Am. J. Hum. Genet. 55:702–709, 1994

A Gene for Episodic Ataxia/Myokymia Maps to Chromosome 12p13

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Summary

Episodic ataxia (EA) is a rare, familial disorder producing attacks of generalized ataxia, with normal or near-normal neurological function between attacks. Families with autosomal dominant EA represent at least two distinct clinical syndromes. One clinical type of EA (MIM 160120) includes individuals who have episodes of ataxia and dysarthria lasting seconds to minutes. In addition, myokymia (rippling of muscles, diagnosable by electromyography) is evident during and between attacks. Since K^+ channel genes are candidate genes for EA, we tested markers near known K^+ channel genes for linkage. Using a group of Genethon markers from one such region—chromosome 12p—we found evidence of linkage in four EA/myokymia families. A maximum combined lod score of 13.6 was obtained at $\theta = 0$, with the marker D12S99. A human Ca^{++} channel gene, CACNL1A1, and three human K^+ channel genes—KCNA5, KCNA6, and KCNA1—map close to D12S99, but the Ca^{++} channel gene is unlikely to be the site of the defect, because crossovers have been observed to occur between the disease gene and a CA-repeat marker located close to this gene. Studies of a large EA family with a different clinical phenotype (MIM 108500), which lacks myokymia but is associated with nystagmus, have excluded the gene causing that disease from the chromosome 12p locus.

Introduction

Episodic ataxia (EA) is a rare neurological disorder in which affected individuals experience attacks of generalized ataxia brought on by physical or emotional stress, with only minimal neurological abnormalities between attacks. Although several inherited recessive metabolic errors can cause EA, most cases of EA occur as dominantly inherited conditions with unknown metabolic derangements. Families with autosomal dominant EA appear to represent at least two distinct clinical syndromes. The first type (MIM 108500) includes affected individuals who have episodes of ataxia and dysarthria that last hours to days. Onset occurs in late childhood or early adolescence, persists through adulthood, and exhibits a high degree of penetrance. Many of these patients respond to acetazolamide, and neurological examination usually reveals nystagmus between attacks. Older individuals may develop progressive, nonepisodic ataxia similar to that shown by individuals with spinocerebellar ataxias. Several families with this syndrome have been described in the literature (Parker 1946; Farmer and Mustian 1963; White 1969; Griggs et al. 1978; Donat and Auger 1979; Margolin et al. 1982; Zasorin et al. 1983; Friedman and Hollman 1986; Gancher and Nutt 1986).

The second clinical type of EA (MIM 160120) is characterized by brief episodes of ataxia and dysarthria typically lasting seconds to minutes. In addition to ataxia, neuromyotonia or myokymia (twitching of small muscles) may occur during attacks. Neurological examination between attacks demonstrates spontaneous, repetitive discharges in distal musculature (myokymia) that arise from peripheral nerves; nystagmus is absent. As a consequence of the involuntary muscle activity, some patients have contractures of their Achilles tendons, which may require surgical release (Van Dyke et al. 1975; Hanson et al. 1977; Gancher and Nutt 1986; Brunt and van Weerden 1990).

In this paper, we describe the localization of a gene for the myokymia-associated form of EA to chromosome 12p13, near a cluster of K^+ channel genes, and we show that the nystagmus-associated form is excluded from this region in one large family.

Subjects and Methods

Families

Figure 1 shows pedigrees of five of the families that we have studied. Affected members of kindreds 1–4 have my-

Received April 5, 1994; accepted for publication June 17, 1994.

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0002-9297/94/5504-0013$02.00

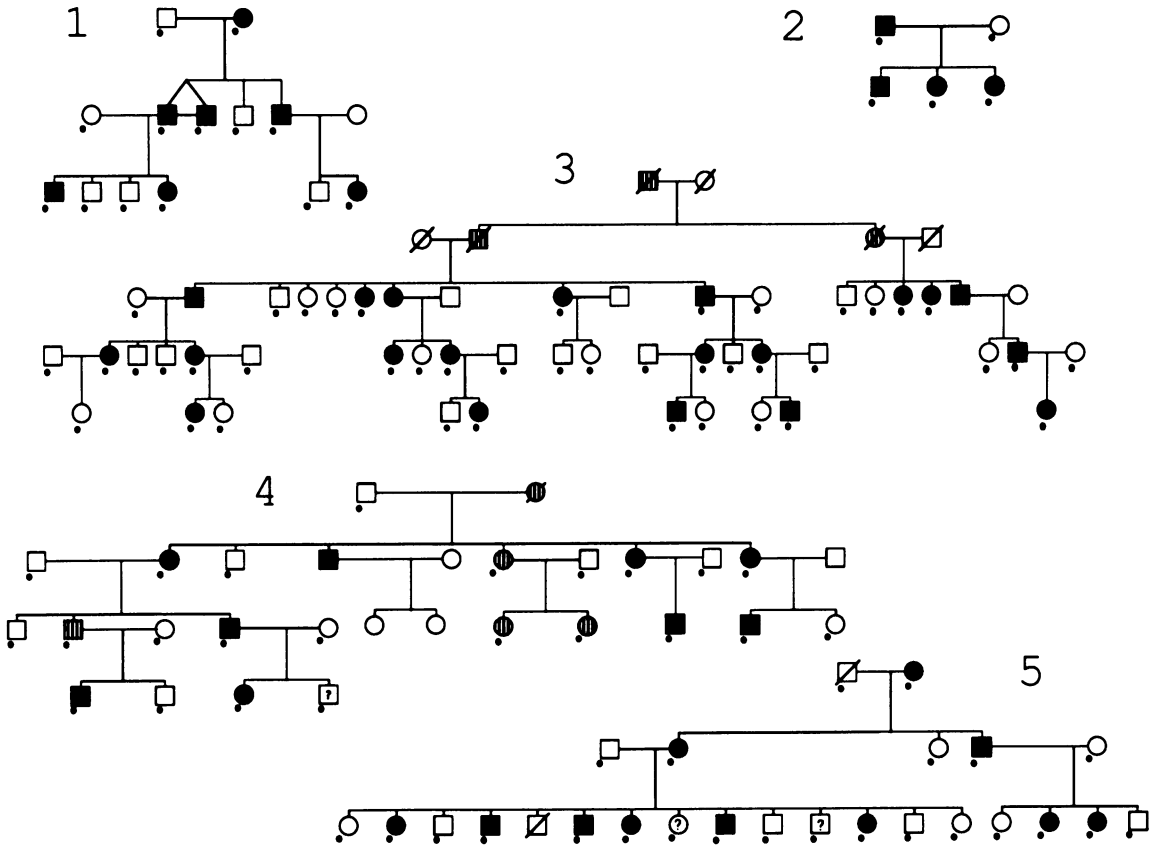


Figure 1 Pedigrees of families studied. Blackened symbols denote affected individuals who have been examined; hatched symbols denote individuals affected by history; and unblackened symbols denote unaffected individuals. Individuals whose affection status is uncertain are indicated by question marks; and sampled individuals are indicated by dots.

okymia and no nystagmus. Affected individuals in kindred 5 respond to acetazolamide; most display nystagmus between attacks; and none have myokymia.

Detailed descriptions of symptoms, signs, and laboratory evaluation of families 4 and 5 have been given by Gancher and Nutt (1986); similar data for family 3 have been presented by Brunt and van Weerden (1990). Affected individuals in families 1–4 were identified by history and by the presence of myokymia on neurological examination. Myokymia was usually detectable on examination, by a fine rippling in periorbital musculature and by lateral finger movements when the hands were held in a relaxed, prone position. In questionable cases, subclinical spontaneous motor-unit discharges were identified by electromyography. Affected individuals in family 5 were identified by a history of attacks of ataxia and by either the presence of nystagmus on lateral gaze, mild truncal imbalance on tandem walking, or, in older individuals, signs of spinocerebellar dysfunction.

DNA Typing

DNA isolated from peripheral blood (Bell et al. 1981), obtained with informed consent of family members, was typed with microsatellite markers as described elsewhere (Litt et al. 1993). In brief, genomic DNA samples were amplified by PCR using primer pairs that flanked (CA)n repeats or other simple sequence repeats. After resolution by electrophoresis on DNA sequencing gels containing urea and formamide, amplification products were capillary blotted onto positively charged nylon membranes and were detected by probing with either 5′[^{32}P] end-labeled $(CA)_{15}$ (for (CA)n repeats) or a 5′[^{32}P] end-labeled PCR primer (for tetranucleotide repeats). Typing results were entered into a PARADOX database for subsequent linkage analysis.

Linkage Analysis

Pairwise and multipoint linkage analyses were conducted using the MLINK and LINKMAP options in the FASTLINK computer package (Cottingham et al. 1993; Schaffer et al., in press). We assumed autosomal dominant inheritance of a rare gene (frequency .0001). Although there is no clear evidence of incomplete penetrance in the five EA pedigrees included here (all affected individuals have an affected parent), these represent only a subset of families with the disorder. In fact, we have data on a small

Table 1

Chromosome 12p Markers Used

Symbol[a]	Marker Name	Heterozygosity	Reference
D12S77	AFM026tb5	.87	Weissenbach et al. 1992
D12S91	AFM182xf10	.69	Weissenbach et al. 1992
D12S93	AFM205ve5	.79	Weissenbach et al. 1992
D12S94	AFM206ze5	.78	Weissenbach et al. 1992
D12S99	AFM2127xa7	.83	Weissenbach et al. 1992
D12S100	AFM205ve5	.71	Weissenbach et al. 1992
D12S372	GATA4HO3	.69	CHLC, 1993
CACNL1A1	cCCCha19.1	.69	Schultz et al. 1993
KCNA5	c7-2a	.60	Phromchotikul et al. 1993
D12S314	AFM207xf8;pY2/1	.80	Gyapay et al. 1994
. . .	pY21/1	.83	Browne and Litt 1994

[a] Human Gene Mapping Workshop.

EA/nystagmus family in which neither parent of two affected siblings shows identifiable symptoms of EA. Therefore, we chose the conservative approach of specifying a high, but incomplete, estimate of penetrance (.95).

Onset of EA occurs no later than adolescence. Since all unaffected individuals for whom data were available were >15 years old, no correction was made for age-dependent penetrance.

Marker allele frequencies were assumed to be equal. In the multipoint analyses, markers with more than five alleles were recoded (reduced in number without losing linkage information), in order to reduce computer processing time.

Linkage Map of Chromosome 12p

Marker loci KCNA5, pY21/1, and CACNL1A1 from chromosome 12p were integrated into the Cooperative Human Linkage Center (CHLC) linkage map (version 2) by typing the markers in the nine largest CEPH families. The markers used are described in table 1. Genotypic data for the Genethon markers and for D12S372 were obtained electronically from the CHLC. To construct the linkage map, we used the BUILD option of the CRIMAP program (Lander and Green 1987). The map so derived was checked by using the FLIPS2 option to derive the odds against inversion of adjacent marker loci.

Results

Although the basic biochemical defects in EA are unknown, both the episodic nature of the attacks and the presence of spontaneous motor unit activity suggested a defect in ion-channel function. As K^+ channels are extremely important in determining the membrane potential and excitability, genes for K^+ channels are candidate genes for EA. Other membrane ion-channel genes, such as those for Ca^{++} channels, are also of interest. Possible candidate genes for EA included those for K^+ channels, related to those encoded by the *Shaker, Shal, Shab,* or *Shaw* loci in *Drosophila.* In humans, related K^+ channel genes have been mapped to chromosomal regions 1p13.3, 1p21, 7q, 11p14, 11p15, 12p13, 13, 19, and 20 (McPherson et al. 1991; Rudy et al. 1991; Curran et al. 1992; Grandy et al. 1992; Grissmer et al. 1992; Albrecht et al. 1993; Klocke et al. 1993).

Three K^+ channel genes and one Ca^{++} channel gene have been localized to chromosome 12p. The K^+ channel genes are KV1.5 or KCNA5 (Curran et al. 1992), KV1.1 or KCNA1 (McPherson et al. 1991), and KV1.6 (KCNA6 or HuKV; Ramaswami et al. 1990; authors' unpublished results). Klocke et al. (1993) have shown that, in mice, these three K^+ channel genes are closely linked and map to a mouse chromosome 6 region that is homologous to human chromosome 12p. A human heart L-type voltage-dependent Ca^{++} channel gene (HGM workshop symbol CACNL1A1) has also been mapped to human chromosome 12p13 by FISH (Schultz et al. 1993). In order to test the involvement of these ion-channel genes in EA, nine polymorphic markers were tested in the candidate region, three of which were developed in order to test specific ion channels within the region.

A polymorphic (CA)n repeat from a cosmid containing the human KCNA5 gene has been described elsewhere (Phromchotikul et al. 1993). To develop markers closely linked to KCNA1 and KCNA6, we screened DNA pools from the CEPH YAC library, with primers designed from the DNA sequences of these genes. From a 1.3-Mb YAC, 730_b_2, we identified two polymorphic (CA)n repeats. One of these, pY2/1, was derived from a λ phage subclone that also contained KCNA6; this (CA)n repeat turned out to be identical to D12S314, a recently described Genethon marker (Gyapay et al. 1994). The physical location of the other (CA)n repeat marker, pY21/1, with respect to

Table 2

Results of Pairwise Linkage Analyses of Chromosome 12 Markers in EA Families (Penetrance = .95)

Marker and Family	Lod Score at θ = .000	.01	.05	.10	.20	.30
D12S91:						
1	.88	.86	.79	.70	.50	.29
2			Uninformative			
3	−19.04	−2.72	.53	1.70	2.24	1.85
4	3.17	3.12	2.91	2.64	2.05	1.38
Total	−14.99	1.26	4.23	5.04	4.79	3.52
D12S100:						
1	1.78	1.75	1.63	1.47	1.11	.73
2			Uninformative			
3	−7.37	−.52	.82	1.23	1.30	1.00
4	2.84	2.86	2.82	2.67	2.18	.76
Total	−2.75	4.09	5.27	5.37	4.59	2.49
CACNL1A1:						
3	1.20	1.17	1.05	.91	.64	.40
4	1.36	1.40	1.45	1.41	1.17	.40
Total	2.56	2.57	2.50	2.32	1.81	.80
D12S99:						
1	1.78	1.75	1.63	1.47	1.11	.73
2	.90	.89	.81	.72	.52	.30
3	6.79	6.68	6.24	5.67	4.46	3.12
4	4.14	4.08	3.82	3.47	2.71	1.86
Total	13.61	13.40	12.50	11.33	8.80	6.01
pY21-1:						
3	5.41	5.67	5.71	5.37	4.32	3.01
4	2.96	2.91	2.72	2.46	1.91	1.28
Total	8.37	8.58	8.43	7.83	6.23	4.29
KCNA5:						
1	.60	.59	.54	.47	.32	.17
2	.30	.29	.26	.21	.13	.06
3	5.98	5.87	5.43	4.86	3.66	2.39
4	−.85	2.38	2.81	2.77	2.31	1.64
Total	6.03	9.13	9.04	8.31	6.42	4.26
D12S93:						
1	1.51	1.48	1.37	1.23	.93	.61
2			Uninformative			
3	7.02	6.93	6.51	5.93	4.60	3.06
4	−3.90	−.59	.13	.40	.53	.45
Total	4.63	7.82	8.01	7.56	6.06	4.12
D12S99:						
5	−13.39	−8.52	−6.84	−5.88	−3.82	−2.02

KCNA6, has not been precisely determined. The (CA)n repeat loci from YAC 730_b_2 are described in a separate report (Browne and Litt 1994). A (CA)n repeat from cosmid cCCCha19.1, which contains CACNL1A1 (Schultz et al. 1993), was also used. Relevant properties of these marker loci are summarized in table 1.

Using microsatellite markers from chromosome 12p, we found evidence of linkage in four EA/myokymia families—kindreds 1–4. Initially, two-point analyses were run on all four families, with D12S91, D12S100, D12S99, KCNA5, and D12S93. In kindreds 1 and 2, no obligate crossovers were observed within the 10-cM region spanned by these markers. Therefore, subsequent pairwise analyses with intervening markers CACNL1A1, D12S372, pY2/1, and pY21/1 were run only in the two large kindreds (3 and 4). All pairwise lod scores are shown in table 2. The highest lod score, 13.61 at θ = .0, was obtained with D12S99. Table 2 also shows pairwise lod scores for D12S99, with family 5, the family with the nystagmus-associated myokymia-negative form of EA. On the basis of these data, the gene for this form of EA is excluded from a 60-cM region centered on D12S99. In this family, exclusions were also obtained for 25–30-cM regions flanking markers D12S62, D12S77, and D12S94 (data not shown).

Table 3

Sex-Average Linkage Map of Human Chromosome 12p, Based on CEPH Data

Marker	θ	Local Support[a]
S94 } ..... S91 }	.01	1.68
..... S100 }	.01	2.01
CACNL1A1 }	.01	2.96
..... S372 }	.03	5.93
PPY21/1 }	.03	9.83
KCNA5 }	.01	1.21
..... S99 }	.01	.83
..... S93 }	.01	3.35
..... S77 }	.04	8.06

[a] Log_{10} of the odds against inversion of adjacent loci.

A sex-average linkage map of the chromosome 12p region containing markers listed in table 1, based on data obtained from CEPH families, is shown in table 3. No significant sex-specific differences in recombination were seen except in the interval D12S372-pY21/1, which showed a sevenfold excess of male recombination (data not shown). Note that, although the order shown for the closely linked markers pY21/1, KCNA5, and D12S99 is the most likely one, statistical support for this order is weak.

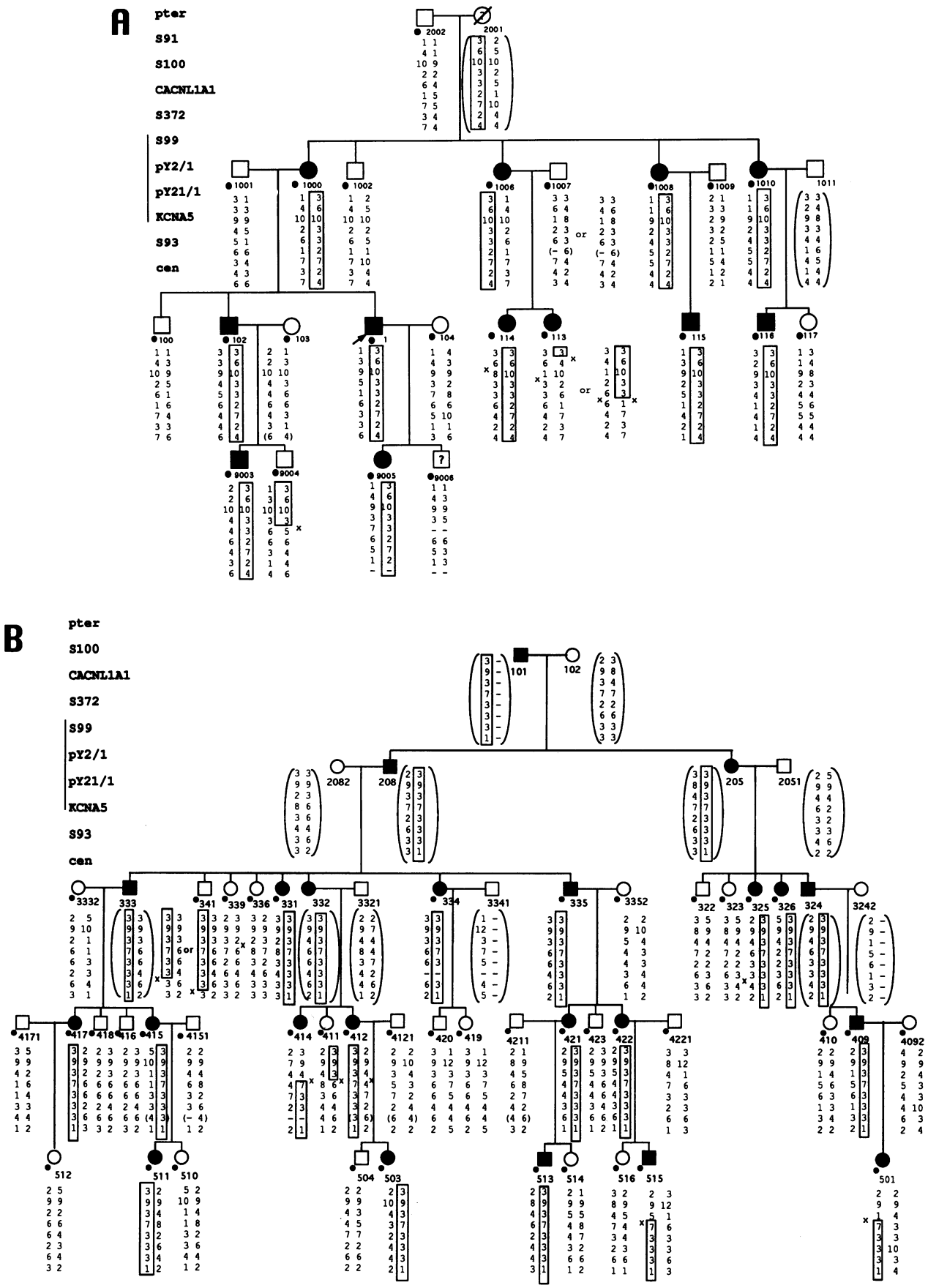
Figures 2*A* and *B* show the segregation of alleles in kindreds 4 and 3, respectively, at 12p marker loci in the 12-cM (sex-average) region bounded by D12S91/S100 and D12S93. The marker order in figure 2 differs from that shown in the linkage map in table 3. In the latter, based on CEPH pedigree data, the odds against inversion of adjacent loci in the triplet pter–pY21/1–KCNA5–D12S99–cen are ≤16:1. In kindred 4, this order would result in an obligate triple crossover, within a 3-cM region, in individual 113. If the order of these markers is flipped (i.e., pter–D12S99–KCNA5–pY21/1–cen), only a single crossover is required in this individual.

In family 4 (fig. 2*A*), a single crossover in the region between D12S91 and the pY2/1-KCNA5 cluster occurred on the maternal chromosome transmitted to affected individual 113, suggesting localization of the EA/myokymia gene distal to these two K^+ channel–associated markers. This observation was confirmed on resampling and retyping individual 113. The crossover on this chromosome could have occurred anywhere between D12S91 and KNCA5; only two of the five possible crossover points are shown. Haplotypes shown for individual 1007 are not unique; to save space, only two possibilities consistent with the postulated haplotypes of his daughters are shown. A crossover between D12S372 and the clustered markers D12S99, pY2/1, pY21/1, and KCNA5 occurred in unaffected individual 9004, suggesting localization of the disease gene proximal to D12S372. If account is taken of incomplete penetrance, the importance of this crossover is diminished. However, taken at face value, these observations would place the disease gene in a 4-cM region flanked by pY2/1-KCNA5 and D12S372 and would rule out the involvement of KCNA5 and KCNA6(pY2/1) as sites of the primary defect.

In family 3 (fig. 2*B*), 14 of the 17 sampled affected family members, including at least one member from each branch, have the same haplotype (39373331) on one of their chromosomes 12. For several affected individuals from the earlier generations of this five-generation family, samples were unavailable, but we inferred their haplotype from offspring and assumed that the affected parent carried the disease-associated haplotype on one of his or her chromosomes 12.

A single case of non-Mendelian inheritance is apparent at the locus D12S372 in family 3. Given the observed genotypes of her daughters, the genotype of affected individual 332 at this locus was inferred to be 3,4. Specifically, since 332 has passed the disease-associated haplotype intact to both her daughter 412 and her granddaughter 503, we assumed that one of her D12S372 alleles must be a 3. Since her daughter 414 is a homozygous 4,4, 332's other D12S372 allele must be a 4. However, the D12S372 genotypes of her parents, as inferred from those of her six sampled sibs, are 2,3 and 3,3, which is inconsistent with her inheritance of allele 4 at that locus. For lack of another explanation, we attribute this non-Mendelian event to a new mutation at the D12S372 locus, which could have oc-

Figure 2 Haplotypes of family members, at chromosome 12p marker loci. Genotypes are listed in the order indicated by the maps at the upper left. Since the order of the four closely linked marker loci S99, pY2/1, pY21/1, and KCNA5 has not been reliably determined, these loci are bracketed. Individuals for whom samples were available are marked with dots. Inferred genotypes or haplotypes are enclosed in brackets. The haplotype present on the disease-bearing chromosome in the proband and in other affected family members is shown boxed, as are regions of this chromosome that are transmitted from affected individuals to their children. Crossovers are indicated by X's. *A*, Family 4. *B*, Family 3.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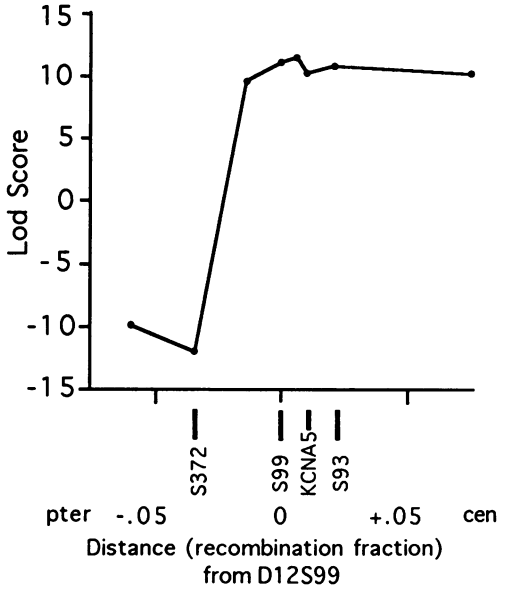

Figure 3 Multipoint linkage analysis of EA/myokymia in families 3 and 4.

curred on either the maternal (332) or the grandmaternal (2082) non–disease-bearing chromosome in this branch of the family.

From inspection of figure 2*B*, three recombination events in affected individuals involving chromosomes bearing the disease-associated haplotype are apparent. These involved (1) the chromosome transmitted from affected mother 422 to her affected son 515, (2) the chromosome transmitted from affected father 409 to his affected daughter 501, and (3) the chromosome transmitted from affected mother 332 to her affected daughter 414. All of these events indicate localization of the disease gene proximal to D11S372, and all are consistent with its localization within the D12S99/KCNA6/KCNA5 cluster.

These data were corroborated by multipoint linkage analysis of kindreds 3 and 4, using D12S372, D12S99, KCNA5, and D12S93. (Because no recombinants in this region were observed in kindreds 1 and 2, these families were not included in the multipoint analysis.) As illustrated in figure 3, the maximum combined multipoint lod score was 11.35, midway between D12S99 and KCNA5.

Discussion

The evidence presented above establishes that a gene for EA/myokymia maps to human chromosome 12p. No recombination between the disease gene and the marker D12S99 occurred in four families, and the combined maximum lod score was 13.6 at $\theta = .00$ (confidence limits .00–.05). Multipoint analysis indicates localization of the disease gene to a 5-cM region flanked by D12S93 and D12S372.

Haplotype analysis provides strong support for localization of the disease gene proximal to D12S372, thereby ruling out CACNL1A1 as a candidate gene for EA/myokymia. A crossover between D12S91 and the KCNA6 marker pY2/1 occurred on the maternal chromosome transmitted to affected individual 113 in family 4, suggesting localization of the EA/myokymia gene distal to KCNA6. A crossover between pY2/1 and D12S93 occurred on the paternal chromosome bearing the disease-associated haplotype transmitted from an affected father to his unaffected son—individual 341 in family 3—suggesting localization of the disease gene proximal to KCNA6. The most likely explanation for this is incomplete penetrance of the EA/myokymia gene. This would imply that individual 341 in family 3 fails to express the EA/myokymia phenotype even though he carries the disease gene. Although mispaternity or sample mix-up could be invoked to explain this result, this is unlikely, because his genotypes at eight highly informative microsatellite loci were consistent with those of his putative parents, as inferred from the genotypes of his five sampled sibs. Furthermore, individual 341 was resampled and retyped at several marker loci, with no change in the results. For this reason, we favor incomplete penetrance as the explanation, and we suggest that the most likely location for an EA/myokymia gene in our families is between D12S372 and the D12S99/KCNA5/KCNA6 cluster.

On the basis of the single crossover in individual 113 from family 4, we suggest that KCNA5 and KCNA6 are unlikely to be sites of the primary defect for EA/myokymia. However, KCNA1, which is located on the same 1.3-Mb YAC as is KCNA6, remains a viable candidate gene, because its genetic and physical distance from the KCNA6-associated (CA)n repeat is unknown.

In kindred 5, which represents a different clinical form of EA (MIM 108500), characterized by nystagmus and lack of myokymia, we have excluded linkage to D12S99, out to 30 cM on either side (see table 2). In addition (data not shown), statistically significant exclusion was obtained for several markers on 6p, in the region associated with SCA1 (Ranum et al. 1991; Zoghbi et al. 1991). This establishes that the clinical heterogeneity seen in EA reflects genetic heterogeneity and that myokymia-negative EA is not a "form fruste" of SCA1.

Acknowledgments

This work was supported by NIH grants HG00022 and NS25370 and by a grant from the National Ataxia Foundation. We thank the Cooperative Human Linkage Center and Genethon for making their maps and genotypic data available electronically, and we acknowledge the excellent technical assistance of Ruth Litt, Nancy Payne, and Eric Smith.

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