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Assignment of the Dystonia-Parkinsonism Syndrome Locus, DYT3, to a Small Region within a 1.8-Mb YAC Contig of Xq13.1

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Summary

A YAC contig was constructed of Xq13.1 in order to sublocalize the X-linked dystonia-parkinsonism (XDP) syndrome locus, DYT3. The contig spans a region of ~1.8 Mb and includes loci DXS453/DXS348/IL2Rγ/GJB1/CCG1/DXS559. For the construction of the contig, nine sequence-tagged sites and four short tandem repeat polymorphisms (STRPs) were isolated. The STRPs, designated as 4704#6 (DXS7113), 4704#7 (DXS7114), 67601 (DXS7117), and B4Pst (DXS7119) were assigned to a region flanked by DXS348 proximally and by DXS559 distally. Their order was DXS348/4704 #6/4704 #7/67601/B4Pst/DXS559. They were applied to the analysis of allelic association and of haplotypes in 47 not-obviously-related XDP patients and in 105 Filipino male controls. The same haplotype was found at loci 67601 (DXS7117) and B4Pst (DXS7119) in 42 of 47 patients. This percentage of common haplotypes decreased at the adjacent loci. The findings, together with the previous demonstration of DXS559 being the distal flanking marker of DYT3, assign the disease locus to a small region in Xq13.1 defined by loci 67601 (DXS7117) and B4Pst (DXS7119). The location of DYT3 was born out by the application of a newly developed likelihood method for the analysis of linkage disequilibrium.

Introduction

The X-linked dystonia-parkinsonism (XDP) syndrome is a severe, adult-onset movement disorder (Lee et al. 1991; Müller 1993) with a mean age at onset of 35 ± 8.0 years. Such initial symptoms as blepharospasm, torticollis, paresthesias, and tremors may involve either the head, the axial musculature, or the extremities. Independent of the site of onset, focal dystonia generalizes within 4.7 ± 2.6 years (range 1–11 years). Parkinsonism including bradykinesia, rigidity, tremor, and loss of postural reflexes is observed in >50% of the cases (K. G. Kupke and U. Müller, unpublished information).

XDP is genetically homogeneous and originated in the Philippine island of Panay. The genetic founder effect and the resulting genetic homogeneity of XDP greatly facilitated fine mapping of the disease locus, DYT3, on the X-chromosome. After initial assignment of DYT3 to the proximal long arm of the X-chromosome by linkage analysis (Kupke et al. 1990, 1992), the locus was further delineated within Xq12-q13 by the analysis of allelic association (Graeber et al. 1992*a*) and of haplotypes (Müller et al. 1994). These studies assigned DYT3 to a region of ~3 Mb in Xq12-q13.1. The short tandem repeat polymorphic (STRP) loci DXS106 and DXS559 flank this interval.

Further delineation of the disease locus requires additional highly polymorphic markers within the DYT3 critical region and their localization on a contig. Although partial YAC contigs of Xq13.1 exist, the order of some loci is still controversial (Willard et al. 1994). Therefore, we set out to construct a YAC contig of Xq13.1 using nine newly developed STS and four STRP markers. Applying these markers to the analysis of allelic association and of haplotypes we assigned DYT3 to a small region defined by the STRP-loci 67601 (DXS7117) and B4Pst (DXS7119).

Patients, Material, and Methods

Patients

DNA samples used were from the same XDP patients and Filipino controls described previously (Graeber et al. 1992*a*).

Statistical Analysis

Δ and Φ values were calculated as parameters of the strength of allelic association, according to Chakravarti et al. (1984) and MacDonald et al. (1991), respectively. Haplotypes were compiled according to Hästbacka et al. (1992). Furthermore, allelic association between DYT3 and various polymorphic marker loci was determined by a recently described likelihood method (Terwilliger

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Table 1

Newly Developed STSs and STRPs in Xq13.1

Marker	Structure	D-Segment Number	Accession Number	Primers 5′–3′	Annealing Temperature (°C)	No. of Alleles Observed	Allele Range (bp)	Heterozygosity		PIC Value	
								Caucasian	Filipino	Caucasian	Filipino
4704#7	$(CA)_{18-25}$	DXS 7114	Z48325	tctcagtgtatttgtttttg acagagcgagactctatctc	53	7	185–201	.65	.69	.61	.66
4704#6	$(CA)_{21-29}$	DXS 7113	Z48324	cttctattggtagcatatcc atgtgaagagacagctaaga	54	9	195–211	.74	.62	.69	.60
67601	$(CA)_{22-27}$	DXS 7117	Z48329	ggtcatcagctctgtcctta ataaataatgccacggacta	58	6	192–202	.54	.56	.51	.52
B4Pst	$(CA)_{19-35}$	DXS 7119	Z48332	acagggaggaagtatggtat ttgtttttctttctttctttc	55	9	388–420	not tested	.83	not tested	.81
4704#8	STS	DXS 7115	Z48326	acccactccaatatctatct tccagcaaccataagtagta	55	1	148				
4704#9E	STS	DXS 7116	Z48327	tcttcccttactttctccta gctttgctacctactgacta	55	1	258				
4704#10E	STS	DXS 7111	Z48322	agaagagtggtggaagatt aactgaagactgggagaaat	54	1	149				
4704#5	STS	DXS 7112	Z48323	tcattttgccgagatagaga aacccagagccattgtcact	60	1	268				
8067#3E	STS	DXS 7118	Z48331	ttctcaaggtcccataaata ccagccttattcttgtttac	56	1	193				
4693#5	STS	DXS 7120	Z48321	aactctttttatctgtc gaggcaggagaatcact	44	1	166				
776#2E	STS	DXS 7122	Z48330	ctccacgacgcacagacagg ccacccacaggccaggact	68	1	45				
p131	STS	DXS 7123	Z48333	ggctaaatcctcaaagaaca gcactgtctctggtctgga	59	1	167				
4775#10	STS	DXS 7121	Z48328	tcctacctcagcctccaaagt agaattgcttgactccagga	62	1	163				

NOTE.—All loci information was entered into the Genome Data Base (submission number: G00-453-893).

Table 2

Characterization of YACs Used for Xq13.1 Contig Construction

YAC	ICRF No.	Library	Size (kb)	FISH	DXS453 (STRP)	4704#10E (STS)	4704#5 (STS)	DXS348 (STS)	4704#6 (STRP)
4852	E06124	ICRF	620	X+8	+	+	–	–	–
4856	B12133	ICRF	500	X+14	+	+	+	+	+
4857	C0376	ICRF	800	X	+	+	+	+	+
4704	D1013	ICRF	450	X	–	+	+	+	+
917 E6		CEPH	1600	X	–	+	+	+	+
776 G10		CEPH	690	X	–	–	–	–	–
8067 #2		ICRF	820	X+7	–	–	–	–	–
381 C9		CEPH	500	X+6+9	–	–	–	–	–
498 C6		CEPH	480	X+13	–	–	–	–	–
WXD945D111B8		Washington	330	X	–	–	–	–	–
401 C11		CEPH	600	X+8	–	–	–	–	–
4693	y900E11144	ICRF	280	X+16	–	–	–	–	–
769 F2		CEPH	800	X	–	–	–	–	–
4775	y900F065	ICRF	380	X+2	–	–	–	–	–

NOTE.—E = end fragment of YAC-insert.

1995). Here, the strength of association with each marker locus is measured by λ, which is the percent association at each locus. Multilocus likelihoods were computed using markers between DXS106 and DXS559 to fine map the location of the disease gene by using an extension of the same algorithm.

PIC and heterozygosity values were calculated according to Botstein et al. (1980). These values were determined by the analysis of 104 Caucasian and of 105 Filipino X chromosomes from healthy individuals.

YACs

YACs were isolated from the CEPH, Imperial Cancer Research Fund (ICRF), and University of Washington libraries by using known STRP markers. STSs and additional STRPs were prepared from these YACs as described elsewhere (Graeber and Müller 1992; Graeber et al. 1992*b*). In brief, YAC-containing yeast DNA was separated by pulsed-field gel electrophoresis (PFGE), and YACs were cut out of the gel. DNA was digested with *Eco*RI and a library constructed in λgt10. The library was screened with a ^{32}P-end-labeled $(CA)_{17}$-oligonucleotide and subsequently with total human DNA. Clones positive for both $(CA)_n$ and human DNA were then subcloned into pBluescript™ (Stratagene) and sequenced.

YACs were checked for chimerism by using FISH according to standard procedures. In brief, YAC containing yeast DNA was labeled with digoxigenin, was hybridized to H-banded chromosomes, and was photographed as given in Köhler et al. (1994). Sizes of the YACs were determined by PFGE (CHEF-DR™II-System, BioRad) using the chromosomes of *Saccharomyces cerevisiae* strain YPH49 as a size standard. End pieces of YACs were isolated by applying the inverse PCR method of Triglia et al. (1988) with several adjustments. The primers were constructed from both right (AAC-GCCCGATCTCAAGATTAC, TCCATTCACTTCCCAGACTTG) and left (AATACTCTCGGTAGCCAAGTTG, TTATCCGGTCCTTCCAAGAT) arms of the YAC vector (pYAC4). The YAC was then cleaved with such frequently cutting enzymes as *Hha*I, *Sau*3A, and *Hae*III that do not have restriction sites between the primers. This was followed by a ligation step that resulted in circularization of the fragment containing the *Eco*RI site of the YAC arm and a part of the human insert. The circularized DNA was cleaved with either *Sma*I (right arm) or *Acc*I (left arm), and the linearized fragment was amplified using right- or left-arm primers.

PCR Conditions

Annealing for PCR amplification of newly developed STSs and STRPs are given in table 1. Each PCR reaction was run for 30 cycles, with annealing at the temperatures listed in table 1 for 1 min, extension at 72°C for 30 s, and denaturation for 30 s at 94°C. This was preceded by 3 min at 94°C. The reaction was terminated with a final extension at 72°C for 5 min. The only marker run differently was 776#2E with annealing at 68°C (1 min), denaturation at 94°C (30 s) and no extension for 30 cycles.

Results and Discussion

YAC Contig in Xq13.1

In initial experiments we isolated YACs from the DYT3 critical region that is flanked by loci DXS453

Locus (Type)														
4704#7 (STRP)	4704#8 (STS)	4704#9E (STS)	IL2Rγ (STS)	67601 (STRP)	8067#3E (STS)	GJB1 (STS)	B4Pst (STRP)	4693#5 (STS)	CCG1 (STS)	4775#10 (STS)	DXS559 (STRP)	776#2E (STS)	DXS131 (STS)	p131 (STS)
−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
−	−	−	+	+	+	+	+	+	+	+	+	+	−	−
−	−	−	+	+	+	−	−	−	−	−	−	−	−	−
−	−	−	+	+	+	+	+	−	−	+	−	−	−	−
−	−	−	−	+	+	+	+	−	−	−	−	−	−	−
−	−	−	−	−	−	−	−	+	+	−	−	−	−	−
−	−	−	−	−	−	+	+	+	+	+	−	−	−	−
−	−	−	−	−	−	−	−	+	+	−	−	−	−	−
−	−	−	−	−	−	−	+	+	+	+	+	+	+	+
−	−	−	−	−	−	−	−	−	−	+	+	+	+	+

and DXS559. Markers used for the isolation of YACs included from proximal to distal DXS453 (Weber et al. 1990), DXS348 (Barker et al. 1989), IL2Rγ (Noguchi et al. 1993), GJB1 (Kumar and Gilula 1986), CCG1 (Sekiguchi et al. 1988) and DXS559 (Roustan et al. 1992). All YACs isolated with these markers were checked for chimerism by FISH. The results are summarized in table 2. The sizes of the YACs isolated were in the range of 280 kb–1.6 Mb (table 2). We then isolated nine STSs and four STRPs from these YACs. Four of the STSs were derived from the left- and right-arm ends of YAC inserts 4704, 8067#2, and 776G10. They are #9E-DXS7116, #10E-DXS7111, #3E-DXS7118, and #2E-DXS7122 of tables 1 and 2. The remaining 5 STSs were either nonpolymorphic $(CA)_n$-containing markers (4704#8-DXS7115, 4693#5-DXS7120, and 4775#10-DXS7121) or were randomly isolated stretches of YAC DNA (4704#5-DXS7112 and p131-DXS7123) that were subcloned into pBluescript™ (Stratagene). The clones were obtained according to the same protocol that was applied to the isolation of YAC end pieces (see Patients, Material, and Methods). The primer sequences of all nine newly developed STSs are given in table 1. The four STRPs were isolated from YAC 4704 (#6-DXS7113 and #7-DXS7114 of table 2), 8067#2 (67601-DXS7117 of table 2) and from a cosmid pool derived from hybridizing a YAC containing CCG1 to the ICRF flow-sorted chromosome X cosmid filters (B4Pst-DXS7119; Nizetic et al. 1991). This YAC (4771 from ICRF) had several deletions, was chimeric (not shown) and thus not used in further experiments. X-specificity was verified of all newly developed STSs and STRPs by PCR amplification of DNA derived from a somatic cell hybrid, containing the X as the only human chromosome. PCR conditions for amplification of all 13 markers as well as allele sizes are given in table 1. PIC and heterozygosity of the four STRPs are also listed in table 1, as is the range of the lengths of the dinucleotide repeats.

The newly developed markers together with pre-

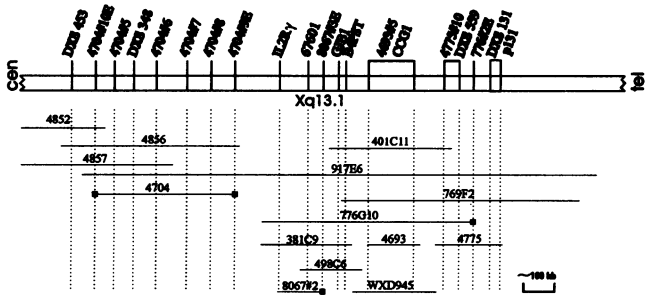

Figure 1 YAC-contig in Xq13.1 The figure is based on the findings listed in table 2. Horizontal lines between bars indicate that the order of loci cannot be determined yet. YAC and locus designations are the same as in table 2. Only X chromosomal portions of chimeric YACs (4852, 4856, 8067#2, 381C9, 498C6, 401C11, 4693, and 4775) are given. Cloned end pieces of YACs are indicated by black squares.

Table 3

Φ and Δ Values for STRPs Associated with DYT3

Locus	Φ	Δ	χ^2	p	df
4704#6	.99	.81	114.8	$<10^{-6}$	8
4704#7	.94	.70	73.2	$<10^{-6}$	6
67601	.98	.83	99.5	$<10^{-6}$	5
B4Pst	.98	.81	93.4	$<10^{-6}$	8

viously known loci allowed the construction of a YAC contig of the region and the unequivocal ordering of loci previously assigned to this region (Willard et al. 1994). Figure 1 gives the order of overlapping YACs and their sizes. This contig is adjacent to the proximal contig of Willard et al. (1994) (cen DXS159 to CCG1 tel). It does not overlap with the distal contig of Lafrenière et al. (1993) (cen RPS4X, DXS227, DXS128E tel) since loci RPS4X, PHKA1, and DXS227 were found to be absent from any of the YACs used for the construction of the present contig. The results clarify several open questions as to the order of known loci in Xq13.1 (Willard et al. 1994). We demonstrate that DXS559 is distal to CCG1 and not vice versa. Furthermore, Il2Rγ was assigned to a region proximal to GJB1. Thus, the order of loci is cen/Il2Rγ/GJB1/CCG-1/DXS559/DXS131/tel.

Mapping of DYT3 within Xq13.1

The alleles were analyzed at the four new STRP loci in XDP patients from 47 not-obviously-related families and in 105 unaffected Filipino male controls. Both Δ and Φ values revealed a high degree of allelic association (table 3). At all four loci the most common disease-associated allele was rare in the Filipino control population (table 4). At locus 4704#6 (DXS7113) the frequency of the most common allele (211 bp) was 38/47 in patients and 1/105 in controls and was comparable to the frequencies previously detected at the closely adjacent locus DXS453 (allele of 174 bp in 37 of 47 patients and in 1 of 105 controls; Müller et al. 1994). The strength of allelic association increased between DYT3 and the more distal markers. Thus, at locus 67601 (DXS7117), the most frequent disease-associated allele of 200 bp was found in 43 of 47 patients and in 9 of 105 controls. Similar frequencies were observed at locus B4Pst (DXS7119; 396-bp allele in 43 of 47 patients and in 11 of 104 controls). Thus, DYT3 must be located in the region defined by loci 67601 (DXS7117) and B4Pst (DXS7119). Yet it must be proximal to DXS559, a locus previously shown by recombination in a three-generation family to flank DYT3 distally (Müller et al. 1994). This recombination did not occur in the same three-generation family at any of the newly developed STRP loci (not shown).

Location of DYT3 was further analyzed by the application of a new likelihood method for the analysis of linkage disequilibrium (Terwilliger 1995). As shown in table 5, the strength of association, as measured by λ, is high for each of the new markers and decreases as one moves away from 67601 (DXS7117) and B4Pst (DXS7119) in either direction. The multipoint likelihood varies across the region between DXS106, the proximal flanking marker of DYT3 (Müller et al. 1994), and DXS559, the distal flanking marker (see above).

Table 4

Allele Sizes and Frequencies at Various Loci in Filipino Male Controls and Patients

Locus and STRPs	Allele Size (bp)	No. of Filipino Male Controls	No. of Patients
4704#6 (DXS7113):			
1	195	14	1
2	197	1	1
3	199	9	1
4	201	0	1
5	203	7	0
6	205	3	0
7	207	62	4
8	209	8	1
9	211	1	38
		105	47
4704#7 (DXS7114):			
1	185	17	2
2	187	2	0
3	191	11	2
4	195	10	37
5	197	52	5
6	199	11	1
7	201	2	0
		105	47
67601 (DXS7117):			
1	192	2	0
2	194	66	4
3	196	21	0
4	198	6	0
5	200	9	43
6	202	1	0
		105	47
B4Pst (DXS7119):			
1	388	1	0
2	392	7	0
3	396	11	43
4	400	34	4
5	404	9	0
6	408	17	0
7	412	9	0
8	416	10	0
9	420	6	0
		104	47

The peak levels of disequilibrium are around the loci 67601 (DXS7117) and B4Pst (DXS7119).

Furthermore, location of DYT3 in close proximity to marker loci 67601 (DXS7117) and B4Pst (DXS7119) was shown by haplotype analysis (table 6). The same alleles (5 and 3) were found at these loci in 42 of 47 patients with the form of the haplotype being NNN53N. This high percentage of identical haplotypes decreases when other adjacent loci are investigated. For example, at the proximally adjacent loci 67601 (DXS7117) and 4704#7 (DXS7114), the most common haplotype, NN45NN is only detected in 37 of 47 patients. It may be that complete allelic association between DYT3 and

Table 5

Locus Disequilibrium Measures

Locus	λ_i	P	Distance (kb)
DXS106	.56	.006	...
DXS453	.46	.14	650
4704#6	.80	1.0×10^{-24}	270
4704#7	.76	5.9×10^{-17}	150
67601	.91	3.3×10^{-24}	480
B4Pst	.90	1.1×10^{-22}	120
DXS559	.84	1.3×10^{-23}	350
DXS227	.84	3.8×10^{-21}	430

NOTE.—Table of single-locus disequilibrium measures for all markers typed along the region from DXS106 to DXS559. The peak levels of disequilibrium in this analysis are found around loci 67601 and B4Pst, but the disequilibrium remains strong at DXS227.

any STRP locus does not exist since slippage mutations at such loci are fairly frequent. In any case, the data demonstrate that DYT3 lies within a small region defined by markers DXS7117 (67601) and DXS7119 (B4Pst).

The genes assigned to this region so far are not good candidates of DYT3. Thus, IL2Rγ was found to be mutated in severe combined immunodeficiency (SCIDXI; Noguchi et al. 1993). GJB1 turned out to be the gene underlying X-linked dominant Charcot-Marie-Tooth disease (Bergoffen et al. 1993; Fairweather et al. 1994), and mutations were not found in a XDP patient by sequence analysis (N. Haites, personal communication). The gene CCG1 also assigned to this region codes for part of transcription factor TFIID (Hisatake et al. 1993; Ruppert et al. 1993), and mutations result in a cell-cycle growth phase I defect. A mutation in this gene would probably be either lethal or result in less specific symptoms than observed in XDP. Therefore, the isolation of new transcripts from the region and their analysis in XDP patients will be required for the identification of DYT3.

Table 6

Haplotypes for Loci Order DXS453/4704#6/4704#7/67601/B4Pst/DXS559

Haplotype	No. of Patients
Haplotypes including allele 5 and 3 at loci 67601 (DXS7117) and B4Pst (DXS7119):	
6 9 4 5 3 6	31
6 9 4 5 3 5	3
6 9 4 5 3 7	1
6 9 4 5 3 8	1
6 9 5 5 3 6	1
3 1 1 5 3 6	1
3 2 1 5 3 6	1
3 8 6 5 3 6	1
3 4 3 5 3 9	1
5 9 4 5 3 6	1
N N N 5 3 *N*	42
Haplotypes including other alleles at loci 67601 (DXS7117) and B4Pst (DXS7119):	
3 7 5 2 4 6	3
3 3 3 2 3 6	1
4 7 5 5 4 5	1

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