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Segregation Analysis of Idiopathic Torsion Dystonia in Ashkenazi Jews Suggests Autosomal Dominant Inheritance

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Summary

The results of segregation analysis applied to a family study of idiopathic torsion dystonia in Ashkenazi Jews are reported. The study is based on 43 probands (with age at onset prior to 27 years) from 42 nuclear families; pedigrees were extended systematically through all available first- and second-degree relatives, who were directly examined and videotaped. Final diagnoses were based on exam information and blinded videotape review. Segregation analysis demonstrated that the data are consistent with autosomal dominant inheritance with 30% penetrance. Recessive and polygenic inheritance were strongly rejected. There was no evidence for sporadic cases or new mutations. The high incidence and dominant inheritance of early-onset idiopathic torsion dystonia in Ashkenazi Jews suggests genetic homogeneity within this population, making it especially useful for linkage studies of this disorder.

Introduction

Torsion dystonia is a neurological condition (movement disorder) characterized by involuntary twisting movements or postures. While dystonia can be secondary both to inherited biochemical abnormalities, such as Wilson disease, and to birth trauma, most cases are idiopathic torsion dystonia (ITD), with etiology unknown. Several lines of evidence suggest that genetic factors may underlie ITD. First, pedigrees with apparent autosomal dominant inheritance with high penetrance have been described in North America and Europe (Zeman et al. 1959; Johnson et al. 1962; Larsson and Sjogren 1966; Hoefnagel et al. 1970). An X-linked recessive pattern of inheritance has been reported in the Philippines (Lee et al. 1976). Another indication of genetic causation is the fact that ITD is roughly 5–10 times more common in Ashkenazi Jews (cumulative incidence about 1/15,000) than in non-Ashkenazi Jews (Zilber et al. 1984) or in non-Jewish Caucasians (Zeman and Dyken 1967).

Reports dating to the beginning of this century describe Ashkenazi Jewish (AJ) families with multiple cases of ITD either in siblings (Schwalbe 1908; Bernstein 1912; Abrahamson 1920) or in parents and offspring (Wechsler and Brock 1922; Mankowsky and Czerny 1929; Regensberg 1930). The first comprehensive evaluation of the mode of inheritance of ITD in Jewish and non-Jewish families was described by Zeman and Dyken (1967), who concluded that the disorder was inherited as an autosomal dominant with incomplete penetrance in both populations. Although they concluded that the gene frequency was higher in the AJ population than in non-Jews, no difference in mode of inheritance or disease mechanism was construed.

Subsequently, in a classic literature review, Eldridge (1970) proposed that distinct modes of inheritance characterize Jewish and non-Jewish ITD—namely, an autosomal dominant pattern in non-Jews and an autosomal recessive form in Jews. For Jewish families with vertical transmission—i.e., an affected parent and child—"pseudodominance" was the attributed expla-

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nation, with the unaffected parent being a heterozygous carrier.

The hypothesis of recessive inheritance in Jews has been challenged by Korczyn et al. (1981) and, more recently, by Zilber et al. (1984), who reported the results of a nationwide study of ITD in Israel. The Israeli data appear to be more consistent with an autosomal dominant pattern of inheritance with reduced penetrance than with a recessive pattern (Zilber et al. 1984). Furthermore, Korczyn et al. (1981) argue that even the data described by Eldridge (1970) are more consistent with dominant than with recessive inheritance. Despite the disagreement regarding mode of inheritance in the AJ population, most current texts describe ITD as autosomal recessive in this population (e.g., see Goodman 1979; McKusick 1988).

Correct characterization of mode of inheritance and penetrance of ITD in the AJ population is extremely important, because both accurate genetic counseling and genetic linkage strategies depend on it. Previous studies have not been based on systematic ascertainment of families and on blinded characterization of disease status in relatives. The current report describes our attempt, in a new study, to remedy these limitations and to provide a clearer picture of the mode of inheritance of ITD in this population.

In fact, evidence indicates that ITD may be an etiologically heterogeneous disorder. Age at onset for ITD can range anywhere from age 5 years upward. However, the age-at-onset distribution is bimodal, with modes at 9 and 55 years of age and with a nadir at age 27 years; age at onset also correlates with severity of symptoms and family history (Fahn 1986). Early-onset patients (before age 21 years) are most likely to have generalized dystonia (58%), while 30% are segmental and 12% are focal. For patients with onset of symptoms after age 21 years, the opposite pattern holds: 2% are generalized, 36% are segmental, and 62% focal. Furthermore, Jewish patients are disproportionately represented in the early-onset subgroup: 48% of Jewish cases had onset prior to age 30 years, compared with 28% of non-Jewish cases. These results suggest that ITD may be etiologically heterogeneous, with the early-onset group being a genetic subform. Therefore, to obtain a homogeneous sample, we limited study probands to cases of ITD with onset by age 27 years.

A full description of proband ascertainment, pedigree extension, procedures for clinical diagnoses, and preliminary results, including pedigree drawings, has been given by Bressman et al. (1989). Although the present report focuses on segregation analysis of these data, a brief synopsis of our study procedures and preliminary results is given below for completeness.

Subjects and Methods

Subjects

Study probands were obtained from a computerized data base of 762 ITD patients seen by the Movement Disorders Group at Neurological Institute, New York City, between September 1973 and January 1987. Cases of symptomatic dystonia (diagnosis based on examination, laboratory evaluation, or history of birth complications or drug exposure) were excluded. Among the ITD patients, 250 were Jewish, of whom 83 had onset of symptoms by age 27 years.

Two patients were Sephardi Jews and were therefore excluded. Of the remainder, two patients were three-fourths Ashkenazi and one-fourth Sephardi, and another was one-fourth Ashkenazi, one-fourth Sephardi, and one-half non-Jewish. These individuals were retained as probands, although their exclusion does not alter the results.

We further restricted our proband group to individuals who were ascertained independent of family history. Six patients had been referred by affected family members already seen and were therefore excluded as probands. However, if a family was independently ascertained through more than one affected individual, each such individual was considered to be a proband. Two patients were adopted and could not provide reliable information about biological relatives and were therefore excluded. The selection process therefore resulted in a study population of 73 AJ probands with ITD who were symptomatic by age 27 years. Systematic review revealed that these probands came to Neurological Institute solely for the purposes of diagnosis and/or treatment and not for genetic counseling or any cause related to family history.

Study probands were contacted, and arrangements were made to examine all available first- and second-degree relatives, including parents, sibs, offspring, grandparents, aunts/uncles, half-sibs, nieces/nephews, and grandchildren. All examinations were performed by neurologists trained in movement disorders and were videotaped according to a standardized protocol. The videotaped exams were reviewed and assessed for evidence of dystonia, by two independent neurologists who were blinded to the subject's identity and to any possible relationship to any other patients or subjects. Diagnoses were assigned on the basis of all available information, which included both on-site exam and

videotape review for 215 (88.8%) of 242 relatives, on-site exam only for 15 relatives (6.2%), and videotape review only for 12 relatives (5.0%). The following diagnostic categories were used: *definite ITD,* for twisting movements or postures that were apparent to all examiners; *probable ITD,* for twisting movements or postures that were apparent to some but not all examiners; and *possible ITD,* for suggestive movements that were not fully diagnostic of ITD. All cases of definite and probable dystonia identified among the relatives were primary (i.e., ITD).

Methods

The pedigree data were subjected to segregation analysis, using the computer programs POINTER (Lalouel and Morton 1981) and MENDEL (Lange et al. 1988). For analysis using POINTER, the pedigrees were decomposed into nuclear families with pointers. To control for variable age at onset, five liability classes were defined on the basis of age, as described in table 1. These classes were determined by the cumulative age-at-onset distribution observed among the affected relatives in the present study, with the final lifetime risk assumed to be 1/15,000 (Zilber et al. 1984). POINTER assumes both a mixed model of a major locus with alleles A and a and a polygenic background. The model parameters are: q, the frequency of the high-risk allele A; t, the displacement at the major locus; d, the dominance at the major locus; H, the polygenic heritability in offspring; Z, the parent-to-child heritability ratio; and τ_1, τ_2, and τ_3, the respective probabilities that genotypes AA, Aa, and aa transmit the allele A.

MENDEL allows for the analysis of intact pedigrees. However, the genetic model is a single major locus without a polygenic background. The parameters include the allele frequency of the high-risk allele A and the respective penetrances f_2, f_1, and f_0 of genotypes AA, Aa, and aa. In this analysis, lifetime risk was also assumed to be 1/15,000. The age-at-onset distribution among the affected relatives (as well as among the probands) was positively skewed and was reasonably approximated by a square-root normal distribution. Therefore, age at onset was assumed to have a square-root-normal distribution, with mean μ and SD σ estimated as part of the analysis. However, because such a large proportion of the sample was beyond the majority of the risk period, the precise characterization of the age-at-onset distribution had little impact on the results. The same age-at-onset distribution was assumed for all three genotypes.

For both POINTER and MENDEL, hypotheses were tested using the likelihood-ratio criterion $-2 \ln LR$, where LR is the ratio of likelihoods under the restricted and unrestricted models. It is assumed that $-2 \ln LR$ has an asymptotic χ^2 distribution with df equal to the number of parameter constraints.

Table 1

Liability Classes as Defined for POINTER

Class	Age Range (years)	Cumulative Incidence
1	0–7	.000007
2	8–11	.000030
3	12–17	.000046
4	18–44	.000060
5	45 +	.000067

Results

Seventy-three individuals were identified as probands for the present study. Of these, nine had died or were lost to follow-up, four refused permission to contact relatives, and seven families were geographically inaccessible (outside North America); for another 10 probands who agreed to participate, family members were not available for examination. The remaining 43 probands and their 242 examined first- and second-degree relatives constituted the study population. Only examined relatives were included in this analysis.

The 43 probands came from 42 nuclear families; one family was ascertained simultaneously through two affected brothers (a case of complete ascertainment). All other nuclear families were singly ascertained. Age at onset for the probands ranged from 5 to 25 years, with a median of 9 years. Twenty-two probands had onset between 5 and 9 years, 13 had onset between 10 and 14 years, six had onset between 15 and 19 years, and two had onset between 20 and 25 years. Many probands were initially seen within the first few years after onset. Age at most recent exam for the probands ranged from 8 to 68 years, with a median of 34 years. One proband was under age 9 years at exam, six were between 30 and 39 years, five were between 40 and 49 years, six were between 50 and 59 years, and three were between 60 and 69 years.

On extension of pedigrees to all first- and second-degree relatives, we discovered that three independently ascertained pairs of probands were related. In one case, the probands were related as aunt and niece; in a second case, the probands were first cousins once removed;

in the third case, the probands were second cousins. These pedigrees have been fully depicted by Bressman et al. (1989). The method for handling the overlapping families in segregation analysis is described below.

A total of 19 first- and second-degree relatives were definitely affected, and two were probably affected. As described by Bressman et al. (1989), age-adjusted lifetime risks (LTR) to age 45 years were calculated for each type of relative. Although the LTRs for first-degree relatives increased from parents (11.4 ± 4.0%) to sibs (17.2 ± 5.7%) to offspring (26.0 ± 14.9%), the values were not significantly different from one another ($\chi^2_2 = 1.68$, $P > .50$), and the LTR for all first-degree relatives combined was 15.5 ± 3.4%. Similarly, the LTRs for second-degree relatives were not significantly different from one another, and the combined value was 6.5 ± 2.6%, slightly less than one-half the value for first-degree relatives. This finding is consistent with any single-locus pattern of inheritance. Discrimination between dominant and recessive inheritance can be made by comparing the risks to parents and offspring (combined LTR 14.2 ± 4.2%) with that to siblings (17.2%). The similarity of these values argues strongly in favor of dominant inheritance—and against recessive inheritance—because recessive inheritance would lead to a much higher risk to siblings than to parents and offspring.

This conclusion was confirmed by the results of segregation analysis. For the analysis using POINTER, the pedigrees were partitioned into nuclear families. For the 41 nuclear families ascertained through a single proband, the ascertainment probability was assumed to be near zero, representing single ascertainment; for the one family ascertained through two affected brothers, the ascertainment probability was assumed to be one, representing complete ascertainment (or ascertainment independent of the number of affected sibs). Complete ascertainment of the offspring was assumed for all nuclear families containing the proband (as parent), his (her) spouse, and for their offspring. Complete ascertainment of offspring was also assumed for the nuclear families containing the proband's parents, grandparents, uncles, and aunts, with the proband as a pointer. Similarly, complete ascertainment of the offspring was assumed in nuclear families containing a sibling and nieces and nephews of a proband, with the proband as a pointer. Two nuclear families from one pedigree were ascertained independently through two different probands (aunt and niece). These families were included twice, once for each ascertainment. Analyses including parents (joint likelihood) and conditioning on parents (conditional likelihood) were performed. The results were negligibly different, so only the results of the conditional analysis, given in table 2, are presented. The Mendelian mixed model converged to a dominant model with gene frequency .00011. The values of q and t give a 30% lifetime penetrance for gene carriers, with no sporadic cases. The recessive model is strongly rejected ($\chi^2_2 = 50.58$, $P < 10^{-11}$), as is the polygenic model ($\chi^2_2 = 34.96$, $P < 10^{-9}$). The transmission probability τ_2 is not significantly different from 1/2 ($\chi^2 = 0.40$, $P > .8$).

For the analysis using MENDEL, pedigrees were left intact. The likelihood of the pedigrees containing all first- and second-degree relatives of each proband were conditioned on the single proband. As with POINTER, this led to the inclusion of two nuclear families twice. The one nuclear family ascertained through two probands (brothers) was also included twice, once for each proband. Because there was only one such family, the precise handling of this family had negligible impact on the results. Table 3 presents the results for the dominant and recessive models. The generalized single-locus model converged to the dominant model. Again, the recessive model is rejected, with a high degree of certainty ($\chi^2 = 65.88$, $P < 10^{-14}$). For the dominant

Table 2

Results of Segregation Analysis Using POINTER

Model	Parameters					
	d	t	q	H	τ_2	$-2 \ln L + c$
Unrestricted	1.000	→∞	.00015	.0	.371	.00
Mendelian mixed[a]	1.000	→∞	.00011	.0	[.5]	.40
Recessive	[.0]	→∞	.01054	[.0]	[.5]	50.98
Polygenic	...	...	...	.998	...	35.36

NOTE.—Values in brackets are fixed.

[a] Converged to a simple dominant model.

Table 3

Results of Segregation Analysis Using MENDEL

Model	Parameters						
	q	f_2	f_1	f_0	μ	σ	$-2\ln L + c$
Dominant	.00012	.27	.27	.00	4.17	1.31	.0
Recessive	.00937	.76	.00	.00	4.28	1.36	65.88

model, the lifetime penetrance is estimated to be 27%, with no sporadic cases; the gene frequency of the high-risk allele is .00012. These results are entirely compatible with those obtained from POINTER.

Discussion

The incidence of ITD in the AJ population has been estimated to be 1/15,000 (Zilber et al. 1984). If the disease were recessive, one would expect a very low incidence of ITD in parents and offspring of ITD probands. For example, the LTR of 17.2% observed for siblings would suggest a penetrance of 67% and a gene frequency of .0099. The risk to parents and offspring of cases would then be .0067, or 1/148. In fact, 7/62 parents and 3/24 offspring were found to be affected, convincingly refuting the possibility of recessive inheritance. This conclusion is not dependent on the specified incidence of ITD in the AJ population. Even if one were to assume a very high incidence of 1/1,000, the predicted risk to parents and offspring would be 2.5%, still far below the observed risk of 14.2%. Furthermore, the estimated penetrance of 30% for the dominant model is also impervious to misspecification of the population incidence; the gene frequency, however, is dependent on its value. This analysis included definite ITD cases only. Including the two probably affected individuals raised the penetrance to 32% (Bressman et al. 1989).

Our results contradict the conclusion of recessive inheritance as proposed by Eldridge (1970). However, Eldridge's data did not include systematic ascertainment and examination of family members—or appropriate quantitative analysis, as pointed out by Korczyn et al. (1981). By contrast, our study was based on a systematic proband ascertainment scheme and extension of pedigrees, direct examination (including videotaping) of family members, and videotape review by trained neurologists blinded to the identity of the subject.

It is notable that there were no cases among the relatives with an age at onset after age 44 years, despite the fact that nearly 60% of the sample was at least age 45 years at time of exam. This finding is consistent with the hypothesis that late-onset ITD is genetically distinct from early-onset ITD. To determine whether genetic factors play a role in late-onset ITD would require a separate family study based on late-onset probands.

ITD (particularly the early-onset form) is believed to be 5–10 times more common among Ashkenazi Jews than among either non-Ashkenazi Jews or non-Jewish Caucasians. Because of the low incidence in the latter group (1/100,000), a sizable percentage of cases may be due to new mutations. In fact, Bundey et al. (1975) suggested the possibility of a paternal age effect among nonfamilial cases. The 5–10-times-higher incidence of ITD in the AJ population is most likely caused by a higher disease-allele frequency. Therefore, one would expect only a very small proportion of cases in the AJ population to be new mutations. This conclusion is consistent with the segregation analysis results, which estimated the proportion of noninherited cases to be zero. As a further test for the presence of new mutations, probands were separated into two groups: those with an affected sib or ancestor (inherited cases) and those without one (possible new mutations). For the latter group, we required that at least both parents had to have been examined and were normal. Median and mean ages of the fathers at the birth of the proband were compared. For the first group (containing 17 inherited cases), the median was age 29 years and the mean was 29.1 years. For the second group (containing 14 "sporadic" cases), the median was age 29 years and the mean 29.3 years. Hence, this analysis produced no evidence for a paternal age effect among the cases representing possible new mutations.

Given that ITD is a dominant disease, the most plausible explanation for its high frequency in the AJ population is genetic drift. If this is the case, then early-onset ITD is likely to be a genetically homogeneous disease in this population (i.e., is likely due to a single mutation). This conclusion makes the AJ population espe-

cially suitable for linkage studies, despite the low penetrance, because genetic heterogeneity may not be a concern. Furthermore, given our conclusions, it is important that affected individuals and their relatives who seek genetic counseling be advised according to a model of dominant inheritance with 30% penetrance.

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