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Vertical transmission of susceptibility to stuttering with sex-modified expression

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ABSTRACT **Stuttering is not usually considered genetic, although it has long been known to be familial. Data collected on 2035 relatives of 397 unrelated adult stutterers confirm and quantify the strong familial concentration. Our analytic approach to these family data, one that does not require specification of a genetic hypothesis, shows that stuttering among relatives occurs in a pattern indicating vertical transmission of a susceptibility to stuttering with sex-modified expression. Although simple Mendelian hypotheses are not sufficient to explain the observed pattern of stuttering in families, more complex genetic models can explain the pattern. In the past, such evidence has been considered sufficient, because it does not preclude the possibility of cultural transmission. However, certain cultural transmission hypotheses previously proposed for stuttering are excluded by these data. The findings in this study support a growing opinion among speech pathologists that most stuttering is a genetically inherited neurologic disorder.**

Stuttering is a readily identifiable disorder of speech characterized by frequent interruptions or blocks in the smooth transition from the production of one sound to the production of the subsequent sound. The primary defect in stuttering, the block, is manifest as a repetition or prolongation of a sound, or as a silent gap in speech (1, 2). A layman's recognition of these symptoms and judgement of the presence of stuttering correspond closely to a speech pathologist's. The block is believed to reflect a basic organic problem (1, 2). Aberrant laryngeal activity (3) and deviant vocal tract events (4) during a stuttering moment may be reflections of this basic organic problem. Secondary aspects of stuttering, such as the severity, are definitely exacerbated by stressful environments. Concomitant behaviors, such as grimaces, eye blinks, and shoulder jerks, may be present as the result of operant learning. About 5% of males and 2% of females stutter for at least six months sometime during childhood (5), but many affected children recover before they become adults and the adult prevalence is not precisely known. Although stuttering is a common disorder, it has an unknown and probably complex etiology.

The probable organic basis and the well-recognized tendency to "run in families" indicate that the etiology of stuttering may have a genetic component. Although there is no simple Mendelian pattern of inheritance, recent analyses have shown that the frequencies of relatives who stutter could be explained by genetic hypotheses. Both polygenic and single-major-locus models have been shown to be compatible with the data (5–9). However, compatibility with two quite different hypotheses cannot be considered strong evidence in favor of a genetic etiology, nor do any analyses eliminate the possibility of cultural inheritance. These considerations motivate the use of different analytic approaches. Methods are needed that are not based on etiologic hypotheses but will allow the testing of factors that might be incorporated into more rigorous specific models of transmission. The logistic model, one of the class of log-linear models, seems an appropriate analytic method because it allows the testing of effects of possibly relevant factors on the familial frequency of stuttering. Moreover, while the logistic model is not an etiological model, it can reveal patterns in the familial occurrences and thereby allows broad inferences about etiology. This is especially useful in the initial exploratory analysis of family data. Specifically, our analyses of data on stuttering show that susceptibility to stuttering is vertically transmitted and has sex-modified expression. These findings are consistent with, but do not prove, genetic transmission.

METHODS

Selection Criteria for Probands. The families studied were ascertained through a single adult family member, the proband, previously diagnosed as a stutterer by a trained clinician. Most adult probands were referrals by speech pathologists in local speech clinics or intensive therapy programs in California, New York, and Virginia. A small number were contacted through local chapters of the Council of Adult Stutterers and various third-party referrals. We excluded probands with mental retardation, epilepsy, cerebral palsy, or indications of any neurological disfunction. We included only probands of European descent with English as a first language. These criteria reduce cultural differences and genetic heterogeneity. Probands were accepted into the study without regard to family size or our knowledge of stuttering in the remainder of the family. The manner in which we obtained our sample corresponds closely to single selection with an ascertainment probability of close to zero. Most (≈95%) of the stutterers who were enrolled in the intensive therapy programs agreed to participate in our study. The other adult probands represent a small, but unknown, fraction of potential subjects contacted through the other sources, primarily the Councils of Adult Stutterers.

Data Collection. We collected detailed pedigrees of every proband, including information on sex and speech patterns for every family member. Though some pedigrees were more extensive than others, all pedigrees included all first-degree relatives (parents, siblings, children); initial analyses are limited to that subset of the data. A relative was considered to be or have been a stutterer whenever the proband identified him/her as such based on either first-hand knowledge or information from other relatives. These data were obtained in two ways. Whenever possible we interviewed probands directly. When this was not possible (≈50% of the sample) the probands completed a self-report questionnaire identical to the interview form. Any

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questionnaire responses that were ambiguous or contradictory were clarified by letter or telephone follow-up.

Statistical Methods. The dependent variable in our analysis was the binary response variable created by classifying each relative as having ever stuttered (affected) or having never stuttered (unaffected). Relatives were grouped into a multiway contingency table by the factors in Table 1. These qualitative classifications were chosen because previous work had indicated such divisions were meaningful [e.g., sexes of proband and relative (6, 10)] and because of their obvious relevance to vertical transmission hypotheses (e.g., type of relative and parental effects). In preliminary analyses an additional classification was used to test for differences between the two major methods of ascertainment: adults ascertained through intensive therapy programs and other adults. These two ascertainment groups had no significant differences in the frequencies of affected relatives.

The logistic model describes the frequency of affected individuals (θ) as: $\theta = e^y/(1 + e^y)$. y can be thought of as a dependent variable in a multiple linear model, $y = \beta_1 + \beta_2 x_1 + \beta_3 x_2 + \ldots$, with a finite number of unknown parameters, the β_i. The number of unknown parameters is determined by the number of independent factors and interactions between these factors hypothesized to have some effect upon the frequency of affected individuals. Specifically, we used $y = \mu \pm a \pm b \pm c \pm d \pm e \pm \ldots$, in which μ represents the overall mean frequency in the contingency table, a–e represent the parameters in Table 1, and the sign of each is that appropriate for the specific state of the classification variable as defined in Table 1. Thus, μ and a–e correspond to the β_i and the x_i are represented by ± 1 for the dichotomous classifications. Other parameters are added as necessary for any interaction terms considered. The saturated model with all interactions has 32 parameters. The unknown parameters can be estimated by using either maximum likelihood methods or weighted least squares [the empirical model of Cox (11)]. By use of asymptotic theory we have available three different methods for approximating the significance of a factor: standard errors of the empirical model estimates, standard errors of the maximum likelihood estimates, and likelihood ratio tests between a specific hypothesis and one of its subhypotheses.

Table 1. Dichotomous classification variables used for final tabulation of the occurrences of stuttering among siblings and children of adult stutterers

Parameter	Classification and associated sign
μ	Baseline or intercept
a	Sex of proband
	+, male
	−, female
b	Sex of Relative
	+, male
	−, female
c	Paternal stuttering
	+, father ever stuttered
	−, father never stuttered
d	Maternal stuttering
	+, mother ever stuttered
	−, mother never stuttered
e	Type of relative
	+, sibling
	−, child

In the analysis each classification variable became a single parameter with sign dependent on specific alternative as indicated.

Any mathematical model that attempts to describe the stochastic relationship between affected individuals and possible causal factors must include two types of assumptions: etiological and statistical. We have attempted to choose a model with minimal dependence upon etiological hypotheses. The statistical assumptions required are discussed in full by Cox (11) (see also ref. 12). One that is of particular importance in this analysis is that, within a cell of the multiway contingency table, each observation of the binary variable is an independent observation of a single logistic function. Some cells may contain observations from several different distributions. For example, offspring of the probands are not distinguished by whether or not the nonproband parent was also a stutterer. Consequently these cells do not separate the various parental mating types. If genetic transmission is involved, we do not expect a one-to-one relationship of genotypes to phenotypes and so even a single mating type would be genotypically heterogeneous and different sibships would represent samples from different multinomial distributions.

No solution to this problem is entirely adequate. Exact definitions of the expected frequencies within each family can be calculated if a specific etiological hypothesis is assumed. However, this is precisely what we wish to avoid at this stage of analysis. For the moment, we shall assume our data can be adequately represented by this model. Our purpose is to gain insight into factors that should be incorporated into a rigorous etiological model and a strong emphasis on exact significance tests is not necessary. The spirit of the analysis is to explore, not to explain, etiology.

RESULTS

We studied the families of 294 adult male probands and 103 adult female probands, with a total of 2035 first-degree relatives (parents, siblings, offspring). The samples obtained by the two methods of ascertainment were not significantly different and have been pooled. Table 2 contains the observed distribution of affected and unaffected siblings and offspring tabulated according to the classifications in Table 1. Because some cells have no observations, we cannot consider the saturated model. Likelihood ratio tests start with the model with main effect and all two- and three-way interactions (26 parameters) and compare it with subhypotheses; no interaction terms are statistically significant ($\chi^2 = 22.6$, 20 degrees of freedom). Likelihood ratio tests also show that each main effect is separately significant at $P \leq 0.05$ except for paternal stuttering, for which $P = 0.074$ ($\chi^2_1 = 3.2$). All main effects, including paternal stuttering, are individually significantly different from zero at $P < 0.05$ by at least one method. Maximum likelihood estimates for the parameters in the model with all main effects are given in Table 3. Though the magnitude of the overall effect of paternal stuttering is relatively large, its less clear significance is attributable to the higher variance of that effect over the different parts of the table. The expected values calculated for the model with no interactions by using the maximum likelihood estimates in Table 3 are given in Table 2 for convenient comparison with the observed. The agreement between observed and expected is quite good ($\chi^2 = 11.63$, 12 degrees of freedom).

DISCUSSION

These analyses show that the classifications chosen (Table 1) result in a contingency table in which different subgroups of relatives do have significantly different risks of having ever stuttered. None of the interaction terms was significant, so the pattern can be summarized by the directions and magnitudes of the factors in Table 3. As elaborated below, we interpret the

Table 2. Observed and estimated frequencies of affected relatives of adult stutterers

Parents who stutter		Relative type: Sibling, Male (brother) No. individuals	%	Sibling, Female (sister) No. individuals	%	Offspring, Male (son) No. individuals	%	Offspring, Female (daughter) No. individuals	%
				Male probands (n = 294)					
Neither	Obs S	54	18.0	4	1.8	22	22.2	9	9.2
(n_N = 229)	Est	46.4	15.5	11.1	4.9	21.7	22.0	7.2	7.3
	n	300		226		99		98	
Father	Obs S	14	25.5	7	11.5	7	35.0	2	9.5
(n_F = 52)	Est	14.9	27.0	5.7	9.4	7.3	36.3	2.9	13.8
	n	55		61		20		21	
Mother	Obs S	3	33.3	0	0.0	0	0.0	0	0.0
(n_M = 11)	Est	2.3	25.6	0.4	8.8	1.4	34.6	0.4	12.9
	n	9		5		4		3	
Both	Obs S	0	0.0	1	33.3	0		0	
(n_B = 2)	Est	0.8	41.0	0.5	16.4		51.7		23.1
	n	2		3		0		0	
Total	Obs S	71	19.4	12	4.1	29	23.6	11	9.0
(n = 294)	n	366		295		123		122	
				Female probands (n = 103)					
Neither	Obs S	13	17.8	9	9.5	12	31.6	4	13.3
(n_n = 71)	Est	17.0	23.3	7.5	7.9	12.1	31.9	3.5	11.6
	n	73		95		38		30	
Father	Obs S	8	32.0	6	21.4	5	55.6	1	12.5
(n_F = 20)	Est	9.5	38.1	4.1	14.8	4.4	48.6	1.7	21.0
	n	25		28		9		8	
Mother	Obs S	3	50.0	1	11.1	2	40.0	2	33.3
(n_M = 11)	Est	2.2	36.4	1.2	13.8	2.3	46.8	1.2	19.8
	n	6		9		5		6	
Both	Obs S	0		1	100.0	0	0.0	1	100.0
(n_B = 1)	Est		53.6	0.2	24.5	0.6	64.0	0.3	33.3
	n	0		1		1		1	
Total	Obs S	24	23.1	17		19	35.8	8	17.8
(n = 103)	n	104		133		53		45	

The data on stuttering among 1241 siblings and children classified according to the factors in Table 1, which include parental stuttering. The observed numbers (Obs S) are the contingency table analyzed. The numbers of families by sex of proband and parental types are given in parentheses. For convenience, the expected values (Est) based on the best final model (Table 3) are also included here. n is the number of probands or relatives of each type.

pattern of risks as indicating vertical transmission of susceptibility to stuttering with sex-modified expression.

The baseline frequency of stuttering for an individual in the table—sibling or child of a known stutterer—can be calculated from the estimate of the parameter μ. This frequency, $\theta = 0.23$, is at least 4 times the estimated prevalence of stuttering in the general population: with at least one stutterer in the family, an individual is at greater risk of stuttering than an individual drawn at random from the general population. Parental stuttering had a positive effect on the risk: with at least two known stutterers in the family (proband and at least one parent) there is a large increase in frequency of remaining relatives who stutter. The three-generation data presented show that the presence of stuttering in a grandparent (the proband's parent) even increases the frequency of stuttering in the grandchild (proband's offspring). The increased risk to a relative of a proband and especially the increased risk if a parent also is a stutterer indicate that vertical transmission of stuttering does occur.

The statistical significance of the sex-of-proband and sex-of-relative classifications supports a model of transmission of susceptibility with sex-specific thresholds for expression. The sex-of-relative effect, showing that males run over twice the risk of females, indicates that whatever contributes to susceptibility to stuttering, more would need to be present for a female to surpass the stuttering threshold than for a male to cross the threshold. The higher frequencies of affected relatives of female stutterers support hypotheses in which the susceptibility factors are transmitted within families: more factors promoting stuttering are required to make a female stutter; if those factors are transmitted, families of female stutterers would have more factors and hence more stutterers.

Demonstrating vertical transmission of susceptibility to stuttering does not specify mode of transmission. It is a necessary prerequisite of Mendelian transmission but cannot prove that it is genetic. Indeed, simple modes of inheritance are not compatible with the data. The high frequency of affected father–affected son pairs excludes X-linked inheritance (see Table 2). The frequencies (Table 2) and published pedigrees

Table 3. Maximum likelihood estimates of the parameters for the logistic model with no interactions included

	Parameter	Maximum likelihood estimates: Value	Maximum likelihood estimates: Standard error	Associated ratio of odds of stuttering
μ		−1.20	0.18	—
a	Sex of proband			
	Female	0.25	0.09	$e^{0.50} = 1.65$
	Male	−0.25		
b	Sex of relative			
	Male	0.63	0.09	$e^{1.26} = 3.53$
	Female	−0.63		
c	Paternal stuttering			
	Present	0.32	0.17	$e^{0.64} = 1.90$
	Absent	−0.32		
d	Maternal stuttering			
	Present	0.35	0.09	$e^{0.70} = 2.01$
	Absent	−0.35		
e	Type of relative			
	Child	0.22	0.09	$e^{0.44} = 1.55$
	Sibling	−0.22		

Also given for each of the classification variables is the ratio of the odds of stuttering in the cell with the positive classification to the odds in the cell with the negative for any combination of other classifications. In the logistic model, this ratio is a function of the single classification variable being considered, e^{2c} for factor *c*. Thus, the odds of a sibling or offspring stuttering are 1.9 times greater if the father ever stuttered than if he never stuttered.

(9, 10) eliminate fully penetrant autosomal inheritance, both dominant and recessive. However, sophisticated genetic models with incomplete penetrance appear to be compatible with the data. Even the effect of a stuttering grandparent on the risk to the grandchild is consistent with genetic models of complex traits. Sex-specific threshold versions of both the single-major-locus model and the multifactorial-polygenic model have given acceptable fits to preliminary data from this study (8).

Nongenetic hypotheses must also be considered before any firm conclusion can be reached. Certain models of purely cultural inheritance can be excluded by the data. The simplest cultural model—imitating the speech of a family member who stutters—could not explain more than a small fraction of all stuttering in children (10). This finding is consistent with the high familial concentration of stuttering because most stutterers recover before adulthood. For example, in 20% of our families the father had at some time stuttered but in half of those cases he had recovered before the birth of the proband. Certain parental attitudes about speech have been postulated to promote stuttering through pathologic parent–child interactions. Assuming such a hypothesis, our data require the relevant attitude to be correlated with stuttering in the parent or parent's relatives. The distributions of family types do not indicate a greater social role of the mother, although offspring of female probands are at the highest risk (Table 2). Other analyses of the possible relationship between family structures and stuttering (13) show (*i*) stutterers are randomly distributed among the birth ranks, (*ii*) the age separation of siblings is independent of occurrences of stuttering, and (*iii*) the frequency of stutterers among birth ranks before the proband is not significantly different from that in birth ranks after the proband.

More complex cultural hypotheses have involved a general "nervousness" being culturally transmitted because, for example, anxiety is known to exacerbate symptoms in a stutterer. Such hypotheses predict that the severity of stuttering would be associated with the frequency of relatives who stutter. One reliable measure of the severity of stuttering is the frequency of words on which a stutterer has some difficulty. This measure of severity is *not* associated with the frequency or distribution of stuttering among relatives (14). Hypotheses with exacerbating factors or attitudes being the culturally transmitted cause of stuttering also appear to be excluded by this result. These findings do not exclude all models of cultural inheritance; others might be found to fit our data.

Some aspects of these data do suggest a cultural element. The significance of the type-of-relative classification may reflect only an underreporting of transitory childhood stuttering among the siblings and parents of our adult probands. Alternatively, it may indicate that the presence of a currently stuttering parent does increase the risk of a child's stuttering. Additional analyses and possibly additional data will be required to resolve this question. This estimate of the effect of a currently stuttering parent is practically equal for male and female parents (Table 3). Though the offspring of stuttering mothers have the highest risks (bottom right section of Table 2), these high risks are consistent with the "sum" of the female proband effect and the general offspring effect. The equality of the offspring effect for male and female probands and the distributions of family types in the margin of Table 2 provide no evidence that the mother is "responsible" for stuttering in the child.

The very old notion that stuttering is caused by forcing a left-handed child to use his/her right hand has not been substantiated by any study in the last 40 years (1, 2). Also, the distribution of handedness among stutterers, including the probands in this study (15), is not different from that in age- and sex-matched control groups. However, while most stutterers are, and always have been, right-handed, a few individual case reports have impressed some researchers with the possibility that laterality is a factor in some cases (1, 2).

The validity of our conclusions depends in part on the accuracy of our data. We consider our probands to be reliable informants on stuttering in their families not only because they are familiar with their own symptoms but also because they are likely to evaluate correctly the occurrence of symptoms in others. Also, we obtained consistent reports whenever there was more than one informant in a family. However, two specific biases may well be present in the data: (*i*) milder cases of stuttering may be missed and (*ii*) individuals who stuttered only in childhood and have since recovered may not be known as stutterers to the proband. Underreporting of mild cases, if present, represents a conservative bias with the true frequency even greater than observed. In the unlikely event that such a bias accounts for the pattern observed, then the pattern of the bias becomes highly significant and interesting. The significantly greater frequency of stuttering reported among children may be a direct measure of the underreporting of recovered stutterers among parents and siblings of the proband. While such a bias might alter the numeric results in this study, it should not alter the other significant aspects of the pattern of risks. Future analyses incorporating knowledge of recovery from stuttering or its persistence into adulthood may clarify these issues. We found that a very large percentage of probands had discussed stuttering, including childhood stuttering, with many members of their families; we are confident that our data accurately reflect the pattern of occurrences of stuttering in these families.

The method used deserves comment. A very important aspect of this approach is that it exposes possibly relevant sources of heterogeneity within the data. Attempting to summarize the familial data on a complex disorder such as stuttering by using a single correlation coefficient or estimate of heritability simply obscures these interesting patterns. Ultimately, it is these pat-

terns that must be explained. Moreover, we find that these patterns allow inferences about the disorder without necessitating the assumption of a specific etiologic hypothesis. At the current level of our understanding of complex human disorders that seems a conservative yet advisable approach.

This study has demonstrated vertical transmission of a behavioral disorder by using a method that is not based on genetic hypotheses. The demonstration of a familial aggregation and vertical transmission might once have been considered sufficient to invoke a genetic etiology. It is a necessary prerequisite, but it is not sufficient.

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1. Van Riper, C. (1971) *The Nature of Stuttering* (Prentice-Hall, Englewood Cliffs, NJ).
2. Bloodstein, O. (1975) *A Handbook on Stuttering*, revised Ed. (National Easter Seal Society for Crippled Children and Adults, Chicago).
3. Freeman, F. J. & Ushijima, T. (1978) *J. Speech Hear. Res.* **21,** 538–562.
4. Adams, M. R. & Haydon, P. (1976) *J. Speech Hear. Res.* **19,** 290–296.
5. Kidd, K. K. & Records, M. A. (1979) in *Neurogenetics: Genetic Approaches to the Nervous System*, ed. Breakefield, X. O. (Elsevier/North-Holland, New York), pp. 311–344.
6. Kay, D. W. (1964) in *The Syndrome of Stuttering*, eds. Andrews, G. & Harris, M. (Heineman, London), pp. 132–143.
7. Kidd, K. K., Reich, T. & Kessler, S. (1973) *Genetics* **74,** s137 (abstr.).
8. Kidd, K. K. (1978) *J. Fluency Disord.* **2,** 259–269.
9. Kant, K. & Ahuja, Y. R. (1970) *Acta Med. Auxolog.* **2,** 179–191.
10. Kidd, K. K., Kidd, J. R. & Records, M. A. (1978) *J. Fluency Disord.* **3,** 13–23.
11. Cox, D. R. (1970) *Analysis of Binary Data* (Chapman & Hall, New York).
12. Bishop, Y. M. M., Fienberg, S. E. & Holland, P. W., (1975) *Discrete Multivariate Analysis: Theory and Practice.* (MIT Press, Cambridge, MA).
13. Gladstien, K., Seider, R. & Kidd, K. K. (1981) *J. Speech Hear. Res.*, in press.
14. Kidd, K. K., Oehlert, G., Heimbuch, R. C., Records, M. A. & Webster, R. L. (1979) *J. Speech Hear. Res.* **23,** 539–545.
15. Records, M. A., Heimbuch, R. C. & Kidd, K. K. (1977) *J. Fluency Disord.* **2,** 271–282.