Am. J. Hum. Genet. 63:1777–1782, 1998

Search for a Founder Mutation in Idiopathic Focal Dystonia from Northern Germany

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Summary

Both the discovery of the *DYT1* gene on chromosome 9q34 in autosomal dominant early-onset torsion dystonia and the detection of linkage for one form of adult-onset focal dystonia to chromosome 18p (*DYT7*) in a family from northern Germany provide the opportunity to further investigate genetic factors in the focal dystonias. Additionally, reports of linkage disequilibrium between several chromosome 18 markers and focal dystonia, both in sporadic patients from northern Germany and in members of affected families from central Europe suggest the existence of a founder mutation underlying focal dystonia in this population. To evaluate the role of these loci in focal dystonia, we tested 85 patients from northern Germany who had primary focal dystonia, both for the GAG deletion in the *DYT1* gene on chromosome 9q34 and for linkage disequilibrium at the chromosome 18p markers D18S1105, D18S1098, D18S481, and D18S54. None of these patients had the GAG deletion in the *DYT1* gene. Furthermore, Hardy-Weinberg analysis of markers on 18p in our patient population and in 85 control subjects from the same region did not support linkage disequilibrium. Taken together, these results suggest that most cases of focal dystonia in patients of northern German or central European origin are due neither to the GAG deletion in *DYT1* nor to a proposed founder mutation on chromosome 18p but must be caused by other genetic or environmental factors.

Received April 7, 1998; accepted for publication September 25, 1998; electronically published November 11, 1998.

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0002-9297/98/6306-0025$02.00

Introduction

Recent advances in the molecular genetics of different forms of dystonia provide the opportunity to investigate the role of known dystonia genes in idiopathic (both hereditary and sporadic) focal dystonia (for review, see Gasser 1997; Müller et al. 1998). The *DYT1* gene (MIM 128100), located on chromosome 9q34 and responsible for the majority of cases of autosomal dominantly inherited early-onset torsion dystonia, has recently been identified (Ozelius et al. 1997). Most individuals with this syndrome share a unique 3-bp (GAG) deletion in the *DYT1* gene, resulting in loss of one of a pair of glutamic acid residues in a conserved region of a novel ATP-binding protein (Ozelius et al. 1997). Most of the patients with this mutation present with early-onset generalized dystonia (Bressman et al. 1994*a*); however, some features of this condition overlap the phenotypic spectrum of adult-onset (focal) types of dystonia. For example, a carrier of this *DYT1* mutation has been described with only focal dystonia of the neck, starting at age 34 years (Bressman et al. 1994*a*), and we examined another patient with the GAG deletion and focal dystonia of the jaw, which started in her 60s (authors' unpublished observation).

A gene causing adult-onset focal dystonia (*DYT7* [MIM 602124]) has been mapped to chromosome 18p in one large family (family K) from northern Germany (Leube et al. 1996). Fifteen sporadic cases from the same geographic area and 15 cases among 18 families from central Europe who have focal dystonia have been reported to share, with affected members of family K, specific alleles, in a subregion of chromosome 18p, linked to the disease gene (Leube et al. 1997*a,* 1997*b*). This finding of apparent allelic association led the authors of those studies to conclude that, because of a founder effect in this population, most of these apparently sporadic patients and families have inherited the same mutation as is seen in family K (Leube et al. 1997*a,* 1997*b*). The primary evidence for this linkage disequilibrium was seen with the markers D18S1098 and D18S481, which are ~1.2 cM apart. We collected 85 patients from north-

ern Germany, all with adult-onset focal dystonia, and, with the two microsatellite repeat markers noted above and two additional flanking microsatellite markers (D18S1105 and D18S54) covering a region of ~6 cM, examined them for the putative founder haplotype in the *DYT7* region on chromosome 18p; 85 patients with idiopathic Parkinson disease who were from the same geographic region were used as a control group. In addition, the dystonia cohort was tested for the GAG deletion in the *DYT1* gene.

Patients and Methods

Patients

Eighty-five consecutive patients with idiopathic focal ($n = 83$) or segmental ($n = 2$) dystonia who either visited the Neurology Department of Lübeck University Hospital for diagnosis and treatment of dystonia or gathered at meetings of the local dystonia support groups in northern Germany were included in our study. The geographic catchment area comprised the northernmost province of Germany, Schleswig-Holstein; the city of Hamburg and its suburbs; and the German coastal region of the Baltic Sea. Informed consent for clinical examination and DNA analysis was obtained from each patient. The clinical manifestations of all patients studied conformed to published diagnostic criteria of idiopathic focal dystonia (Fahn et al. 1986). Secondary dystonia was excluded by history, lack of additional neurological signs, measurement of copper metabolism, and brain imaging (computed tomography or magnetic resonance imaging). In addition, 85 patients with idiopathic Parkinson disease who were from the same geographic region served as a control group.

Identification of the GAG Deletion on Chromosome 9q34

After DNA had been extracted from whole blood, we used published primers 6418 and 6419 (Ozelius et al. 1997) for PCR amplification across the critical region of the *DYT1* gene. PCR products were resolved in a denaturing 6% polyacrylamide gel and were visualized by silver staining (von Deimling et al. 1993). Samples from affected individuals carrying the GAG deletion displayed two distinct bands, of 250 and 247 bp, whereas noncarriers showed a single 250-bp fragment.

Markers on Chromosome 18p

Genotyping was performed under standard conditions as specified by Research Genetics, with the following simple sequence repeat DNA markers: D18S1105–3.2 cM–D18S1098–1.2 cM–D18S481–1.5 cM–D18S54, spanning a 6-cM region on chromosome 18p (the genetic distances are from Leube et al. 1997*b*). PCR products were analyzed on a LICOR automated sequencer. To ensure comparison of identical alleles, a control DNA sample (CEPH [Centre d'Étude du Polymorphisme Humain] 1331-02) was run for each marker, and alleles were assigned on the basis of data in table 1 of Leube et al. (1997*b*).

Allele Frequencies and Hardy-Weinberg Equilibrium

To assess linkage disequilibrium at each marker, we compared the allele frequencies for the associated alleles in our patients and controls with those reported elsewhere by Leube et al. (1997*a,* 1997*b*). The genetic model proposed for late-onset focal dystonia is a rare, autosomal dominant founder mutation with reduced penetrance (Leube et al. 1997*a,* 1997*b*). Implicit in this model is the premise that the patients' genotype will be Dd, whereas the controls' genotype will be dd. At a linked marker locus M, let allele 1 be associated with disease allele D, and let all other alleles be denoted by "X." Let p be the frequency of allele 1 on chromosomes carrying allele d, and let $q = 1 - p$. Similarly, let r be the frequency of allele 1 on chromosomes carrying allele D, and let $s = 1 - r$. The strength of linkage disequilibrium is measured by the parameter δ (Bengtsson and Thomson 1981; Hastbacka et al. 1992; Devlin and Risch 1995), given by $\delta = (r - p)/q$. As a consequence, $r = p + q\delta$. Therefore, according to this model, if we assume that D is rare, then the genotype frequency distribution in patients will be pr for 11 homozygotes, $ps + qr$ for 1X heterozygotes, and qs for XX homozygotes (here, "X" refers to all other alleles, so these individuals are technically homozygous and heterozygous for all other alleles).

Feder et al. (1996) have described the use of Hardy-Weinberg disequilibrium for fine mapping the gene for hemochromatosis, a heterogeneous recessive disorder, and also have indicated that this approach could be used for a dominant disorder with a founder mutation, since an allele in linkage disequilibrium with the founder mutation will show a heterozygote excess. The extent of this excess, of course, will depend on the allele frequencies and on the strength of disequilibrium as measured by δ.

Herein we assess the evidence for linkage disequilibrium, by examining both (1) the difference, between patients and controls, in the frequency of the associated, 1 allele and (2) the genotype distribution in patients. We use a likelihood formulation, as follows. Let n_{11}, n_{1X}, and n_{XX} be the numbers of patients with genotypes 11, 1X, and XX, respectively. We assume Hardy-Weinberg disequilibrium for the controls, and thus measure only the number of 1 and X alleles in controls, denoted by "m_1" and "m_X," respectively. The log likelihood of these data can then be written as

Table 1

Clinical Data and Classification of Probands

Diagnosis	No. (%) of Patients	Sex (% Male/ % Female)	Age[a] (years)	Disease Duration[a] (years)	Age at Onset[a] (years)
Combined subgroups	85 (100)	38/62	54.4 ± 11.0 (29–76)	9.4 ± 8.0 (1–40)	44.8 ± 12.5 (13–73)
Spasmodic torticollis	62 (72.9)	42/58	53.8 ± 10.8 (29–76)	10.7 ± 8.9 (1–40)	42.8 ± 12.4 (13–65)
Writer's cramp	9 (10.6)	44/56	51.2 ± 14.3 (33–74)	5.2 ± 3.2 (1–12)	46.0 ± 14.1 (27–73)
Cranial dystonia	12 (14.1)	8/92	58.3 ± 9.0 (45–75)	6.2 ± 2.8 (1–9)	52.1 ± 8.5 (36–67)
Segmental dystonia	2 (2.4)	50/50	62 and 71	4 and 11	51 and 67

[a] Data are mean ± SD (with the range in parentheses), except for entries in the "Segmental dystonia" row, in which the values for both of the two patients are given.

$$\begin{aligned}\ln L &= n_{11}\ln(pr) + n_{1X}\ln(ps+qr)\\ &\quad + n_{XX}\ln(qs) + m_1\ln(p) + m_X\ln(q)\\ &= (n_{11}+m_1)\ \ln(p) + (n_{XX}+m_X)\ln(q)\\ &\quad + n_{11}\ln(r) + n_{XX}\ln(s) + n_{1X}\ln(ps+qr)\ . \qquad (1)\end{aligned}$$

Substituting $r = p + (1-p)\delta$, $q = 1-p$, and $s = 1-r$ gives a log likelihood that is a function of the two parameters p and δ. This log likelihood can then be maximized with respect to both parameters, to estimate p and δ. In this case, equation (1) can be easily maximized, by the EM algorithm, with respect to the parameters p and r, since direct allele counts can be obtained by estimating the proportion of patient heterozygotes who have allele 1 on a D chromosome, by $qr/(ps+qr)$. The parameter δ is then obtained by means of the formula $\delta = (r-p)q$. Equation (1) can also be used to test hypotheses about the parameter δ. For example, we can determine the largest value of δ that is compatible with the data, by finding the smallest value of δ that leads to rejection in a likelihood-ratio test (LRT) that compares that value of δ with the maximum-likelihood value of δ. We assume that such LRTs, calculated as twice the log-likelihood difference, have a χ^2 distribution with 1 df.

Analysis of Clinical Data

We either applied χ^2 tests or, when appropriate, the Fisher exact test to compare clinical patient data for qualitative variables and have used a parametric t test for quantifiable disease characteristics.

Results

A total of 85 patients with focal or segmental dystonia (average age 54.4 ± 11.0 years, range 29–76 years) were analyzed, including 62 patients (72.9%) with spasmodic torticollis, 9 patients (10.6%) with writer's cramp, and 12 patients (14.1%) with cranial dystonia. The latter group comprised 7 patients (8.2%) with blepharospasm and 5 patients (5.9%) with Meige syndrome. Two patients (2.4%) had both cranial and cervical dystonia. All patients were unrelated; 5 (5.9%) reported a positive family history with at least one first-degree relative affected by focal dystonia. Among the 85 patients, there were more women than men ($n = 53$ [62%] vs. $n = 32$ [38%], respectively; $P < .05$). Analysis of the different subgroups separately revealed that significantly more women than men had cranial dystonia ($n = 11$ [92%] vs. $n = 1$ [8%], respectively; $P < .01$), whereas the female:male ratio did not differ significantly in any of the other groups. The mean age at disease onset was significantly higher in the patients with cranial dystonia (52.1 ± 8.5 years) than in the patients with torticollis (42.8 ± 12.4 years; $P < .005$) but was not higher than in the patients with writer's cramp (46.0 ± 14.1 years; $P > .05$). The subgroup of only two patients with segmental dystonia was too small for separate analysis. The clinical data are summarized in table 1.

The GAG deletion in the *DYT1* gene was not found in any of the patients studied. The results of our genotype analysis for markers D18S1098 and D18S481 are given in table 2, along with those from two studies by Leube et al. (1997*a*, 1997*b*). Leube et al. found that the strongest evidence for disequilibrium was at locus D18S1098: in their first study (Leube et al. 1997*b*), they found that 60% of unphased patient chromosomes carried allele 1 at D18S1098, compared with 28% of control chromosomes; in their second study (Leube et al. 1997*a*), they detected the same allele in 8 (73%) of 11 phased, disease-bearing chromosomes, compared with 32% of control chromosomes. In contrast, we found allele 1 in only 37% of unphased patient chromosomes, a frequency similar to the control frequencies reported by Leube et al. (1997*a*, 1997*b*), whereas our controls had a frequency of 45% for the same allele. Furthermore, we found no significant evidence of heterozygote excess in our patient data ($\chi^2 = .1$; not significant). The likelihood analysis gave a maximum-likelihood estimate of $\delta = 0$, and all values of $\delta > .18$ could be excluded.

Table 2

Genotype and Allele Frequencies at Loci D18S1098 and D18S481, in the Work of Leube at el. (1997*a*, 1997*b*) and in Our Patients

	Frequency (No.)			
	Genotype			
Locus	11	1X	XX	Allele 1
D18S1098:				
Leube et al. (1997*a*):[a]				
Patients (n = 15)	...	...	...	73%
Controls (n = 63)	...	...	...	32%
Leube et al. (1997*b*):[b]				
Patients (n = 15)	27% (4)	67% (10)	6% (1)	60%
Controls (n = 20)	...	...	...	28%
Present study:[a]				
Patients (n = 85)	13% (11)	48% (41)	39% (33)	37%
Controls (n = 85)	19% (16)	52% (44)	29% (25)	45%
	77	7X	XX	Allele 7
D18S481:				
Leube et al. (1997*a*):[a]				
Patients (n = 15)	...	...	...	50%
Controls (n = 63)	...	...	...	32%
Leube et al. (1997*b*):[b]				
Patients (n = 15)	13% (2)	60% (9)	27% (4)	43%
Controls (n = 20)[c]	...	...	...	NR
Present study:[a]				
Patients (n = 85)	25% (21)	44% (37)	32% (27)	46%
Controls (n = 85)	13% (11)	51% (43)	36% (31)	38%

[a] Sporadic cases without disease-chromosome status.

[b] Phased chromosomes from familial cases with disease-chromosome status (n = 11 for D18S1098; n = 12 for D18S481).

[c] NR = not reported.

The δ value obtained from the data of Leube et al. is .60; this value could be strongly rejected ($P < .001$).

At locus D18S48l, our patients had an allele frequency of 46% for allele 7, the associated allele. This frequency is slightly lower than that in phased patient chromosomes in the study by Leube et al. (1997*a*), comparable to that in their unphased patients (43%) (Leube et al. 1997*b*), and higher than that in their controls (32%) (Leube et al. 1997*a*); in our controls, the frequency was 38%. However, neither our patient data nor the data reported by Leube et al. (1997*b*) show a heterozygote excess when submitted to Hardy-Weinberg analysis. In fact, our patients showed a modest deficit of heterozygotes. Because of the elevated allele frequency in patients, maximum-likelihood analysis gave a δ estimate of .21, whereas values >.47 were rejected; a δ value of 0 was not rejected ($\chi^2 = 1.87$, $P > .10$). The two adjacent markers, D18S1105 and D18S54, also showed no evidence of either increased frequency or Hardy-Weinberg deviation.

Only 1/85 of our patients (a woman with blepharospasm who was age 51 years at disease onset) shared, with family K, the same haplotype at all four markers. Genealogical analysis revealed that her parents had originated from Holstein and Mecklenburg, ~250 miles from the residence of family K (Emsland). In fact, at three of the four markers tested, the most prevalent alleles found in our patient sample (D18S1105, allele 7; D18S1098, allele 6; and D18S54, allele 3) were different from those that were found on the disease-bearing chromosome in family K (D18S1105, allele 2; D18S1098, allele 1; and D18S54, allele 2). When we took the former as the putatively overrepresented alleles in our population, we still did not detect any deviation from Hardy-Weinberg genotype frequencies.

Discussion

We analyzed 85 patients from northern Germany, both clinically and genetically. Our data confirm the results from the literature—that is, that the female:male ratio for patients seeking medical evaluation for cranial dystonia is shifted toward women (Waddy et al. 1991; Soland et al. 1996; Leube et al. 1997*c*). In agreement with Soland et al. (1996), we found that, among the affected men, there was a higher proportion of writer's cramp, although the number of women still exceeded the number of men, even in this small subgroup. Patients with cranial dystonia had a significantly higher age at disease onset than was seen in patients with torticollis, as has been described elsewhere (Waddy et al. 1991; Leube et al. 1997*c*).

Among our 85 patients, 5 (5.9%) reported a positive family history for focal dystonia. Similar numbers have been reported in other studies; for example, 5 (5.5%) of 91 patients with writer's cramp had similarly affected relatives, by history (Sheehy et al. 1988), and 11 (9.5%) of 116 patients with spasmodic torticollis had a positive family history of dystonia (Friedman and Fahn 1986). Because of the unreliability of family-history reports, however, these small numbers may not represent the actual frequency of patients with affected relatives. It has also been shown that relatives of patients with dystonia are often unaware of their own dystonic signs but that many can be identified on careful clinical examination (Waddy et al. 1991; Leube et al. 1997*c*).

None of our patients had the GAG deletion in the *DYT1* gene. Similarly, the *DYT1* locus has been excluded, by linkage, in several families with adult-onset idiopathic torsion dystonia (Bressman et al. 1994*b;* Holmgren et al. 1995; Bressman et al. 1996), and the GAG deletion was not found in 76 unrelated individuals with late-onset dystonia (Ozelius et al. 1997). However, because of phenotypic overlap between early-onset and late-onset dystonia in individual cases, we recommend screening for the GAG deletion in patients with early-onset (age <40 years) focal dystonia, especially when it starts in the arms and/or in patients with a positive family history for dystonia.

Linkage-disequilibrium studies—and the resulting haplotype analyses—based on the comparison of allele frequencies in controls versus those in affected individuals have proved to be a powerful tool for the identification and cloning of various disease genes (MacDonald et al. 1991; Ozelius et al. 1992). In addition, for a dominant disease or a recessive disease with heterogeneity, linkage disequilibrium between markers and a founder disease mutation can be identified on the basis of deviations from Hardy-Weinberg equilibrium, as recently has been shown for hereditary hemochromatosis (Feder et al. 1996).

Both the linkage, in family K, to several markers on chromosome 18p (Leube et al. 1996) and the description of patients affected with dystonic symptoms as having a deletion in chromosome 18p (Kakinuma et al. 1994; Page et al. 1998) provide evidence that the short arm of chromosome 18 may harbor a gene responsible for dystonia. Nevertheless, in contrast to previously published data (Leube et al. 1997*a,* 1997*b*), our analysis of 85 patients with focal dystonia who are from northern Germany did not reveal any clear evidence for linkage disequilibrium at the markers tested on chromosome 18p, including those markers previously identified in family K. Although marker D18S481 did show a modest excess frequency of allele 7 in our patients versus that seen in controls, this allele was only weakly associated with dystonic symptoms in the data reported by Leube et al. (1997*a,* 1997*b*). In contrast, at locus D18S1098 we could find no evidence of disequilibrium; this marker was most significantly associated in the data reported by Leube et al. (1997*a,* 1997*b*). Indeed, combining our data with those of Leube et al. gives a total allele frequency of 43% for allele 1 in patients, versus 39% in controls; this difference is not significant ($\chi^2 = 1.73$, $P > .20$). In their initial linkage-disequilibrium study, Leube et al. (1997*b*) tested 22 markers. By chance alone, with no corrections made for multiple testing, one would expect to find linkage disequilibrium for 1/20 markers (Bonferroni analysis). Several other aspects of the studies by Leube et al. (1996, 1997*a,* 1997*b*) warrant reconsideration. For example, shared haplotypes are inconsistent among the 15 sporadic patients (Leube et al. 1997*b*), as well as among affected individuals from the 15 European families (Leube et al. 1997*a*). Only one sporadic patient and one of the familial cases share the complete haplotype with family K, whereas in six sporadic patients and eight familial cases "haplotype sharing" is based on a single marker (D18S1098, Dl8S481, or Dl8S54) (Leube et al. 1997*a,* 1997*b*). In fact, on the basis of allele frequencies for the CEPH population (Genome Database), 41% of northern Europeans share with family K the same allele at the marker D18S1098, 13.1% share with family K the alleles at both markers D18S1098 and D18S481, and 1.7% share with family K the same haplotype across all four markers. In our patient sample, 1 (1.2%) of 85 individuals shared the complete haplotype with family K, as did one of the sporadic patients of Leube et al. (1997*b*) and one of their European families (Leube et al. 1997*a*). Given the population-migration trends in central Europe during this century, it is difficult to imagine a common founder mutation for *DYT7* in the central European population. Even though most of the families in the studies by Leube et al. (1997*a*) seem to be of German extraction, the population in that geographic area is large, and panmixia can be assumed. Nevertheless, stable populations can be found, and subsets of our patients are derived from such—mostly rural—areas. If a common ancestor were responsible for *DYT7* in a majority of German (or even central European) patients with focal dystonia, one would expect to find, among the 85 patients from northern Germany whom we tested, at least a subgroup of patients who share the haplotype with family K.

Taken together, neither other studies nor our data support the conclusion that the majority of sporadic cases of focal dystonia in northern Germany and central Europe are due to the same (founder) mutation, on chromosome 18p, that has been described in family K (Leube et al. 1996). Furthermore, it has not yet been clearly demonstrated that the majority of cases of focal dystonia are indeed genetic in origin, since, in an investigation in the United Kingdom, careful examination demonstrated that only 25% of the index cases had affected relatives (Waddy et al. 1991). Another recent study showed an increase in the proportion of sporadic cases with a positive family history—from 4 (23.5%) of 17, by history alone, to 14 (82.4%) of 17, by examination (Leube et al. 1997*c*). These data, however, may reflect an ascertainment bias, since only 17 (3.5%) of 488 index patients agreed to examination of their relatives. However, inheritance of focal dystonia is still consistent with an autosomal dominant mode with low penetrance (Waddy et al. 1991; Leube et al. 1997*c*), at least in some families. As recently has been shown for the α-synuclein gene in Parkinson disease (Polymeropoulos et al. 1997), a specific genetic defect may account for the disease in selected families only and not for the majority of familial (Gasser et al. 1997; Scott et al. 1997) or sporadic patients.

Acknowledgments

We thank all the patients who participated in these studies, for providing samples and inspiration. This work was supported by grants from the Dystonia Medical Research Foundation (to L.J.O. and X.O.B.) and by National Institutes of Health grants NS28384 (to X.O.B.) and HG00348 (to N.J.R.) C.K. is a fellow of the Deutsche Forschungsgemeinschaft.

Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Genome Database, http://gdbwww.gdb.org/ (for frequency of alleles 1 and 7 in the CEPH population)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/omim (for autosomal dominant early-onset torsion dystonia linked to *DYT1* [MIM 128100] and adult-onset focal dystonia linked to *DYT7* [MIM 602124])

Research Genetics, http://www.resgen.com (for genotyping protocol)

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