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Dystonia-Parkinsonism Syndrome (XDP) Locus: Flanking Markers in Xq12–q21.1

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Summary

The study of rare genetic forms of dystonia and parkinsonism permits positional cloning of genes potentially involved in more common, multifactorial forms of these diseases. One movement disorder amenable to molecular genetic analysis is the X-linked dystonia-parkinsonism syndrome (XDP). This disease is endemic to the Philippines where it originated by a genetic founder effect. Linkage analysis was performed with DNA from 14 XDP kindreds by using 12 polymorphic DNA sequences in Xp11–Xq22. Two-point analysis demonstrated maximum lod scores of 5.45, 4.95, 4.28, and 5.99 for *DXS106, DXS159, PGK1,* and *DXS72,* respectively, at recombination fractions of zero (*DXS106* and *DXS159*), .01 (*PGK1*), and .04 (*DXS72*). Multipoint analysis resulted in a maximum-likelihood score (Z_{max}) of 8.41 with a (Z_{max} − 1) support interval of 9 cM between *DXS159* and *DXS72* (Xq12–q21.1). In 19 XDP kindreds significant linkage disequilibrium was found for loci *DXS72* (Δ = .47), *PGK1* (Δ = .36), *DXS95* (Δ = .30), *DXS106* (Δ = .28), and *DXS159* (Δ = .26). These data indicate that the gene mutated in XDP (locus *DYT3*) is located in Xq12–q21.1.

Introduction

Dystonia and parkinsonism are movement disorders and may be either idiopathic, sometimes genetic in origin, or may occur secondary to known etiologies. Dystonia is defined as involuntary, sustained muscle contractions resulting in twisting or repetitive movements and in abnormal postures (Fahn et al. 1987). Parkinsonism is characterized by a constellation of rigidity, bradykinesia, resting tremor, and loss of postural reflexes (Factor and Weiner 1988). These symptom complexes are ascribed to malfunctions of the basal ganglia, a set of telencephalic nuclei.

The structural and functional interrelationships of the basal ganglia nuclei are highly complex (McGeer et al. 1987). Several neural pathways involving different neurotransmitters have been described, but knowledge of their synaptic organization is far from complete. The study of genetic movement disorders may foster a better understanding of the neurobiology of the basal ganglia.

Positional cloning facilitates the isolation of a gene on the basis of its map position alone, without knowledge of its defective gene product. Subsequently, the gene product can be isolated, and its function can be studied. This approach has been successfully applied to various human disorders including chronic granulomatous disease (Royer-Pokora et al. 1986), Duchenne muscular dystrophy (Monaco et al. 1986), retinoblastoma (Friend et al. 1986), cystic fibrosis (Rommens et al. 1989), Wilms tumor (Call et al. 1990; Gessler et al. 1990), neurofibromatosis (Cawthon et al. 1990; Wallace et al. 1990), and choroideremia (Cremers et al. 1990).

Common movement disorders, including Parkinson disease, have not been amenable to this approach, mainly because of their multifactorial etiology. However, there are rare instances in which movement abnormalities such as parkinsonism occur as Mendelian traits (Golbe et al. 1990). Molecular genetic approaches to such rare conditions may therefore yield insights into the understanding of both the neurobiology of normal movement and the pathogenesis of movement disorders.

Accordingly, we chose to investigate the X-linked

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dystonia-parkinsonism syndrome (XDP) which occurs endemically in the Philippines (Lee et al. 1976; Kupke et al. 1990*b*). This syndrome is characterized by a progressive adult-onset dystonia that frequently concurs with parkinsonism (Johnston and McKusick 1963; Fahn and Moskowitz 1988; Lee et al. 1991). XDP is particularly suited for genetic analyses because of the homogeneous patient population arising from a founder effect. Preliminary studies of seven families linked the XDP locus (*DYT3*) to two markers on the proximal long arm of the X chromosome (Xq21) (Kupke et al. 1990*a*). In the present paper, we demonstrate the existence of flanking marker loci for *DYT3* in Xq12–Xq21.1 by linkage analysis and by the finding of significant linkage disequilibrium for these markers.

Material and Methods

Patient Population

We studied 1 three-generation and 13 two-generation nuclear families and five affected males from additional unrelated families. Seventeen families resided on the Philippine island of Panay, and two resided in the metropolitan Manila area. A total of 99 subjects were evaluated, including 21 carrier females, 39 affected males, and 39 unaffected males. Each individual underwent a standardized history and neurologic evaluation. The diagnosis of XDP was made on the basis of clinical criteria (Fahn et al. 1987). The phenotype of all patients has been described elsewhere (Lee et al. 1991). Extensive pedigree data were obtained, and all kindreds demonstrated X-linked recessive inheritance.

Blood samples were obtained from each individual, as well as from 50 unrelated female Filipino controls residing on Panay. All controls had a negative family history for XDP. Furthermore, on the basis of an estimated 1/4,000 incidence of XDP in males from Panay (Kupke et al. 1990*b*), less than one carrier—i.e., less than one disease-bearing X chromosome—could possibly have been included in the control population. Since this would not significantly alter the Δ values (see below), population frequency of the disease gene was not included in the calculations.

DNA Analysis

Genomic DNA was extracted from peripheral blood samples from all study subjects by using standard techniques (Aldridge et al. 1984). DNA was digested with restriction endonucleases according to manufacturers' recommendations, was separated by electrophoresis on 0.7% agarose gels, and was blotted to nylon membranes (Hybond N+; Amersham) (Southern 1975). Filters were hybridized at 42°C with ^{32}P-labeled X-chromosomal DNA sequences (Feinberg and Vogelstein 1984) and were further processed as described by Müller et al. (1986). Autoradiography was performed at −70°C with X-ray film (X-O-Mat; Kodak), using intensifying screens for 3–7 d. Each hybridization was repeated at least once.

A total of 11 informative loci in Xq12–21 and 1 locus in Xp11 were used for linkage analysis. These loci included *DXS14, DXS159, DXS106, PGK1, DXS72, DXS95, DXYS1X, DXYS5X, DXYS2X, DXS3, DXS87,* and *DXS94* (table 1). The following markers were not informative: *DXS1, DXS17, DXYS12X, DXS91,* and *DXS135*.

Data Analysis

The order of the loci, including regional assignments and estimated map distances, are given in table 1 (data are based on Keats et al. 1989, 1990). RFLP allele frequencies were obtained from the Filipino control population. The mutation of XDP was estimated at $\mu = 10^{-6}$, with a disease frequency estimate of 10^{-6}, on the basis of the occurrence of the disorder in the Philippines (Kupke et al. 1990*b*). Age-related male penetrance was assumed to be 100% by age 50 years. Ten liability classes based on 5-year age intervals were utilized to denote penetrance of the 73 male members of the 14 families with living carrier mothers. Specifically, no individuals were younger than 25 years old (liability classes 1–4), 9 were 26–30 years old, 4 were 31–35 years old, 4 were 36–40 years old, 4 were 41–45 years old, 5 were 46–50 years old, and 47 were older than 50 years (see also Lee et al. 1991). All mothers of affected individuals were coded as nonpenetrant carriers. The two-point lod score value (Z) was calculated using the MLINK program of the LINKAGE package (v5.04) (Lathrop and Lalouel 1984).

Multipoint linkage analysis was performed with *DYT3* and the eight marker loci *DXS14, DXS159, PGK1, DXS72, DXYS1X, DXYS2X, DXS3,* and *DXS94*. The LINKAGE program LINKMAP was used (Lathrop et al. 1984). The Haldane mapping function, $x = -\frac{1}{2} \ln (1 - 2\theta)$ (with x being the map distance and θ being the recombination fraction), was applied to convert map distances into recombination fractions. Both the order of the eight marker loci and the genetic distances between them were assumed to be

Table 1

Informative X-chromosomal Markers Used for Linkage Study

Locus	Probe	Regional Assignment	Map Location (cM)	Reference
DXS14	p58-1	Xp11.21	29.6	Bruns et al. 1984
DXS106	cpX203	Xq12	. . .	Hofker et al. 1987
DXS159	cpX289	Xq12	33.9	Arveiler et al. 1987
PGK1	pXPGK-RI0.9	Xq13	40.0	Smead et al. 1989
	pSPT/PGK	Xq13	40.0	Vogelstein et al. 1987
DXS72	pX65H7	Xq21.1	44.2	Schmeckpeper et al. 1985
DXS95	pXG-7	Xq21.2-q21.3	. . .	Davatelis et al. 1985
DXYS1X ...	pDP34	Xq21.31	48.8	Page et al. 1982
DXYS2X ...	7b	Xq21.3	51.2	Koenig et al. 1985
DXYS5X ...	p31	Xq21	. . .	Schwartz et al. 1988
DXS3	p19-2	Xq21.3	56.6	Aldridge et al. 1984
DXS87	pA13.RI	Xq21.33-q22	. . .	MacDermot et al. 1987
DXS94	pXG-12	Xq22	63.4	Davatelis et al. 1987

[a] Estimated map positions with *DXS84* arbitrarily set at zero, according to Keats et al. (1990). Map positions for the four framework loci *DXS159*, *PGK1*, *DXYS1X*, and *DXS3* were obtained from HGM 10.5 (Keats et al. 1990). Map positions for the other loci listed are based on estimates from HGM 10 (Keats et al. 1989) and are given in relation to the map positions of the preceding four loci. An ellipsis (. . .) denotes that exact map location is unknown.

fixed. A multilocus Z was calculated for each possible location by comparing the likelihood of each location to the likelihood that *DYT3* was unlinked to the multilocus map. The absence of interference was assumed. A one-unit support interval ($Z_{max} - 1$) was determined from the maximum-likelihood estimates.

Linkage disequilibrium was calculated by the disequilibrium parameter Δ (Chakravarti et al. 1984) and by χ^2 tests for significance with one df. It was determined for those loci for which no recombination events were observed between *DYT3* and the respective marker locus. The RFLP haplotype frequencies of the control population were assumed to be in equilibrium.

Results

Twelve loci spanning Xp12–q22 were informative in the 14 families analyzed. Two-point Z and confidence intervals are given in table 2. Z_{max} at $\theta = .0$ were 5.45, 4.95, and 3.30 for loci *DXS106*, *DXS159*, and *DXYS2X*, respectively. For *PGK1*, the Z_{max} was 4.28 at $\theta = 0.01$, because of recombination events detected in two XDP patients from two different families and in one each of their respective unaffected brothers (ages 28 years and 35 years). The comparatively young age of these unaffected brothers does not rule out the possibility that they are carriers of the mutated XDP gene and will develop the disorder in the future. *DXS72*, located approximately 4.2 cM distal to *PGK1* (Keats et al. 1989), demonstrated a Z_{max} of 5.99 at $\theta = .04$. Figure 1 gives a pedigree showing critical individuals with their respective haplotypes for informative RFLP alleles at marker loci spanning the region from *DXS106* to *DXS94*. Given that the maternal grandfather was unaffected at age 78 years, the disease gene in one of his grandsons must have derived from the grandmother. One of the two unaffected grandsons carries the X chromosome of his grandfather, and the other carries that of his grandmother. A recombination between the two maternal X chromosomes was detected in the affected brother, thus placing *DYT3* proximal to *DXS72*. The presently 35-year-old unaffected brother is likely to develop XDP. With the exception of *DXYS2X*, recombination events between *DYT3* and informative marker loci were also observed with all probes distal to *DXS72*. Moreover, *DXS87* (Xq22) demonstrated a highly negative Z. Recombinations were also observed with *DXS14*, which is proximal to *DXS106* and which has been assigned to Xp11.21.

Multipoint linkage analyses were performed to determine the most probable location of *DYT3* relative to eight fixed loci: *DXS14–DXS159–PGK1–DXS72–DXYS1X–DXYS2X–DXS3–DXS94*. The results are shown in figure 2. The plot demonstrates the likeli-

Table 2

Two-point *Z*'s between *DYT3* and X-chromosomal Markers

Locus	Z Values at .0	.01	.05	.10	.20	.30	Z_{max}	θ_{max}	Confidence Interval[a]
DXS14	$-\infty$	0.26	1.54	1.93	1.92	1.47	2.00	.15	.03–.36
DXS106	5.45	5.34	4.90	4.32	3.13	1.95	5.45	.0	.0–.09
DXS159	4.95	4.91	4.69	4.35	3.49	2.44	4.95	.0	.0–.15
PGK1	4.27	4.28	4.17	3.86	2.99	1.93	4.28	.01	.0–.17
DXS72	$-\infty$	5.65	5.98	5.67	4.46	2.93	5.99	.04	.0–.16
DXS95	$-\infty$	2.44	2.89	2.89	2.34	1.62	2.90	.06	.0–.26
DXYS1X ...	$-\infty$	−.67	.59	.98	1.08	.82	1.10	.16	.02–.46
DXYS2X ...	3.30	3.22	2.91	2.52	1.73	.98	3.30	.0	.0–.13
DXYS5X ...	$-\infty$	6.20	6.46	6.05	4.71	3.08	6.48	.04	.0–.15
DXS3	$-\infty$	5.69	5.70	5.10	3.57	1.95	5.83	.03	.0–.12
DXS87	$-\infty$	−10.00	−4.99	−2.91	−1.10	−.35	.0	.5	.20–.50
DXS94	$-\infty$	1.33	2.56	2.86	2.57	1.85	2.87	.11	.02–.30

[a] Derived from (Z_{max} − 1) interval.

hood of *DYT3* being located along the genetic distance defined by these loci. For this analysis, Z_{max} was 8.41 for *DYT3* being located 4.6 cM distal to *DXS159* and 1.5 cM proximal to *PGK1*. A similarly high Z_{max} of 8.34 was observed at 1.6 cM distal to *PGK1* and 2.6 cM proximal to *DXS72*. The one-unit support interval (Z_{max} − 1) extends from 0.8 cM distal of *DXS159* to *DXS72*.

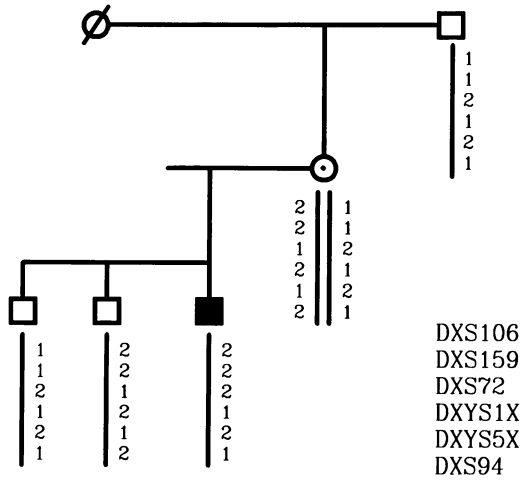

Figure 1 Segregation of informative RFLP alleles at loci *DXS106, DXS159, DXS72, DXYS1X, DXYS5X,* and *DXS94* (top to bottom) in critical family. The smaller allele is designated as "1," the larger as "2." Absolute allele sizes are given in table 3. Note the recombined X chromosome of the affected patient, which places *DYT3* proximal to *DXS72*. The two unaffected brothers are 39 and 35 years old, and the affected individual is 41. For further details, see text.

Linkage disequilibrium for *DYT3* and those marker loci without detectable recombination events in affected individuals was assessed by applying the Δ value and χ^2 analysis. Haplotype frequencies (Chakravarti et al. 1984) were as follows: $g_1 = 12/19, g_2 = 7/19, g_3 = 87/100, g_4 = 13/100$ for *DXS106;* $g_1 = 15/19, g_2 = 4/19, g_3 = 51/94, g_4 = 43/94$ for *DXS159;* $g_1 = 18/19, g_2 = 1/19, g_3 = 66/100, g_4 = 34/100$ and $g_1 = 17/18, g_2 = 1/18, g_3 = 70/100, g_4 = 30/100$ for *PGK1;* $g_1 = 14/19, g_2 = 5/19, g_3 = 26/98, g_4 = 72/98$ for *DXS72;* and $g_1 = 16/19, g_2 = 3/19, g_3 = 78/98, g_4 = 20/98$ for *DXYS2X*. The highest degree of linkage disequilibrium was observed between *DYT3* and *DXS72*, with a Δ value of .47 and $\chi^2 = 15.7$ ($P < .005$). Significant degrees of linkage disequilibrium were also observed between *DYT3* and *DXS106* (Δ = .28), *DXS159* (Δ = .26), and *PGK1* (Δ = .36 and .32, respectively) with significance levels of $P < .05$. The data are summarized in table 3.

Discussion

The present investigation places the XDP locus (*DYT3*) within Xq12–q21.1. Two-point linkage analysis demonstrates that *DXS72* is a distal flanking marker of *DYT3,* and analyses of multipoint linkage and linkage disequilibrium suggest that *DXS159* flanks *DYT3* proximally. Furthermore, multipoint analysis narrows down the confidence interval surrounding *DYT3* to approximately 9 cM and clearly

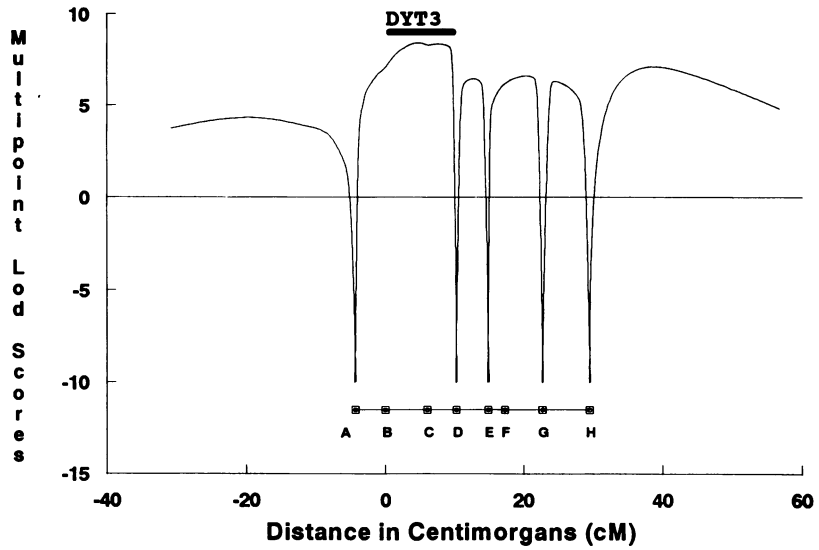

Figure 2 Multipoint *Z*'s obtained with test locus *DYT3* and fixed loci *DXS14* (A), *DXS159* (B), *PGK1* (C), *DXS72* (D), *DXYS1X* (E), *DXYS2X* (F), *DXS3* (G), and *DXS94* (H). The highest lod scores—8.41 and 8.34—were obtained between *DXS159* and *PGK1* and between *PGK1* and *DXS72*, respectively. The (Z_{max} − 1) unit support interval is denoted by the horizontal bar.

excludes the assignment of *DYT3* to proximal Xp (Wilhelmsen et al. 1991).

More distal loci on Xq21.3–q22, including previously linked *DXYS2X* and *DXS3*, still showed significant linkage, with *Z* greater than 3. However, the absence of linkage disequilibrium with these loci indicates that numerous recombinations have occurred between *DYT3* and these loci since the original common ancestor introduced the mutation to the Filipino population. Conversely, the high degree of linkage disequilibrium observed with proximal Xq probes (*DXS106, DXS159, PGK1, DXS72,* and *DXS95*) demonstrates their closer physical proximity to *DYT3*. The high degree of linkage disequilibrium observed for *PGK1* and *DXS72* indicates that *DYT3* is in close proximity to these two loci. The absolute Δ value for *PGK1* was lower than that for *DXS72*, because of the allele frequencies in the Filipino control population. In the case of *PGK1*, the same marker allele was found on the chromosome with the disease allele, in 18 of 19

Table 3

RFLP Frequencies Demonstrating Linkage Disequilibrium in XDP Kindreds for Xq12–q21 Markers

Locus	Enzyme: RFLP(s)	Published Frequency[a]	Filipino Frequency[b] (n^c)	XDP Frequency[d]	Δ[e]	χ^2 (P^f)
DXS106	*Bgl*II: 5.8/1.0	.36/.64	.13/.87 (100)	.37/.63	.28	6.5 (<.05)
DXS159	*Pst*I: 5.5/1.6	.67/.33	.46/.54 (94)	.21/.79	.26	4.0 (<.05)
PGK1	*Pst*I: 5.2/1.8	.85/.15	.34/.66 (100)	.05/.95	.36	6.4 (<.05)
	*Bgl*I: 12/5.5	.21/.79	.70/.30 (100)	.95/.05	.32	5.1 (<.05)
DXS72	*Hin*dIII: 7.2/0.7	.45/.55	.74/.26 (98)	.21/.79	.47	15.7 (<.005)
DXYS2X ...	*Pst*I: 12/9	.29/.71	.20/.80 (98)	.16/.84	.06	.2 (NS)

[a] Obtained from HGM10 (Kidd et al. 1989).
[b] In individuals without a family history of XDP.
[c] Total number of X chromosomes.
[d] Allelic frequencies in XDP patients from 19 unrelated kindreds.
[e] Calculated according to Chakravarti et al. (1984).
[f] NS = nonsignificant.

affected individuals; however, this ratio was only 14/19 for *DXS72*. At present, one cannot conclude that *DYT3* is closer to *DXS72* than to *PGK1*. The next step toward cloning *DYT3* involves the isolation of additional polymorphic DNA sequences proximal and distal to *PGK1*, extending from *DXS159* to *DXS72*. A region of complete allelic homogeneity among XDP patients will allow the definition of a smaller candidate region containing *DYT3*.

Mendelian disorders of adult onset may pose limitations to the application of linkage analysis to gene mapping. The paucity of two- or three-generation families available for investigation, as well as the frequent occurrence of reduced penetrance, can make linkage studies difficult. XDP provides a unique model of an adult-onset neurogenetic disease that circumvents these potential problems: (1) because of the high incidence of the disease on the Philippine island of Panay, a reasonable number of two-generation families is available; (2) the penetrance of this condition is high and appears to approach 100% by the end of the fifth decade of life; and (3) the founder-effect nature of this X-linked disorder permits the analysis of linkage disequilibrium, which can greatly facilitate gene mapping, by the use of highly polymorphic DNA markers.

On the basis of clinical criteria, at least five autosomal forms of primary (idiopathic) dystonia can be distinguished (Müller and Kupke 1990). Gene mapping has been successfully applied to one autosomal dominant form, idiopathic torsion dystonia (ITD), among both Jewish and non-Jewish populations (Ozelius et al. 1989; Kramer et al. 1990). The disease gene, *DYT1*, has been assigned to 9q32–34 by linkage analysis. Genetic investigations into other monogenic dystonias are underway, including investigations of autosomal dominant dystonia-parkinsonism (dopa-responsive dystonia) and myoclonic dystonia. Preliminary results suggest that these disease loci are located on autosomes other than chromosome 9 (X. O. Breakefield, personal communication). Given the predominant symptom of dystonia in all of these genetically distinct disorders, one may predict that the underlying mutations act on different but interrelated steps of the same cellular-neurochemical pathway involved in basal ganglia function.

Previous neuropathological and neurochemical studies of Parkinson disease have well established the importance of the striato-nigral dopaminergic pathway in the pathogenesis of parkinsonism. However, Parkinson disease, which affects over 1% of all Americans older than age 50 years (Adams and Victor 1989), is considered a multifactorial disorder (Ward et al. 1983). Mendelian inheritance is extremely rare (Golbe et al. 1990), as shown by the low concordance rate in twin studies (Marsden 1987; Marttila et al. 1988). Therefore no single-gene defect has been associated with idiopathic Parkinson disease. By studying neurogenetic disorders (such as XDP) associated with parkinsonian symptoms, we are likely to learn more about specific genes involved in the pathogenesis of Parkinson disease.

There are several additional hereditary conditions that manifest concurrent symptoms of dystonia and parkinsonism, such as dopa-responsive dystonia (Segawa et al. 1986; Nygaard et al. 1988), Hallervorden-Spatz disease, Huntington disease, olivopontocerebellar atrophy, Joseph disease, and Wilson disease (reviewed in Fahn et al. 1987; Weiner and Lang 1989). The frequent concurrence of these two symptom complexes suggests the existence of interrelated neural pathways. Thus, by studying a monogenic disorder (such as XDP) that manifests both dystonia and parkinsonism, we have a means to better understand normal and abnormal function of the basal ganglia.

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