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Familial Infantile Convulsions and Paroxysmal Choreoathetosis: A New Neurological Syndrome Linked to the Pericentromeric Region of Human Chromosome 16

Pierre Szepetowski,[1,*] Jacques Rochette,[2,3,*] Patrick Berquin,[2] Charles Piussan,[2] G. Mark Lathrop,[1] and Anthony P. Monaco[1]

[1]The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford; [2]Pédiatrie I and Centre de Génétique Clinique, CHU d'Amiens, and [3]Laboratoire de Génétique Moléculaire Médicale, Faculté de Médecine, Université Jules Verne, Amiens, France

Summary

Benign infantile familial convulsions is an autosomal dominant disorder characterized by nonfebrile seizures, with the first attack occurring at age 3–12 mo. It is one of the rare forms of epilepsy that are inherited as monogenic Mendelian traits, thus providing a powerful tool for mapping genes involved in epileptic syndromes. Paroxysmal choreoathetosis is an involuntary-movement disorder characterized by attacks that occur spontaneously or are induced by a variety of stimuli. Classification is still elusive, and the epileptic nature of this movement disorder has long been discussed and remains controversial. We have studied four families from northwestern France in which benign infantile convulsions was inherited as an autosomal dominant trait together with variably expressed paroxysmal choreoathetosis. The human genome was screened with microsatellite markers regularly spaced, and strong evidence of linkage for the disease gene was obtained in the pericentromeric region of chromosome 16, with a maximum two-point LOD score, for D16S3133, of 6.76 at a recombination fraction of 0. Critical recombinants narrowed the region of interest to a 10-cM interval around the centromere. Our study provides the first genetic evidence for a common basis of convulsive and choreoathetotic disorders and will help in the understanding and classification of paroxysmal neurological syndromes.

Introduction

Epilepsy is one of the most common neurological disorders, affecting ~4% of individuals at least once in their life. Epileptic seizures involve an abnormal electrical activity of cerebral neurons, leading to paroxysmal clinical manifestations of different types (motor, sensitive, sensorial, and/or psychic). "Convulsions" are defined as epileptic seizures with abnormal motor activity, whereas the term "epilepsy" should be restricted to the occurrence of recurrent and persisting seizures in a given individual.

A genetic contribution to the etiology of epilepsy has long been suspected. In addition to the understanding of pathogenetic mechanisms, genetic studies should also help in classification of the different forms of epilepsies. In most forms of familial epilepsy, no simple Mendelian mode of inheritance can be seen, with both genic and environmental factors influencing susceptibility (for a review, see Ottman et al. 1997). This inherent complexity may explain why, until recently, only few genetic studies had been performed successfully. However, evidence now exists for genetic linkage of an increasing number of susceptibility loci to specific chromosomal regions. In benign neonatal familial convulsions, linkages to chromosome 20q13.2 markers (Leppert et al. 1989) and to chromosome 8q24 markers (Lewis et al. 1993) have been demonstrated. Region 20q13.2 has also been associated with autosomal dominant nocturnal frontal lobe epilepsy (Phillips et al. 1995), which could be due to mutations in the gene encoding the α4 subunit of neuronal nicotinic acetylcholine receptors (Steinlein et al. 1995, 1997), whereas an affected-pedigree-member analysis was used to map a putative disease gene for idiopathic generalized epilepsy to chromosome 8q24 (Zara et al. 1995). Suggestive linkage has also been proposed for febrile convulsions, at band q13-q21 of chromosome 8 (Wallace et al. 1996). Progressive myoclonus epilepsy of the Unverricht type has been localized to chromosome 21q22 (Lehesjoki et al. 1991), and mutations of the cystatin B gene have been identified (Pennacchio et al. 1996), whereas a gene for the Lafora type has been mapped to 6q23-q25 (Serratosa et al. 1995). A gene associated with auditory partial epilepsies is situated on chromosome 10q22-q24 (Ottman et al. 1995). In families of probands with juvenile myoclonic epilepsy, evidence for (Greenberg et al. 1988; Durner et al.

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Address for correspondence and reprints: Dr. Anthony P. Monaco, The Wellcome Trust Centre for Human Genetics, University of Oxford, Windmill Road, Headington, Oxford OX3 7BN, United Kingdom. E-mail: anthony.monaco@well.ox.ac.uk

*These authors contributed equally to the study.

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1991; Weissbecker et al. 1991; Liu et al. 1995), as well as against (Whitehouse et al. 1993; Elmslie et al. 1996), linkage to the short arm of chromosome 6 has been shown.

Most forms of epilepsy develop during the first years of life, puberty or in young adulthood. Whereas epilepsy is generally considered as a chronic disturbance of brain function, convulsive disorders of infancy and childhood, a relatively large percentage of which are idiopathic, may reflect developmental processes. According to the Commission on Classification and Terminology of the International League Against Epilepsy (1990), three distinct entities are classified among the idiopathic forms with onset in the 1st year of life: benign neonatal convulsions, benign neonatal familial convulsions, and benign myoclonic epilepsy in infancy. In addition, nonfebrile convulsions, with the first seizure at age 3–12 mo, have been described (Vigevano et al. 1992; Lee et al. 1993; Echenne et al. 1994). In each case the disorder was familial, with an autosomal dominant mode of inheritance. These convulsions have a favorable outcome, and the term "benign infantile familial convulsions" has been proposed (Vigevano et al. 1992). Genetic linkage to the long arm of chromosome 19 has recently been published (Guipponi et al. 1997).

We have identified four French families in which benign infantile convulsion was inherited as an autosomal dominant trait together with variably expressed paroxysmal choreoathetosis. The strong association of both neurological symptoms in the same families defined a new syndrome, familial infantile convulsions and choreoathetosis (ICCA), which, although its convulsive component is similar to the one initially described by Vigevano et al. (1992), can be distinguished as a separate entity. Paroxysmal choreoathetosis is a rare, involuntary-movement disorder usually segregating in families (Mount and Reback 1940; Richards and Barnett 1968). It is characterized by attacks occurring spontaneously (in the dystonic form) or induced by movements (in the kinesiogenic form), exertion, being startled, or anxiety. Although it has long been suspected to be related to epileptic seizures (Stevens 1966), and despite similarities between the symptoms, the epileptic nature of at least some forms of paroxysmal choreoathetosis—namely, the kinesiogenic ones—remains controversial (Hirata et al. 1991; Beaumanoir et al. 1996). Significant linkage of paroxysmal dystonic choreoathetosis to chromosome 2q has been shown (Fink et al. 1996; Fouad et al. 1996), whereas a more complex form of paroxysmal choreoathetosis and episodic ataxia has been linked to chromosome 1p (Auburger et al. 1996).

In the present study, linkage of the ICCA syndrome has been excluded from all of the regions where genes have been mapped for either benign infantile familial convulsions or different forms of paroxysmal choreoathetosis. By a search of the genome, strong evidence for linkage in the four families has been identified in the pericentromeric region of human chromosome 16.

Subjects and Methods

Clinical Data Collection

Individuals were considered as affected if they had either nonfebrile convulsions at age 3–12 mo, with a favorable outcome and no recurrence of similar seizures after drug discontinuation, or paroxysmal choreoathetotic movements, or if they had both a history of convulsions and choreoathetotic movements. Appropriate informed consent was obtained from all subjects. Partial epileptic seizures started with a psychomotor arrest and a deviation of head and eyes to one side, followed inconstantly by unilateral jerks. In some cases, these seizures generalized secondarily. Generalized seizures were of the classical tonic-clonic type. None of the interictal electroencephalograms showed epileptiform abnormalities, and computed-tomography scanning or magnetic-resonance imaging were normal. Choreoathetotic movements either were of the dystonic type, occurring at rest, or could be induced by exertion or anxiety. In some patients, attacks could occur as often as 20 times/d. In one case, a videotape recording was made during an exertional test. No history of CNS disease or damage was found. Neurological examinations between attacks were entirely normal, as was psychomotor development in all affected patients. Calcemia and other biological parameters were normal in all individuals of the last generations and were not determined in the other patients.

Linkage Analysis

High-molecular-weight genomic DNA was isolated from whole blood by use of the Nucleon kit (Scotlab). Highly polymorphic microsatellites markers (Reed et al. 1994; Dib et al. 1996) were analyzed by PCR amplification of 40 ng of genomic DNA in a 15-μl reaction containing 25 ng of each primer, 1–3 mM $MgCl_2$, 200 μM each nucleotide, and 0.2 units of *Taq* polymerase. Forward primers were labeled at the 5′ terminus with a fluorescent dye (FAM, HEX, or TET). Fluorescent PCR products were analyzed on a 373A Sequencer (Applied Biosystem) using the GENESCAN™ and GENOTYPER™ software. Linkage analysis was performed under the assumption of an autosomal mode of inheritance with penetrance at .8 and with frequency of the disease allele at .0001, by use of the MLINK modification of the LINKAGE computer package (Lathrop and Lalouel 1984). To take into account the later age at onset of the choreoathetotic trait, the analysis was performed again by classifying unaffecteds of age <20 years as phenotypically unknown. Multipoint analyses were

done with LINKMAP (Lathrop et al. 1985), under the assumption of either no sex difference or a sex-difference recombination rate in favor of females (Kozman et al. 1995; Dib et al. 1996), with intermarker distances and order as previously published (Dib et al. 1996). Genetic heterogeneity was tested with the HOMOG program (Ott 1991).

Results

Individuals were considered as affected if they had either nonfebrile convulsions at age 3–12 mo, with a favorable outcome and no recurrence of similar seizures after drug discontinuation, or paroxysmal choreoathetotic movements, or if they had both a history of convulsions and choreoathetotic movements (table 1; see Subjects and Methods). Before a search of the whole genome, candidate regions where linkage to different types of epilepsies previously had been shown were tested. Significant negative LOD scores (data not shown) were found for each (6p21-p11, 6q23-q25, 8p, 8q13-q21, 8q24, 10q, 19q, 20q13.2, and 21q22). In particular, benign infantile familial convulsion has been linked to 19q12 in a recent analysis (Guipponi et al. 1997). D19S220, D19S250, and D19S425 gave negative LOD scores (table 2), which unambiguously excluded this area. In addition, linkage to the candidate regions that may contain susceptibility loci for paroxysmal choreoathetosis was also clearly excluded, with markers D1S197 and D2S126 (table 2).

A whole-genome screen with highly polymorphic markers regularly spaced across the genome (Reed et al. 1994) was then performed. After analysis of the data for 119 markers, preliminary evidence for linkage was obtained with two adjacent markers on chromosome 16, D16S420 (two-point LOD score 2.69 at a recombination fraction [θ] of .05) and D16S411 (two-point LOD score 2.68 at $\theta = .1$). To explore this region further, markers were selected around D16S420 and D16S411, from the Généthon map (Dib et al. 1996), and 10 additional pedigree members were collected (II.5, III.1–III.7, and IV.1 in pedigree A and III.4 in pedigree D; see table 1). A maximum two-point LOD score of 6.76 at $\theta = .0$ was obtained with D16S3133, whereas additional significant LOD scores were obtained for seven surrounding markers (table 2).

Penetrance was not complete, as can be seen in pedigree D (individual II.1; see fig. 1). Linkage analysis was performed under the assumption of an autosomal dominant mode of inheritance with penetrance at .8. The analysis was also done with different penetrance values (.7–.9), without drastic modification of the results (data not shown). For example, LOD scores for D16S3133 were slightly increased under penetrance at .7 (LOD score 6.98 at $\theta = .0$) and remained highly significant for penetrance at .9 (LOD score 6.05 at $\theta = .0$). Age at onset was 4–10 mo for the convulsive trait and was later for choreoathetosis, since it appeared in patients age 5–19 years in our families. This is consistent with previous publications, which have reported mean age at onset of 5–16 years (Kinast et al. 1980). LOD scores and θ values did not change significantly when the linkage analysis was conducted under the assumption that unaffected individuals age <20 years had an unknown phenotype (table 2).

Multipoint LOD scores were calculated for a subset of markers (fig. 2). A maximum multipoint LOD score of 7.06 was found at D16S3133, when male and female recombination rates were assumed to be equal. Since the pericentromeric region of chromosome 16 has a sixfold increase in recombination rates in female compared with male meioses (Kozman et al. 1995), the multipoint analyses were repeated, with incorporation of sex-specific recombination distances. The maximum LOD score increased slightly, and the region of interest remained identical (data not shown). Multipoint LOD scores were also calculated under the assumption of the age-dependent-penetrance model (fig. 2). In this latter case, multipoint LOD scores became higher between D16S3068 and D16S517, thus confirming the increase of two-point LOD scores for more-pericentromeric markers, under the age-dependent model.

Meiotic-recombination events were revealed by analysis of the haplotypes of affected individuals (fig. 1). The order of markers was similar to that reported by Dib et al. (1996), except that D16S401 and D16S3133 were inverted with respect to each other, because of the recombination event, in pedigree C, between D16S401 and D16S3133, mapping the former more proximal to D16S420 than to D16S3133. For similar reasons, D16S3120, although previously mapped between D16S411 and D16S416, was undoubtedly located between D16S517 and D16S261 (see fig. 1). The critical minimal region containing the susceptibility gene could be reduced to a 10-cM interval. The proximal boundary is situated between D16S401 and D16S3133, the distal one between D16S3093 and D16S517. This locates the disease locus between marker D16S401, on the short arm, and marker D16S517, on the long arm, in a 10-cM region around the centromere of human chromosome 16.

Discussion

We have shown that a gene responsible for a new familial form of infantile convulsions associated with paroxysmal choreoathetotic movements is located in a 10-cM region around the centromere of human chromosome 16. Highly significant total LOD scores, 3.10–6.76, for eight adjacent 16p12-q12 markers

Table 1

Clinical Information on Affected Subjects

Pedigree and Individual (Sex)	Age (years)	Infantile Convulsion: Age at Onset/Type	Choreoathetosis: Age at onset/Form
A:			
II.2 (male)	62	5 mo/unknown	. . .
II.3 (male)	75	5 mo/unknown	. . .
III.3 (male)	35	5½ mo/partial seizure with secondary generalization	7 years/dystonia
III.4 (male)	31	4½ mo/unknown	. . .
III.8 (female)	42	6 mo/partial seizure	. . .
III.10 (female)	32	. . .	7 years/dystonia and movements induced by anxiety, movements induced by exertion
III.11 (male)	31	6 mo/partial seizure	7 years/dystonia
III.13 (female)	40	6 mo/unknown	. . .
III.17 (female)	38	. . .	8 years/movements induced by anxiety; movements induced by exertion
IV.4 (male)	8	6 mo/partial seizure	. . .
IV.5 (male)	6	. . .	6 years/dystonia and movements induced by anxiety, movements induced by exertion
IV.7 (male)	15	7 mo/pratial seizure	. . .
IV.10 (female)	9	4 mo/partial seizure with secondary generalization	8 years/dystonia and movements induced by anxiety, movements induced by exertion
IV.11 (male)	7	5½ mo/partial seizure with secondary generalization	7 years/movements induced by anxiety, movements induced by exertion
B:			
II.1 (male)	21	5½ mo/partial seizure	. . .
II.2 (female)	24	. . .	6 years/dystonia
II.3 (female)	26	6 mo/partial seizure with secondary generalization	19 years/dystonia
III.2 (female)	6	6 mo/partial seizure	. . .
C:			
I.2 (female)	31	6 mo/partial seizure with secondary generalization	7 years/dystonia
II.1 (female)	7	6 mo/partial seizure and generalized seizure	5 years/dystonia and movements induced by anxiety, movements induced by exertion
II.2 (male)	2	6 mo/partial seizure and generalized seizure	. . .
D:			
III.2 (male)	29	5 mo/partial seizure	. . .
III.3 (male)	24	8 mo/partial seizure with secondary generalization	9 years/dystonia
III.4 (male)	27	6 mo/partial seizure	. . .
III.5 (female)	30	10 mo/partial seizure	. . .
IV.1 (male)	3	6 mo/partial seizure	. . .

provide strong evidence of linkage. In a disorder suspected to exhibit genetic heterogeneity, it is desirable to demonstrate significant linkage in at least one single pedigree. This was the case for our largest pedigree (A) in which nine markers gave significant two-point LOD scores (table 2). Moreover, all families had positive LOD scores, and homogeneity was not rejected in a HOMOG test (data not shown). It is noteworthy that all four families originated from the same region in the north of France. Their common geographic origin could be helpful in narrowing further the region of interest: if the disease chromosomes in all four families were descended from a single ancestral mutation, then linkage disequilibrium could be successfully used to detect historical recombination events (Jorde 1995).

Linkage analysis has been performed under the assumption of an autosomal dominant mode of inheri-

Table 2

Two-Point LOD Scores for Candidate Regions 1p, 2q, and 19q and for 12 Markers at 16p12-q12

	LOD Score (Penetrance .8) at θ =[a]						
Locus and Pedigree(s)	0	.01	.05	.1	.2	.3	.4
D1S197:							
A	−13.25	−5.78	−3.48	−2.37	−1.20	−.55	−.18
All	−16.33	−7.65	−4.57	−3.08	−1.54	−.71	−.25
D2S126:							
A	−9.82	−4.37	−2.29	−1.43	−.64	−.26	−.07
All	−20.06	−10.03	−5.44	−3.45	−1.61	−.71	−.22
D19S220:							
A	−11.37	−5.53	−2.41	−1.13	−.09	.25	.25
All	−14.58	−6.37	−2.65	−1.19	−.08	.23	.21
D19S250:							
A	−12.79	−6.27	−3.07	−1.71	−.54	−.08	.05
All	−19.33	−8.63	−4.10	−2.23	−.64	−.03	.12
D19S425:							
A	−9.89	−4.79	−2.30	−1.28	−.43	−.09	.02
All	−13.01	−6.19	−3.02	−1.73	−.62	−.17	.00

	Maximum LOD Score (Maximum θ)	
	Penetrance .8[a]	Age-Dependent Penetrance[b]
D16S420:		
A	2.91 (.063)	2.31 (.066)
All	2.66 (.099)	2.07 (.105)
D16S401		
A	4.31 (0)	4.43 (0)
All	4.82 (.050)	4.82 (.040)
D16S3133		
A	4.12 (0)	4.47 (0)
All	6.76 (0)	6.75 (0)
D16S3068		
A	4.34 (0)	4.47 (0)
All	6.53 (0)	6.69 (0)
D16S3131		
A	3.64 (0)	4.47 (0)
All	5.83 (0)	6.69 (0)
D16S3100		
A	.74 (.135)	1.83 (0)
All	1.71 (0)	2.59 (0)
D16S3093		
A	2.86 (.031)	4.42 (0)
All	3.63 (.017)	5.24 (0)
D16S3044		
A	3.11 (0)	3.68 (0)
All	3.28 (.076)	3.62 (.051)
D16S3120		
A	3.17 (0)	3.74 (0)
All	2.70 (.068)	3.82 (0)
D16S261		
A	3.23 (0)	4.06 (0)
All	3.10 (.045)	4.60 (0)
D16S411		
A	3.64 (0)	4.47 (0)
All	3.56 (.066)	4.14 (.043)
D16S416		
A	3.60 (0)	4.43 (0)
All	2.63 (.147)	2.73 (.122)

[a] Linkage analysis was performed under the assumption of an autosomal dominant mode of inheritance with frequency of the disease allele at .0001, and penetrance at .8, by use of the MLINK modification of the LINKAGE computer package.

[b] Linkage analysis was performed under the assumption of an autosomal dominant mode of inheritance with frequency of the disease allele at .0001, by classifying unaffecteds of age <20 years as phenotypically unknown, to take into account the later age at onset of the choreoathetotic trait.

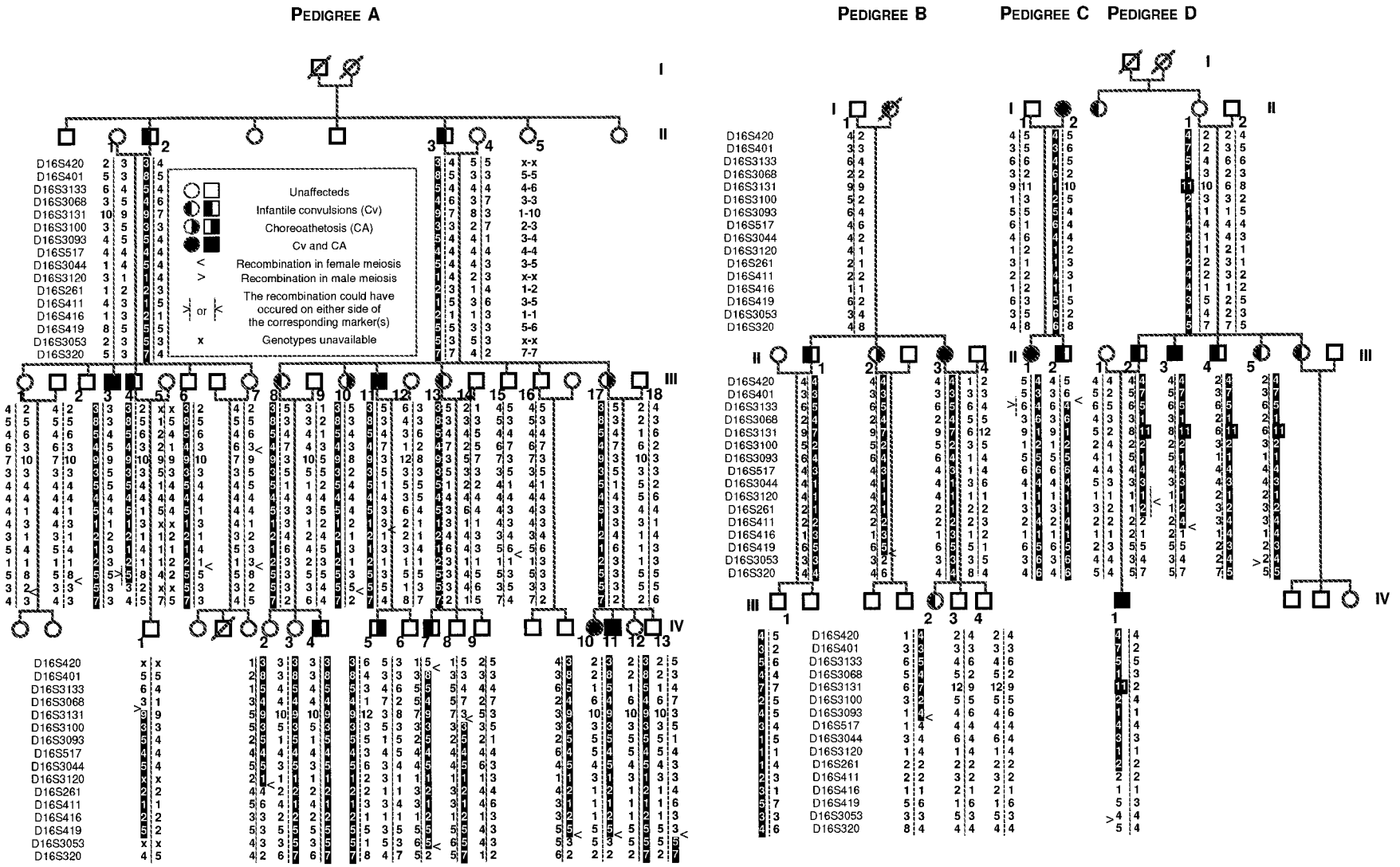

Figure 1 Pedigrees and haplotype analysis of the families with autosomal dominant infantile convulsions and paroxysmal choreoathetosis. Marker genotypes are shown from the p terminus to the q terminus and cover ~30 cM in the region 16p12-16q12.

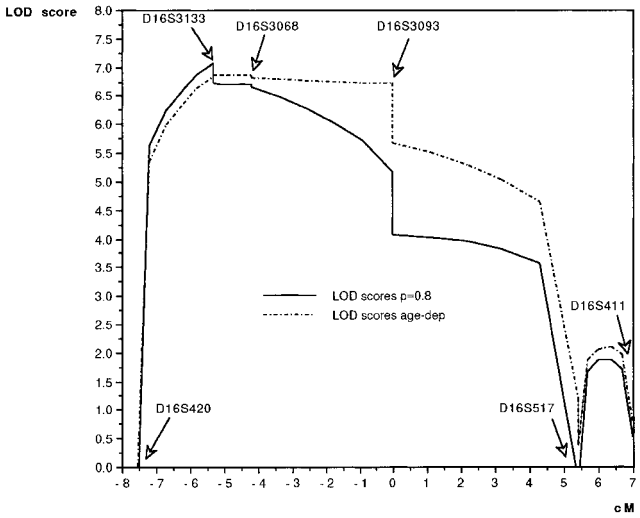

Figure 2 Multipoint LOD scores. Multipoint analyses were done with LINKMAP, with intermarker distances and order as previously published (Dib et al. 1996).

tance with penetrance at .8. As can be seen in figure 1, two unaffected members in pedigree A (IV.3 and IV.12, ages 11 and 4 years, respectively) had the full disease haplotype, as did one member of pedigree B (III.1, age 5 years) as well as the obvious one in pedigree D (II.1, age 52 years). Also, at least one of the three unaffecteds (IV.1, IV.2, and IV.8, ages 3, 14, and 14, respectively) in pedigree A who had partial disease haplotypes did inherit the disease gene, since these haplotypes overlapped. This is consistent with incomplete penetrance, and the derived penetrance (number of true affected patients/number of disease haplotypes) is $P = .78$, which is in the same range as that (.8) assumed prior to the analysis. Most recombination events occurred in females (20 in females vs. 5 in males), which is consistent with the sixfold excess in recombination rates, in favor of females, that has been described for this region (Kozman et al. 1995). In two cases (III.7 and IV.7 in pedigree A; see fig. 1), a double-recombination event was seen. This can be easily explained by the large distance separating these female crossovers (minimal female distances of 47.8 and 25.7 cM, respectively, according to Dib et al. [1996]).

Haplotype analysis narrowed the region of interest to 10 cM, between D16S401 and D16S517. Among all the genes and expressed sequence tags that have been localized to the critical area (Callen et al. 1995; Schuler et al. 1996), some are good candidates for being involved in convulsive and choreoathetotic disorders. The β-2 type of protein kinase C is situated around D16S420 and D16S401 (Callen et al. 1995). Ionic channels and transporters could also play a role in the pathogenesis of paroxysmal neurological diseases: the γ subunit of a sodium channel (Voilley et al. 1995), a sodium/glucose co-transporter (Wells et al. 1993), and an ATPase, calcium-transporting protein (Callen et al. 1991), are encoded by genes situated in the region of interest. The STM gene, also situated at 16p11-p12 (Aksoy et al. 1994), encodes the monoamine-preferring form of sulfotransferase and is responsible for the sulfate conjugation of monoamine neurotransmitters. Mutations in the Batten disease gene (The International Batten Disease Consortium 1995), located at 16p12, have been associated with an early loss of vision, followed by mental deterioration and epileptic seizures. In parallel with the genetic and physical characterization of the critical region at 16p12-q12, direct mutational analysis of candidate genes will be performed in order to exclude them—or, conversely, to identify one of them—as the ICCA gene. Mutations in the putative ICCA gene probably account for a small proportion of familial epilepsies of childhood. In most forms of epilepsy, both genetic and environmental factors may influence susceptibility (Ottman et al. 1997), whereas involuntary choreoathetotic movements clearly display clinical as well as genetic heterogeneity. However, even if ICCA mutations were rare, identification of the gene product and function should provide information on the basic pathogenetic mechanisms and relationships of convulsive and movement disorders.

To our knowledge, this is the first time that epileptic seizures and paroxysmal choreoathetosis have been studied genetically as a unique syndrome. This was rendered possible by the association, in all four families, of both clinical manifestations. Genetic studies have already been performed on both symptoms separately: the so-called benign infantile familial convulsions, whose clinical manifestations are the same as those seen in our patients, has been linked to chromosome 19, band q12 (Guipponi et al. 1997), whereas susceptibility loci for two forms of paroxysmal choreoathetosis have been mapped to chromosomes 1p (Auburger et al. 1996) and 2q (Fink et al. 1996; Fouad et al. 1996), respectively. We have definitely excluded linkage to any of these regions, which emphasizes the complexity, heterogeneity, and difficulties in classification of these diseases.

In all four families, both infantile convulsions and choreoathetotic movements could be found, and the two clinical manifestations were even present together in eight patients. In four patients (see table 1), the choreoathetotic movements were present without any history of convulsion. It is important to note that one of these four patients (III.17 in pedigree A) had two affected sibs with both choreoathetotic movements and convulsions, which emphasizes the variable expressivity of this syndrome. In fact, even when the convulsive disorder alone is considered as the affected trait, region 19q was still

excluded without ambiguity, and LOD scores at 16p12-q12, although lower (maximum two-point LOD score 4.91 at $\theta = .0$, for D16S3133, D16S3068 and D16S3131, with penetrance .7), remained significant for six markers. On the basis of this latter hypothesis, isolated choreoathetotic movements occurred only in individuals sharing at-risk haplotypes. Taken together, these arguments make it very unlikely that the two symptoms—that is, convulsive seizures and choreoathetotic movements—are unrelated in these families. Moreover, although their relative prevalence is not known with precision, both symptoms are rare (Kinast et al. 1980; Vigevano et al. 1992; Guipponi et al. 1997), thus reinforcing the probability of their nonrandom association in the families studied. This association is not surprising if one considers (*a*) that paroxysmal choreoathetosis and epileptic seizures have already been described in the same patients (Pryles et al. 1952; Fukuyama and Okada 1968), or even in three patients of the same family (Hudgins and Corbin 1966), and (*b*) the possible epileptic nature of paroxysmal choreoathetosis. The pathophysiology of this disorder is controversial, and the epileptic origin of paroxysmal choreoathetotic movements has been and is still a matter of debate (Hudgins and Corbin 1966; Stevens 1966; Kinast et al. 1980; Beaumanoir et al. 1996). Attacks of paroxysmal choreoathetosis share several features in common with epileptic seizures: the crises are paroxysmal, the disorder tends to remit, and the response to anticonvulsants is usually good. Some studies have described electroencephalographic abnormalities consistent with an epileptogenic basis (Hirata et al. 1991; Lombroso 1995). The term "reflex epilepsy" has even been applied to these putative epileptic seizures (Stevens 1966), and the epileptogenic source could be within subcortical structures (basal ganglia), rather than in the cortex (Stevens 1966; Hirata et al. 1991). Our study provides the first genetic evidence of an epileptic nature for paroxysmal choreoathetosis. More generally, it raises the importance of genetic studies in the pathogenic and etiologic understandings of several paroxysmal cerebral syndromes related to or associated with other forms of epilepsy, as recently has been shown in the case of migraine and ataxia (Fletcher et al. 1996; Hess 1996; Ophoff et al. 1996).

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