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Familial Periodic Cerebellar Ataxia without Myokymia Maps to a 19-cM Region on 19p13

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Summary

Familial periodic cerebellar ataxia (FPCA) is a heterogenous group of rare autosomal dominant disorders characterized by episodic cerebellar disturbance. A potassium-channel gene (KCNA1) has been found to be responsible for one of its subgroups, familial periodic cerebellar ataxia with myokymia (FPCA/+M; MIM 160120). A different subgroup that is not associated with myokymia (FPCA/−M; MIM 108500) was recently mapped to chromosome 19p. Here we have performed linkage analysis in two large families with FPCA/−M that also demonstrated neurodegenerative pathology of the cerebellum. Three markers in 19p13 gave significant lod scores (>3.0), while linkage to KCNA1 and three known loci for spinocerebellar ataxia (SCA1, SCA2, and SCA3) was excluded. The highest lod score was obtained with the marker D19S413 (4.4 at recombination fraction 0), and identification of meiotic recombinants in affected individuals placed the locus between the flanking markers D19S406 and D19S226, narrowing the interval to 19 cM. A CAG trinucleotide-repeat expansion was detected in one family but did not cosegregate with the disease.

Introduction

Familial periodic cerebellar ataxia (FPCA) is a rare syndrome first described by Parker, in 1946, in two pairs of brothers from two families (Parker 1946). It is transmitted in an autosomal dominant fashion with complete penetrance and is characterized by lifelong recurrent attacks of cerebellar ataxia, dysarthria, and nystagmus (Bain et al. 1992). In the majority of cases, its age at onset ranges from early childhood to no later than adolescence, and the attacks, which usually last from minutes to hours, are often precipitated by alcohol, emotional, and/or physical stress. The patients usually respond to acetazolamide, a carbonic anhydrase inhibitor (Griggs et al. 1978; Friedman and Hollmann 1987). On the basis of the description of various families, it is now considered to be clinically heterogenous, consisting of at least two distinct subtypes: (1) FPCA with myokymia (FPC/+M; MIM 160120) and (2) FPCA without myokymia (FPCA/−M; MIM 108500). In FPCA/−M, longer duration of the attacks, presence of vertigo, nausea, and headache during attacks, and presence of nystagmus both during and between attacks are found (Brunt and Van Weerden 1990). Cerebellar atrophy has also been demonstrated in some patients with FPCA/−M (Gancher and Nutt 1986; Vighetto et al. 1988; Feeney and Boyle 1989). Recently, the gene responsible for FPCA/+M was found to be a potassium-channel gene, KCNA1, in chromosome 12p13 (Browne et al. 1994; Litt et al. 1994). More recently, the gene for FPCA/−M was mapped to chromosome 19p in two families (Kramer et al. 1994), in the region where a gene for familial hemiplegic migraine is located (Joutel et al. 1993). These loci are different from those responsible for the autosomal dominant cerebellar ataxias (ADCA), which are a clinically heterogeneous group of neurodegenerative disorders. In ADCA, cerebellar atrophy and anticipation are important features, and repeat expansions have been found to be responsible for two of its subgroups, namely, SCA1 and SCA3 (Orr et al. 1993; Kawaguchi et al. 1994).

Here we have carried out genetic studies on two FPCA/−M families, one of which showed cerebellar atrophy and suggestive features of anticipation. Linkage analysis was performed using markers from 19p, 12p13, and ADCA loci SCA1, SCA2, and SCA3; and, in addition, repeat-expansion detection (RED) was carried out.

Families, Material, and Methods

Families

All affected and unaffected members studied were examined by one of us (R.B.), who is a neurologist. Both families are of Caucasian origin, with autosomal domi-

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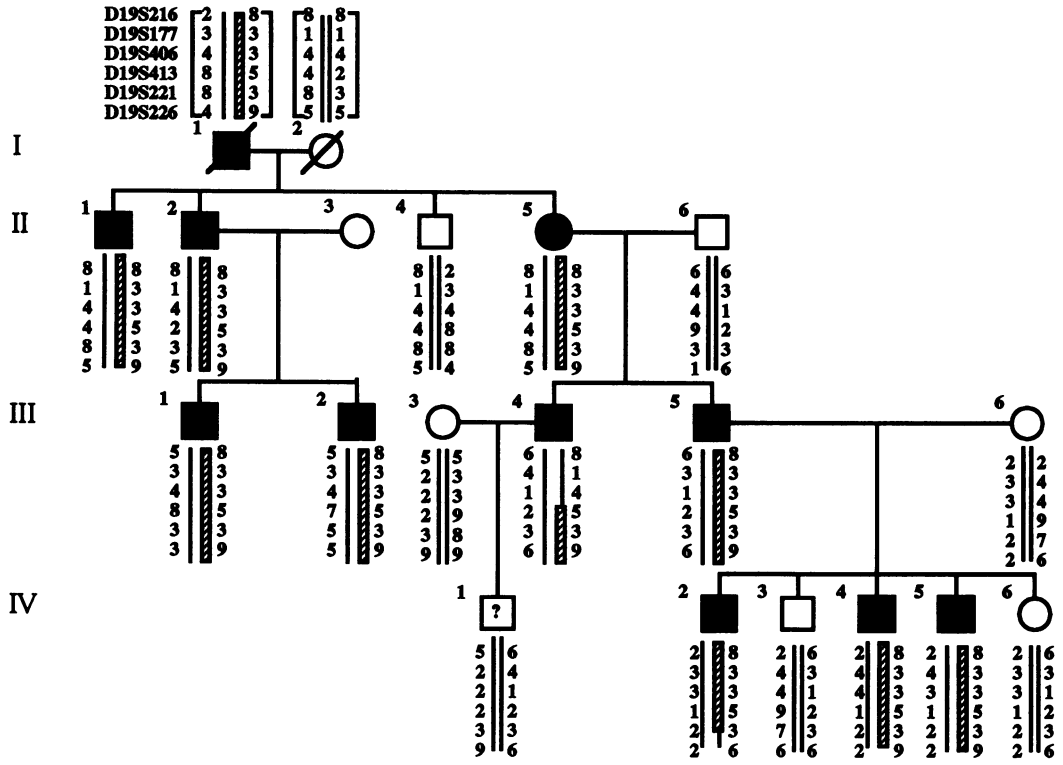

Figure 1 Haplotypes of chromosome 19p in family 1. The markers are listed in order, from telomere to centromere, at the upper left. Blackened symbols denote affected family members, and unblackened symbols denote unaffected family members. Since individual IV-1 is <15 years of age, she is regarded as "unknown," which is indicated by the question mark (?). The haplotypes for each individual are depicted along an illustrated chromosome segment. The wild-type chromosome is indicated by a line, and the inferred disease-bearing chromosome is hatched. The bracketed haplotypes represent those inferred from the haplotyping of the children. Note that recombination in individual IV-2 could occur with either marker D19S221 or marker D19S226 but that, to be conservative in determining the mapping region, the more distal one was chosen.

nant transmission. The patients presented with intermittent ataxic attacks precipitated by alcohol and emotional and/or physical stress but were all responsive to acetazolamide. Family 1 (fig. 1) has been followed for >7 years, and the clinical details have been reported elsewhere (Feeney and Boyle 1989). Cerebellar and brain-stem atrophy, a feature commonly found in autosomal dominant cerebellar ataxia (ADCA) (Harding 1993), was demonstrated in patients investigated with magnetic resonance imaging (MRI). When both the age at onset and the duration of attacks are compared between generations, there are indications of anticipation, a feature that has been explained genetically by detection of trinucleotide expansion in some types of ADCA (Orr et al. 1993; Kawaguchi et al. 1994). The second family (fig. 2) was recently identified by one of us (R.B., unpublished data), on the basis of clinical and family studies.

Linkage Analysis

Blood samples were obtained from consenting members of both families, and high-molecular-weight DNA was isolated using standard methods. Ten polymorphic microsatellite markers previously reported to be linked to the three ADCA type 1 loci (SCA1, SCA2, and SCA3) and to KCNA1 were selected: (1) D6S89, D6S289/AFM200wc9, and D6S260/AFM056xe1 for SCA1 in chromosome 6p (Keats et al. 1991; Ranum et al. 1991; Zoghbi et al. 1991; Khati et al. 1993); (2) IGF1 and PLA2 for SCA2 in chromosome 12q (Gispert et al. 1993; Lopes-Cendes et al. 1994); (3) D14S68/AFM164tb12, D14S67/AFM137xh12, and D14S73/AFM203za11 for SCA3 in chromosome 14q (Stevanin et al. 1994); and (4) D12S100/AFM220zc7 and D12S99/AFM217xa7 for KCNA1 in chromosome 12p (Litt et al. 1994). For 19p, the following microsatellite markers were analyzed: D19S216/AFM164zb8, D19S177/MFD120, D19S406/AFM205zf2, D19S413/AFM292wd9, D19S221/AFM224ye9, and D19S226/AFM256yc9 (Gyapay et al. 1994; Kramer et al. 1994). The primers and conditions for the PCR described in previous reports for each marker were used in amplifications using incorporation of ^{32}P-dCTP, followed by PAGE and autoradiography. Haplotyping was performed in these two families. Two-point lod scores were generated using the MLINK pro-

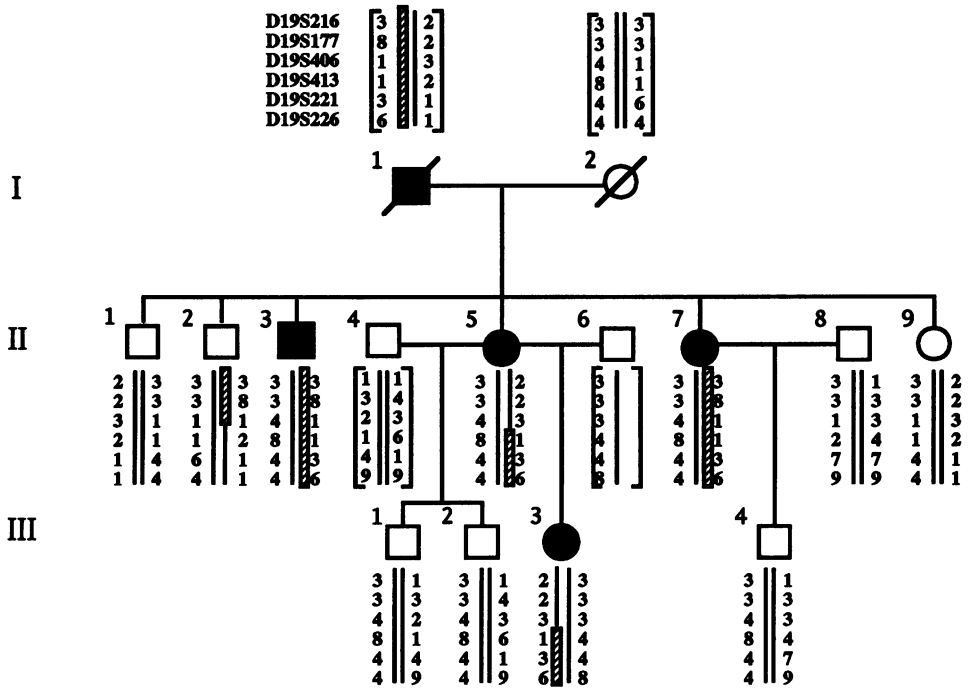

Figure 2 Haplotypes of chromosome 19p in family 2. Symbols are as in fig. 1.

gram of the LINKAGE software package (version 5.1) (Lathrop et al. 1984). The gene frequency and the disease state were assigned as in the FPCA/+M mapping described elsewhere (Litt et al. 1994). Basically, any individual >15 years of age who has been asymptomatic after several years of follow-up was scored as unaffected. The allele frequencies of the short tandem-repeat–polymorphism markers were assumed to be equal.

RED

The method permits the direct identification of expanded repeat sequences in genomic DNA (Schalling et al. 1993; Lindblad et al. 1994). In brief, the RED reactions were performed on a GeneAMP PCR System 9600 (Perkin Elmer Cetus) using 1 μg of genomic DNA, 50 ng of 5′-end phosphorylated $(CTG)_{10}$ oligonucleotide (Pharmacia Biotech), 10 U of ampligase (Epicentre Technologies), and its buffer. The samples were incubated at 94°C for 5 min and were taken through 396 cycles of 80°C for 30 s and 94°C for 10 s. The products were denatured in 50% formamide for 5 min and electrophoresed in a 6% polyacrylamide gel that was then electrotransferred onto a Hybond N+ membrane. After UV immobilization, membranes were hybridized, for 16 h at 60°C, to $(CAG)_{10}$ oligonucleotide that had been 3′-end labeled using terminal deoxynucleotidyl transferase (Bethesda Research Laboratories) and ^{32}P-dATP. The membranes were washed in 1 × SSC, 0.1% SDS for 2 h at 60°C, and this was followed by autoradiography.

Results

The two pedigrees with FPCA/−M are shown in figures 1 and 2. Clinically there is no clear evidence of incomplete penetrance in the two families, which represent only a subset of families with the disorder. The disease state of the deceased parents in the first generation was based on history from their children. Individual IV-1 in family 1 (fig. 1) thus far is asymptomatic and is <15 years of age, and thus he was scored as "unknown." The genetic linkage analysis was performed on a total of 14 affected and 14 unaffected members from the two families, by using microsatellite markers from 19p and flanking the KCNA1, SCA1, SCA2, and SCA3 loci. Two-point lod scores for each of these markers are shown in table 1. Linkage to KCNA1 (12p), SCA1 (6p), SCA2 (12q) and SCA3 (14q) was excluded, on the basis of both haplotype analysis (not shown) and the fact that the total lod scores for each of them were <−2. The three markers D19S413, D19S221, and D19S226 in 19p13 gave significant positive lod scores (>3.0), and the highest lod score was obtained with D19S413 (4.4 at recombination fraction 0).

The order and the sex-average recombination fractions between the 19p loci are shown in figure 3. The markers were ordered with odds ratios >1,000:1, on the basis of genotyping in eight CEPH families (Gyapay et al. 1994). D19S177 was placed between D19S216 and D19S406 in the Genome Data Base (GDB) map.

Table 1

Total Lod Scores for Linkage of FPCA/−M to Different Microsatellite Marker Loci

Locus and Family	Lod Score at Recombination Fraction of						
	.000	.010	.050	.100	.200	.300	.400
D19S216:							
1	2.132	2.095	1.948	1.756	1.345	.903	.445
2	−∞	−2.230	−.933	−.458	−.115	−.016	−.002
Total	−∞	−.135	1.015	1.298	1.230	.887	.443
D19S177:							
1	−∞	−1.304	−.605	−.326	−.113	−.043	−.013
2	−∞	−1.935	−.660	−.216	−.060	−.083	−.032
Total	−∞	−3.239	1.265	.542	−.173	−.126	−.045
D19S406:							
1	−∞	−10.778	−5.976	−3.985	−2.117	−1.124	−.480
2	−∞	−1.920	−.627	−.163	−.149	−.185	−.095
Total	−∞	−12.698	−6.603	−4.148	−1.968	−.939	−.385
D19S413:							
1	3.311	3.255	3.022	2.717	2.053	1.317	.565
2	1.086	1.056	.938	.792	.537	.328	.133
Total	4.397	4.311	3.960	3.509	2.590	1.645	.698
D19S221:							
1	.903	.881	.792	.676	.434	.205	.047
2	2.107	2.068	1.907	1.695	1.236	.729	.217
Total	3.010	2.949	2.699	2.371	1.670	.934	.264
D19S226:							
1	−∞	.962	1.464	1.507	1.249	.815	.345
2	2.408	2.365	2.185	1.951	1.439	.866	.276
Total	−∞	3.327	3.649	3.458	2.688	1.681	.621
D6S89:							
1	−∞	−3.622	−1.647	−.896	−.292	−.054	.029
2	−∞	−1.224	−.564	−.310	−.087	.007	.018
Total	−∞	−4.846	−2.211	−1.206	−.379	−.047	.047
D6S260:							
1	−∞	−3.622	−1.647	−.896	−.292	−.054	.029
2	−∞	−3.618	−1.627	−.861	−.249	−.033	.012
Total	−∞	−7.240	−3.274	−1.757	−.541	−.087	.041
D6S289:							
1	−∞	−1.333	−.528	−.191	.053	.101	.071
2	−∞	−3.618	−1.267	−.861	−.249	−.033	.012
Total	−∞	−4.951	−2.155	−1.052	−.196	.068	.083
PLA2:							
1	−∞	−2.707	−1.325	−.763	−.273	−.056	.028
2	−∞	−3.317	−1.327	−.565	.031	.211	.184
Total	−∞	−6.024	−2.652	−1.328	−.242	−155	.212
IFG1:							
1	−∞	−.783	−.151	.059	.159	.131	.072
2	−∞	−3.919	−1.926	−1.152	−.497	−.200	−.050
Total	−∞	−4.702	−2.077	−1.093	−.338	−.069	.022
D14S67:							
1	−∞	−3.618	−1.629	−.866	−.268	−.075	−.038
2	−∞	−5.315	−2.617	−1.542	−.614	−.213	−.043
Total	−∞	−8.933	−4.246	−2.408	−.882	−.288	−.081
D14S68:							
1	−∞	−2.216	−.907	−.423	−.075	.000	−.021
2	−∞	−5.315	−2.617	−1.542	−.614	−.213	−.043
Total	−∞	−7.531	−3.524	−1.965	−.689	−.213	−.064
D14S73:							
1	1.540	1.512	1.427	1.398	.939	.611	.287
2	−∞	−4.082	−2.045	−1.227	−.522	−.214	−.064
Total	−∞	−2.570	−.618	.171	.417	.397	.223
D12S99:							
1	−∞	−2.778	−.855	−.177	.249	.268	.134
2	−∞	−3.618	−1.628	−.866	−.263	−.057	−.004
Total	−∞	−6.396	−2.483	−1.043	−.014	.211	.130
D12S100:							
1	−∞	−2.220	−.926	−.455	−.118	−.021	−.001
2	−∞	−.236	−.016	−.134	.172	.113	.036
Total	−∞	−2.456	−.942	−.589	.054	.092	.035

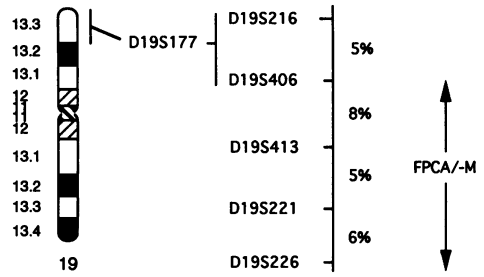

Figure 3 Mapping of the FPCA/−M locus to a 19-cM region on the short arm of chromosome 19 (indicated by arrows). The localization of D19S177 is marked on a chromosome 19 ideogram to the left. An enlarged map of the region shows the order and sex-average recombination fractions of the loci for microsatellite markers used in the present study, as determined from linkage analysis in reference families (Gyapay et al. 1994).

The recent mapping in two FPCA/−M families identifies a region of 30 cM between the flanking markers D19S226 and D19S209, and the latter is located 8 cM telomeric of D19S216 (Kramer et al. 1994). In the present study, telomeric meiotic crossovers were identified between D19S406 and D19S413, both in individual III-4 in family 1 and in individual II-5 in family 2 (figs. 1 and 2). Proximally, recombination occurs between D19S226 and D19S221 in individual IV-2 in family 1 (fig. 1). Thus, the region for FPCA/−M was narrowed to 19 cM flanked by D19S406 and D19S226 (fig. 3). An additional telomeric crossover was detected in individual II-2 in family 2. The patient is 64 years old and has never developed any of the disease-related features. A CAG-repeat expansion of >50 copies was detected in a branch of family 1 but originated from the unaffected spouse (II-6), and, furthermore, it does not cosegregate with the disease in this family (data not shown).

Discussion

A potassium channel has recently been found to be responsible for FPCA/+M (Browne et al. 1994). This places the potassium channels alongside the other two cation channels—the sodium and calcium channels—which are known to be responsible for human periodic neurological disorders. The fact that FPCA, both with and without myokymia, is relieved by carbonic anhydrase inhibitors has previously led to the postulation that its underlying pathophysiology might be related to changes in pH at the cellular level. This was demonstrated, in the cerebellum of FPCA patients, by Bain et al. (1992), by ^{31}P nuclear magnetic resonance spectroscopy. With the involvement of a voltage-gated potassium channel whose main biological function is to modulate electrical activities in tissues, it can now be further deduced that a defect in the potassium channel might lead to this change in pH; but further functional studies at the cellular levels are required.

The current study confirms that the gene for FPCA/−M is located in chromosome 19p. When this is considered together with the results of the previous report (Kramer et al. 1994), total lod scores of 7.33 and 6.35 are obtained for D19S413 and D19S221, respectively. Furthermore, this study has narrowed the region between D19S406 and D19S221, from 30 cM to 19 cM, on the basis of identification of meiotic recombinations. Since more than a dozen of highly related potassium channels have been identified (Gutman and Chandy 1993), it is natural to postulate that the gene responsible for FPCA/−M is one of the members of this family. The exclusion of linkage in the present study rules out the involvement of KCNA1 as well as the other two potassium channels in the same region in chromosome 12p13, namely, KCNA5 and KCNA6. To date, no known gene for potassium channels has been mapped to chromosome 19p, although three of them—KCNC2, KCNC3, and KCNA 7—are located in 19q13 (Lock et al. 1994). This does not exclude the involvement of a potassium channel in this disease, since other yet-to-be cloned potassium channels could still be located in this region. In this case the candidate-gene approach might be the best way to identify the gene. Until then, conventional positional cloning might be the alternative that would be facilitated by extended linkage analysis in order to further narrow the region.

Besides the absence of myokymia, the presence of midline cerebellar atrophy, which has been demonstrated in some FPCA families (Gancher and Nutt 1986; Vighetto et al. 1988), including family 1 in the present study (Feeney and Boyle 1989), is another unique feature that is associated with FPCA/−M but not with FPCA/+M. Cerebellar atrophy is commonly associated with ADCA, a heterogenous group of neurodegenerative disorders in which at least five different genes have been identified (Gardner et al. 1994; Ranum et al. 1994). In addition, in family 1 a suggestive feature of anticipation is present that has not been previously described in other FPCA families. In the fourth generation, the age at onset for all three affected cases is 2–3 years, whereas their father and uncle were thought to develop the disease at age 15 and 13 years, respectively. Although one has to take into account that this finding is based solely on history taken from the parents and that it might be easier for younger parents to recall the symptoms after being informed by the clinicians, this feature of anticipation has been found in the subtypes of ADCA type 1, including SCA1, SCA2, SCA3, and SCA5. Both SCA1 and SCA3 have been explained genetically by identification of CAG-repeat expansions in each gene (Orr et al. 1993; Kawaguchi et al. 1994). Although a long (>40) repeat expansion was detected in family 1, it was found to

originate from an unaffected spouse (II-6), and it does not cosegregate with the disease. These results, together with the exclusions of linkage to SCA1, SCA2, and SCA3, confirm that FPCA/–M does not have the same genetic triggers as does ADCA, despite the overlapping clinical features.

Although the clinical course of FPCA/–M is considered relatively benign compared with some forms of ADCA, it can be socially inhibitive and disturbing. The ultimate cloning of the gene not only will shed lights onto the underlying pathophysiology of the disease, but it might also improve its management. Furthermore, the mapping of familial hemiplegic migraine to a 30-cM region on 19p (Joutel et al. 1993) encompassing the FPCA/–M region suggests the possible involvement of the same gene in both diseases, and obviously this will make the gene even more interesting.

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