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ORIGINAL INVESTIGATION

Wendy H. Raskind · Tamara Bolin · John Wolff
John Fink · Mark Matsushita · Michael Litt
Hillary Lipe · Thomas D. Bird

Further localization of a gene for paroxysmal dystonic choreoathetosis to a 5-cM region on chromosome 2q34

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Abstract Paroxysmal dystonic choreoathetosis (PDC) is a rare neurological disorder characterized by episodes of involuntary movement, involving the extremities and face, which may occur spontaneously or be precipitated by caffeine, alcohol, anxiety, and fatigue. PDC is transmitted as an autosomal dominant trait with incomplete penetrance. A gene implicated in this paroxysmal disorder has been mapped to a 10–15 cM region on chromosome 2q31–36 in two families. We describe a third family with PDC. Two-point linkage analyses with markers linked to the candidate PDC locus were performed. A maximum two-point LOD score of 4.20 at a recombination fraction of zero was obtained for marker D2S120, confirming linkage to the distal portion of chromosome 2q. The anion exchanger gene, SLC2C, maps to this region, but the family was poorly informative for polymorphic markers within and flanking this candidate gene. Haplotype analysis revealed a critical recombination event that confines the PDC gene to a 5-cM region bounded by the markers D2S164 and D2S377. We compared the haplotype in our family with that in another chromosome 2-linked PDC family, but did not detect a region of shared genotypes. However, identifying a third family whose disease maps to the same region and narrowing the critical region will facilitate identification of the 2q-linked PDC gene.

W. H. Raskind (✉)
Department of Medicine, Division of General Internal Medicine, Box 357720, University of Washington, Seattle, WA 98195, USA
Tel.: +1-206-543-3177; Fax: +1-206-616-7366;
e-mail: wendyrun@u.washington.edu

W. H. Raskind · T. Bolin · J. Wolff · M. Matsushita · T. D. Bird
Department of Medicine, Division of Medical Genetics, University of Washington, Seattle, WA 98195, USA

J. Fink
Department of Neurology, University of Michigan and GRECC, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, MI 48104, USA

M. Litt
Departments of Biochemistry and Medical Genetics, Oregon Health Sciences University, Portland, OR 97201, USA

H. Lipe · T. D. Bird
Department of Neurology, University of Washington and Seattle Veterans Affairs Medical Center, Seattle, WA 98108, USA

Introduction

Movement disorders comprise a diverse group of syndromes that can be sporadic or familial, congenital or acquired. They are classified by distinct types of movement, precipitating factors, age of onset and duration of symptoms (Richards and Barnett 1968; Lance 1977; Goodenough et al. 1978; Demirkiran and Jankovic 1995). Paroxysmal dystonic choreoathetosis (PDC, MIM11880) is characterized by episodes of dystonic posturing and choreoathetotic movement. Attacks, which usually begin in childhood or young adulthood, typically start with a tugging sensation, usually in one hand or one foot, followed by dystonic spasms of the face and limbs, which may progress to involve the entire body. The facial dystonia may cause slurred speech. Attacks can be precipitated by caffeine, alcohol, chocolate, emotional stress, anxiety or fatigue, but may also occur spontaneously. Physical exertion does not bring on attacks. Episodes may last for minutes to hours. Clonazepam has been helpful in controlling the spasmodic attacks, whereas other barbiturates and phenytoin are less effective. Its prolonged duration, precipitating factors, and the ineffectiveness of certain treatments distinguish PDC from similar syndromes, such as paroxysmal kinesiogenic choreoathetosis, which are characterized by shorter lasting, movement-induced symptoms and often respond to phenytoin (Kertesz 1967; Demirkiran and Jankovic 1995).

Molecular linkage analyses have demonstrated heterogeneity in the paroxysmal disorders associated with dystonia and choreoathetosis. Recently, a PDC locus has been mapped to the distal region of chromosome 2q in two unrelated families with choreoathetosis and dystonia (Fink et al. 1996; Fouad et al. 1996), whereas a locus for a syndrome associated with choreoathetosis and spastic-

ity has been mapped to chromosome 1p (Auberger et al. 1996).

Abnormalities in gated calcium, sodium, chloride, and potassium ion channels have been found to be responsible for several familial paroxysmal neurologic diseases (e.g., Cannon et al. 1991; McClatchey et al. 1992; Browne et al. 1994; Jurkat-Rott et al. 1994; Ptacek et al. 1994; Hudson et al. 1995; Mailander et al. 1996). The episodic nature of PDC suggests that it may have as its basis mutations in an ion channel gene. We report linkage studies and preliminary evaluation of a candidate channel gene in a new PDC kindred.

Materials and methods

Subjects

We evaluated a three-generation North American family of German descent segregating an episodic movement disorder characterized by staring, muscle stiffness, and choreoathetotic movement. Part of the pedigree of family ED01 is shown in Fig. 1. Onset was in childhood except in individual IV-9, whose first attack occurred in her late twenties. Episodes progressed from a tightening sensation of the extremities on one or both sides to flexion, contraction and twisting of the arms and legs. Involvement of the muscles of the face resulted in slurred or unintelligible speech and dysphagia. The episodes typically lasted from several minutes to several hours and varied in frequency from once a day to once a month. Attacks generally were precipitated by caffeinated drinks (especially coffee), alcohol, chocolate, cocoa, fatigue, hunger and anxiety, although during a recent evaluation of individual III-6 consumption of strong black tea and a large chocolate bar did not induce an episode. Several affected family members reported that meprobamate, TUMS and vinegar were effective preventive agents. Exercise, muscle stretching or rubbing the extremities were also reportedly of some benefit. Between episodes, physical examinations were entirely normal, with no neurological abnormalities detected. The movement disorder in this family appears to be transmitted as an autosomal dominant trait with incomplete penetrance. One obligate heterozygote, IV-11, is completely asymptomatic at age 36; other unaffected obligate heterozygotes have previously been reported (Fink et al. 1996; Fouad et al. 1996).

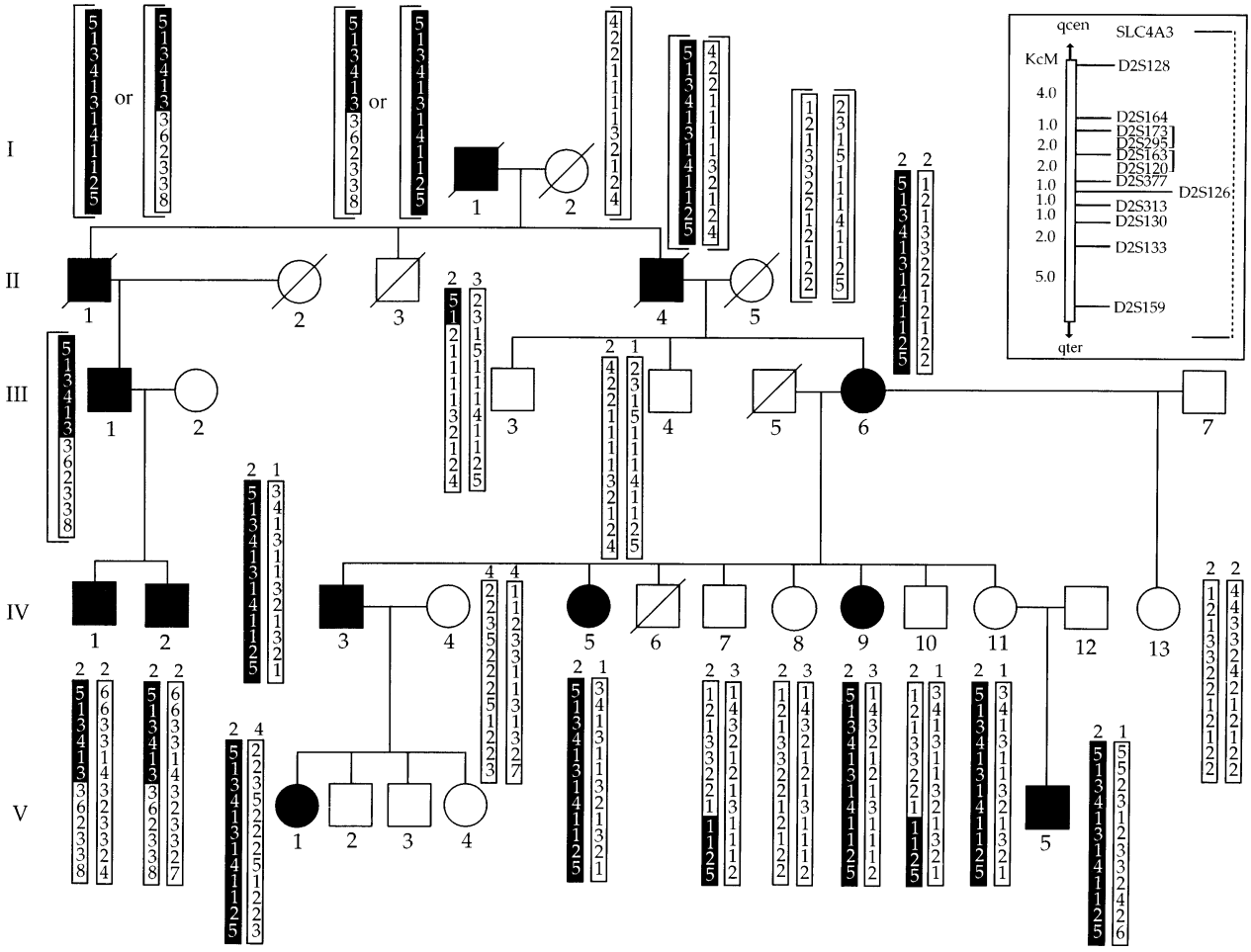

Fig. 1 Partial pedigree of family ED01 showing individuals affected by paroxysmal dystonic choreoathetosis as *black* symbols. The order of markers and distance in centimorgans given in the inset are according to GDB Linkage Map 1212462 and 1996 Chromosome 2 Workshop Integrated Consensus Map 4225469. The putative disease haplotypes is shown in *white letters on a black chromosome segment*. Inferred haplotypes are enclosed in *brackets* and have been constructed to minimize the number of recombination events. The location of SLC2C relative to the other markers is not known. Genotypes for the SLC2C-linked polymorphic marker SLC4A3 are arbitrarily shown above the others

Genotyping

Under protocols approved by the Institutional Review Board of the University of Washington, blood samples from 16 family members were collected into EDTA-containing tubes and genomic DNA was isolated from leukocytes or cell lines according to the salt-chloroform extraction method described by Mullenbach et al. (1989). DNA was PCR-amplified in a MJ Research PTC-100 programmable thermal controller as previously described (Raskind et al. 1995). Genotypes were evaluated for markers linked to PDC (D2S128, D2S164, D2S173, D2S295, D2S163, D2S120, D2S377, D2S126, D2S313, D2S130, D2S133, D2S159), idiopathic torsion dystonia (GSN, D9S282, D9S60, ASS), hereditary progressive dystonia/dopa-responsive dystonia (D14S52, D14S66, D14S566, HSPA2), episodic ataxia and a cluster of potassium channel genes (D12S372, D12S99, D12S93) (Browne et al. 1994; Litt et al. 1994), as well as for a short tandem repeat (STRP) polymorphism (SLC4A3) identified within an SLC2C-containing cosmid (Su et al. 1994). SLC2C is an ion exchanger gene on chromosome 2q36. MapPair oligonucleotide primers were obtained from Research Genetics and one primer of each pair was end-labeled with [γ^{32}]P by a T4 kinase reaction. In some cases, multiplex PCR reactions with two to three primer sets were done when the range of allele sizes allowed clear separation of products. Allele sizes on the autoradiographs were standardized by comparison to DNAs from CEPH family 1331 (Dausset et al., 1990).

Linkage analysis

Two-point linkage analyses were performed with the MLINK and ILINK subroutines of the LINKAGE program, version 5.1 (Cottingham et al. 1993; Lathrop et al. 1984, 1986; Lathrop and Lalouel 1984; Schaffer et al. 1994). Autosomal dominant inheritance with a disease allele frequency or 0.0001 was assumed for the PDC locus and analyses were done for penetrance values of 0.90 and 0.80. Allele sizes and frequencies for polymorphic loci were obtained from the Genome Data Base (GDB). Order and distances between the loci were obtained from GDB Généthon Linkage Map 1212462, 1996 Chromosome 2 Workshop Integrated Consensus Map 4225469 and Chromosome 2 Cytogenetic Map 1012596. The previously unreported alleles of D2S128 (allele 3 is 154 bp), D2S164 (alleles 2 and 6 are 275 bp and 295 bp, respectively), D2S159 (alleles 1, 2, 4 and 8 are 153 bp, 163 kb, 167 bp and 179 bp, respectively) observed were each arbitrarily assigned a frequency of 0.01.

Results

Exclusion analysis

We analyzed polymorphic loci flanking genes responsible for the neurological disorders, idiopathic torsion dystonia (ITD, Bressman et al. 1994; Ozelius et al. 1989, 1992), episodic ataxia (EA, KCNA1; Browne et al. 1994) and hereditary progressive dystonia/dopa-responsive dystonia (HPD/DRD; Ichinose et al. 1994; Tanaka et al. 1995), as possible candidate genes for the disorder in family ED01. Haplotypes were constructed by hand. For each candidate gene, there was no association between a specific haplotype and the phenotype of PDC in family ED01. Therefore, these genes, as well as the other potassium (KCNA5, KCNA6) and calcium (CACNL1A1) ion channel genes linked to EA (Litt et al. 1994), are not etiologic in PDC (data not shown).

Linkage to 2q31–36

Linkage was then evaluated to 12 microsatellite markers localized to 2q31–36, a region recently implicated in two families with PDC whose phenotypes resembled that seen in ED01 (Fink et al. 1996; Fouad et al. 1996). We observed one confirmed instance of incomplete penetrance in family ED01 (individual IV-11), thus leading us to a rough estimate of 8/9 or ≈ 90% for penetrance. Table 1 shows the two-point LOD scores derived under the assumption of autosomal dominance, disease allele frequency of 0.0001 and the estimated penetrance of 90%. However, the small number of subjects analyzed does not allow us to state reliably the actual penetrance of this disorder. Thus, we also calculated the lod scores under a model in which the penetrance was only 80%. With penetrance set at 90% a maximum pairwise lod score of 4.19 at $\theta = 0.001$ was obtained for the marker D2S120. As expected, lower lod scores were obtained when the penetrance was set at 80%, but a significant maximum lod

Table 1 Two-point linkage analysis for markers on chromosome 2q

Marker	Lod score (Z) at recombination fraction (θ) of							Z_{max}	θ_{max}
	0.001	0.01	0.05	0.10	0.20	0.30	0.40		
D2S128	2.06	2.05	1.99	1.86	1.50	1.02	0.45	2.06	0.001
D2S164	3.54	3.51	3.31	3.04	2.39	1.65	0.84	3.55	0.001
D2S173	2.03	1.98	1.77	1.50	0.96	0.47	0.12	2.03	0.001
D2S295	3.84	3.78	3.49	3.11	2.31	1.47	0.63	3.85	0.001
D2S163	2.27	2.23	2.05	1.83	1.37	0.89	0.37	2.27	0.001
D2S120	4.19	4.12	3.82	3.43	2.59	1.70	0.78	4.20	0.001
D2S377	–0.12	0.82	1.33	1.39	1.17	0.79	0.32	1.39	0.088
D2S126	0.48	1.42	1.88	1.87	1.54	1.04	0.46	1.90	0.071
D2S313	–2.34	–1.32	–0.52	–0.18	0.05	0.06	0.00	0.344	0.5
D2S130	–1.58	–0.61	–0.01	0.18	0.26	0.22	0.13	0.262	0.196
D2S133	0.04	0.04	0.05	0.05	0.04	0.02	0.00	0.50	0.069
D2S159	–1.77	–0.75	0.02	0.33	0.50	0.41	0.20	0.50	0.202
SLC4A3	1.68	1.65	1.50	1.31	0.94	0.58	0.26	1.69	0.001

score of 3.96 was still achieved for D2S120 at $\theta = 0.001$. The fact that the maximum lod score was higher at a penetrance of 90% than at 80% supports the validity of the higher penetrance in EDS (Clerget-Darpoux et al. 1986; Elston 1989; Greenberg 1989).

To narrow the critical region containing the PDC gene, haplotypes were evaluated for informative recombination events. Individuals IV-1 and IV-2 share the portion of the haplotype including and proximal to marker D2S120 with all other affected members and obligate heterozygotes in the family. A recombination event must have occurred between PDC and D2S377 in one of the ancestors, II-1, II-4 or III-1.

Linkage to candidate gene SLC2C

Individual III-6 was homozygous for the STRP marker tightly physically linked to SLC2C (Su et al. 1994). Therefore, linkage (Table 1) and haplotype (Fig. 1) analyses were not maximally informative.

Discussion

Given the clinical similarities between disease in our family and PDC, we evaluated linkage to the recently reported PDC locus on chromosome 2q31–36 (Fink et al. 1996; Fouad et al. 1996). We also considered as candidate loci the map positions for ITD (ITD1) on chromosome 9q34 (Ozelius et al. 1992) and HPD (GTP cyclohydrolase I) on chromosome 14q2.1–q22.2 (Ichinose et al. 1994; Tanaka et al. 1995). The paroxysmal nature of the attacks experienced by affected individuals in family ED01 suggests that an abnormal ion channel gene might be responsible. Mutations in sodium, chloride, potassium and calcium ion channel genes have been found to cause other familial neuromuscular diseases characterized by the episodic occurrence of symptoms (e.g., Cannon et al. 1991; Browne et al. 1994; Ptacek et al. 1994; Hudson et al. 1995; Mailander et al. 1996). Therefore, we analyzed linkage to the cluster of potassium channel genes KCNA5, KCNA6, KCNA1 and the calcium channel gene CACNL1A1 at chromosome 12p13 (Litt et al. 1994) mapped to the region containing the locus for EA. Another calcium channel gene, CACNL1A5, maps to chromosome 9q32–34 near ITD1.

The penetrance of PDC appears to be high. In family ED01, there are eight clinically affected individuals and one unexpressing obligate heterozygote. We obtained significant evidence in favor of linkage of disease in family ED01 to chromosome 2q31–36 even under a conservative penetrance estimate of 80%. No evidence for linkage to the other regions was found. Combined haplotype information from two prior studies localized PDC to the 6-cM region bounded proximally by D2S164 (Fink et al. 1996) and distally by D2S126 (Fouad et al. 1996). The recombination event in our family narrows the critical region to the 5-cM interval between D2S164 and D2S377.

The anion exchanger gene SLC2C maps to chromosome 2q between D2S128 and D2S126, but its position relative to the other markers employed in this study is not known precisely (Su et al. 1994). Unfortunately, the genotypes of individuals in ED01 for a polymorphism identified within a SLC2C-containing cosmid were not fully informative and did not allow localization of this candidate gene within the other 12 markers tested on chromosome 2q or exclusion from the critical region for PDC. Additional studies of SLC2C in affected members of this family are underway.

PDC is a very rare member of the syndromes associated with choreoathetotic and dystonic movements. Very few families with PDC have been reported since its first description by Mount and Reback in 1940. Linkage studies in three families with episodic choreoathetosis have demonstrated locus heterogeneity. The disease gene in one family whose illness is characterized by spasticity that persists between attacks in some affected individuals was mapped to chromosome 1p (Auberger et al. 1996). There are striking clinical similarities among ED01 and the two families in which affected individuals showed dystonic posturing, but not spasticity, and who were neurologically normal between episodes (Fink et al. 1996; Fouad et al. 1996). The disease locus in all three of these families maps to chromosome 2q; there is no evidence for genetic heterogeneity within PDC not associated with spasticity. To look for evidence of a common mutational origin in this rare disorder, we compared the haplotypes in ED01 and the kindred described by Fink et al. (1996). A shared region of genotypes was not detected for markers in or near the critical region on chromosome 2q31–36.

Several schemes to classify the dystonic syndromes into subtypes have been proposed, based on the nature of the provocative stimuli (kinesiogenic versus nonkinesiogenic), age of onset of symptoms, duration of symptoms and response to therapy (Lance 1977; Goodenough et al. 1978; Fahn 1994; Demirkiran et al. 1995). Additional mapping studies and the eventual cloning of the causative gene(s) will determine whether this clinical scheme is biologically meaningful. Identification of the gene involved in PDC will advance our understanding of the normal human motor system and suggest possible treatment strategies for the disease.

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