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Benign adult familial myoclonus epilepsy (BAFME): an autosomal dominant form not linked to the dentatorubral pallidoluysian atrophy (DRPLA) gene

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Abstract

The genetic differences between two types of dominant inherited myoclonus epilepsy, dentatorubral pallidoluysian atrophy (DRPLA) and benign adult familial myoclonus epilepsy (BAFME), have been reported. A gene with a CAG repeat expansion responsible for DRPLA has been isolated. We have examined CAG repeat expansion in the DRPLA gene in five BAFME families, and the abnormal CAG expansion was not observed in the affected subjects. Linkage analysis using DNA polymorphisms in the DRPLA gene and the genes for γ-aminobutyric acid (GABA) receptor subunits, GABARβ1, GABARβ3, and GABARα6, showed that these genes were not responsible for BAFME.

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Key words: benign adult familial myoclonus epilepsy; dentatorubral pallidoluysian atrophy; α-aminobutyric acid (GABA) receptor.

Among disorders which include myoclonus epilepsy (ME), dentatorubral pallidoluysian atrophy (DRPLA) and benign adult familial myoclonus epilepsy (BFAME), reported particularly in Japan, are known to be transmitted by autosomal dominant inheritance.[1 2] DRPLA is a progressive neurodegenerative disorder,

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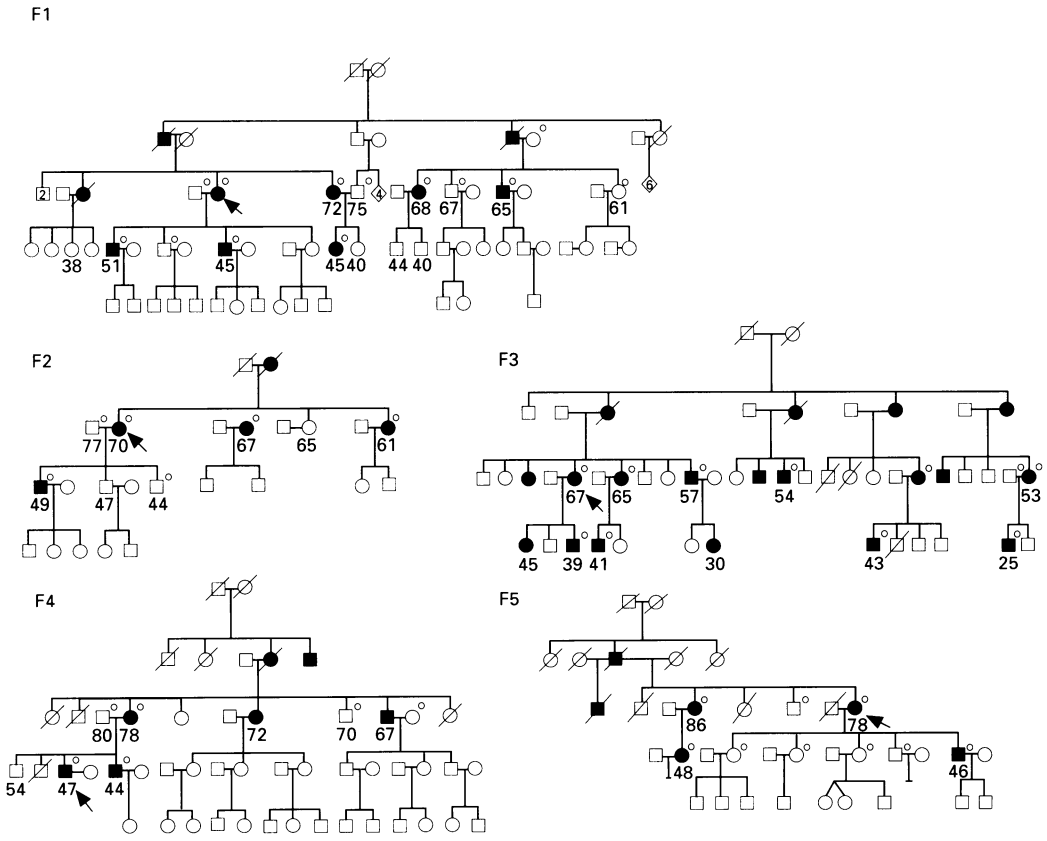

Figure 1 Family pedigrees with myoclonus epilepsy showing phenotypes and age at study. The proband is indicated by an arrow. Numbers under the symbols are ages at examination. Filled symbols = affected with myoclonus and epilepsy, small circles = subjects studied with DNA polymorphisms.

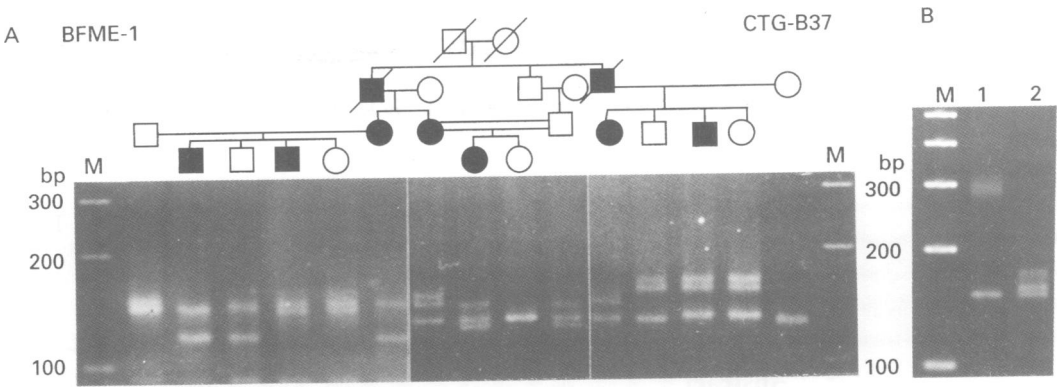

Figure 2 (A) Genotypes of DRPLA gene CTG-B37 in a branch of family 2. Genomic DNA from family members was amplified by PCR using the primer set for the DRPLA gene. (B) CAG expansion seen in the patients with DRPLA (lane 1). Lane 2 is a CAG repeat in a normal subject. Lane M is a 100 bp ladder as a DNA size marker.

characterised by myoclonus, epilepsy, involuntary movements, cerebellar ataxia, and dementia.[1] Recently, a gene for DRPLA, CTG-B37, was isolated and a significant negative correlation was found to exist between the number of CAG repeats in exon 5 of the DRPLA gene and age at onset and clinical symptoms in patients with DRPLA.[3-5] Clinical symptoms in patients with late onset DRPLA are myoclonus and cerebellar ataxia, and the number of CAG repeats is less than 60.[1 4 5] BAFME is characterised by myoclonus and epilepsy and the phenotype sometimes resembles that of late onset DRPLA.[2] To discover whether CAG expansion in the DRPLA gene may cause BAFME, CAG expansion in the DRPLA gene was examined in families with BAFME. BAFME patients respond to sodium valporate and diazepam treatment,[2] and since GABA receptors are the site of action of these drugs, linkage studies of the DNA polymorphisms of the DRPLA and GABA receptors, GABARβ1, GABARβ3, and GABARα6, were performed as described previously.[5-8]

Family pedigrees are shown in fig 1. Patients in family 3 have been previously reported.[1] Clinical symptoms and neurological signs of the remainder were essentially the same as those in family 3. In brief, patients with myoclonus or epilepsy and abnormal EEG findings, particularly photosensitivity in the EEG, were diagnosed as affected. The age at onset of the disorder was between 18 and 50 years, so people aged over 50 years were diagnosed as normal if they had not shown any clinical signs. PCR amplification of the DRPLA gene was performed as previously described[5] (fig 2). The sizes of the PCR products were between 100 bp and 200 bp in all patients, corresponding to the findings in the normal population.[5] These results indicate that CAG expansion in the DRPLA gene is not related to BAFME. In the linkage analysis, the autosomal dominant type, with a gene frequency of the disease allele of 0·00001 and a penetrance of 0·9 in people aged over 44 years with no sex difference, was adapted for the mode of inheritance based on data previously reported. Among the families in which DNA polymorphisms were informative, a gene for BAFME was not linked to the DRPLA gene nor those of the GABA receptors (data not shown). There are many disorders with ME and some genes for ME have been assigned to specific chromosomal regions.[9 10] Further linkage studies with DNA markers for ME will shed light on the aetiology of BAFME.

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