q = .01-.05$), semidominant ($d = .30-.85$) allele leading to affection. The genotypic penetrance estimates for the major locus from the general mixed-model solution for the extended pedigree data are given in table 2. In addition, it can be seen in table 2 that a very small proportion (0.6%) of the observed cases in this sample are assigned to phenocopies.

DISCUSSION

Complex segregation analysis of 35 published pedigrees of Gilles de la Tourette syndrome has been carried out using the method of pointers [12]. The prevalence and ascertainment conditions specified for this analysis are the same as those reported by Comings et al. [8] for their study of Tourette syndrome. Results of my present study agree with those of Comings et al. in implicating a major locus mode of transmission of the disorder. Naturally, given the smaller size and different composition of the published pedigree data used here, the specific parameter estimates obtained in this study do not agree with those obtained by Comings et al. (e.g., $d = .6056$, $t = 4.7326$, $q = .0047$, $H = .0094$). However, the general characteristics of the major locus are similar. Both studies find evidence favoring a rare, semidominant major gene with incomplete penetrance of the three genotypes. Moreover, the contribution of multifactorial background is uniformly negligible.

The only substantial difference between the two studies is the very much smaller proportion of phenocopies estimated here. Comings et al. note that about one-third (35%) of their cases were assigned to phenocopies while in my study less than 1% were. This difference arises, of course, from the composition of the two samples used. The Comings et al. sample allowed only 35 additional nuclear families to be included under the Edinburgh scheme out of a total of 242 pedigrees, whereas the present 35 pedigrees permitted inclusion of 32 additional nuclear families. Since these additional families are all included in the respective studies via pointers, there is a considerably larger proportion of "high-density" (relative to the rarity of the disorder) families in my study. Thus, it is far less likely that single-case families would be assigned to phenocopies than to incomplete penetrance in the parents in this study. In any case, since the primary objective of segregation analysis is hypothesis testing regarding the mode of inheritance of a particular phenotype, such sample-size and composition-dependent discrepancies in parameter estimation should be considered trivial.

Finally, it must be remembered that the evidence favoring a major locus mode of transmission of Gilles de la Tourette syndrome offered by Comings et al., and corroborated here, is a statistical demonstration based upon analysis of family phenotype data. This does not diminish the significance of these results, however, since they will provide the necessary impetus for attempts to more definitely characterize the locus. Proof of the existence of the major gene locus must ultimately come from biochemical and linkage studies of those families indicated by individual likelihood ratios as being those in which this gene is most likely to be segregating.

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