

## Localization of a Gene for Benign Adult Familial Myoclonic Epilepsy to Chromosome 8q23.3-q24.1

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### Summary

Benign adult familial myoclonic epilepsy is an autosomal dominant idiopathic epileptic syndrome characterized by adult-onset tremulous finger movement, myoclonus, epileptic seizures, and nonprogressive course. It was recently recognized in Japanese families. In this study, we report that the gene locus is assigned to the distal long arm of chromosome 8, by linkage analysis in a large Japanese kindred with a maximum two-point LOD score of 4.31 for D8S555 at recombination fraction of 0 (maximum multipoint LOD score of 5.42 for the interval between D8S555 and D8S1779). Analyses of recombinations place the locus within an 8-cM interval, between D8S1784 and D8S1694, in which three markers, D8S1830, D8S555, and D8S1779, show no recombination with the phenotypes. Although three other epilepsy-related loci on chromosome 8q have been recognized—one on chromosome 8q13-21 (familial febrile convulsion) and two others on chromosome 8q24 (KCNQ3 and childhood absence epilepsy)—the locus assigned here is distinct from these three epilepsy-related loci. This study establishes the presence of a new epilepsy-related locus on 8q23.3-q24.11.

### Introduction

Epilepsy is characterized by recurrent, transient disturbances of neuronal synchrony and is one of the most

common medical conditions, affecting ~4% of individuals at some time in their lives (Hauser et al. 1993). Twin studies have demonstrated a substantial genetic influence in epilepsy, among the common medical disorders (Plomin et al. 1994). To identify the pathogenic mechanisms underlying epilepsies, it is important to map and clone the genes responsible for epileptic syndromes with a Mendelian mode of inheritance, and to define their mutations.

Inazuki et al. (1990) pointed out the presence of autosomal dominant Japanese familial cases of epilepsy with adult onset-type myoclonus (40 patients from 12 families) and a benign course, without reporting specific neuropathological findings. Ikeda et al. (1990) reported electrophysiological studies in two Japanese patients who had adult-onset finger tremor, seizure, and family history of the same condition without a progressive course. They demonstrated involuntary movement as a form of cortical reflex myoclonus. Yasuda (1991) reported in detail electrophysiological studies in two similar large Japanese families. He proposed the syndrome of benign adult familial myoclonic epilepsy (BAFME; MIM 601068).

The clinical features of BAFME are (1) autosomal dominant inheritance, tremulous finger movement, and/or myoclonus of the extremities after adolescence; (2) infrequent epileptic seizure; (3) abnormality of polyspikes and waves on examination by electroencephalogram (EEG) and marked photosensitivity; (4) enlarged cortical components of somatosensory-evoked potential; (5) enhanced long-loop reflex (C-reflex); (6) positive spikes preceding myoclonus, ascertained with the jerk-locked-averaging method; and (7) benign nonprogressive course without cerebellar ataxia and dementia. To date, similar familial cases have been reported only from Japan (Okino 1997; Terada et al. 1997). Hashimoto et al. (1993) reported the possible linkage between familial myoclonus epilepsy and human leukocyte antigen-B phenotype, which was reported as a genetic marker linked to juvenile myoclonus epilepsy. Kuwano et al.

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(1996) investigated CAG repeats in the dentatorubral pallidoluysian atrophy (DRPLA) gene and found no abnormal CAG expansion in the subjects affected with BAFME. Their linkage analysis using DNA polymorphisms in the DRPLA gene excluded it as a site for the mutation for BAFME.

Recently, significant progress has been made in the mapping and isolation of genes for epilepsy syndrome. Idiopathic single-gene generalized epilepsies include two types of benign familial neonatal convulsions (BFNC), for which loci have been identified: one that maps to 20q (BFNC1) and was shown to result from mutations in a voltage-gated potassium-channel gene, *KCNQ2* (Singh et al. 1998); and a second that maps to 8q24 (BFNC2) and was demonstrated to be caused by mutations in another voltage-gated potassium-channel gene, *KCNQ3* (Charlier et al. 1998). Benign familial infantile convulsions is an autosomal dominant disorder whose gene was mapped to chromosome 19 by linkage analysis (Guipponi et al. 1997). Scheffer and Berkovic (1997) described a clinical subset, termed "generalized epilepsy with febrile seizures plus" (GEFS+). Wallace et al. (1998) found linkage to 19q13.1 in a large GEFS+ family and identified a mutation in the voltage-gated sodium channel  $\beta 1$  subunit gene (*SCN1B*). Other loci for febrile seizures reported are chromosomes 8q13-21 (Wallace et al. 1996) and 19p (Johnson et al. 1998). Fong et al. (1998) reported the linkage of childhood-absence epilepsy to chromosome 8q24. Recently, autosomal dominant inheritance in idiopathic partial epilepsies has also been described. In autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), a defect in the gene of the  $\alpha 4$  subunit of the nicotinic-acetylcholine receptor located on 20q13.2 was found (Phillips et al. 1995), which was the first genetic defect described in an idiopathic epilepsy. Neubauer et al. (1998) found evidence for linkage of benign epilepsy of childhood with centrotemporal spikes, or rolandic epilepsy, to a region on chromosome 15q14. The chromosomal area, 15q14, has been reported to be linked to the phenotype in families with an auditory-neurophysiologic deficit, as well as in families with juvenile myoclonic epilepsy (Elmslie et al. 1997). In familial temporal lobe epilepsy, linkage to chromosome 10q has been reported (Ottman et al. 1995). In this report, we report evidence that a new epilepsy-related locus for BAFME is localized to chromosome 8q23.3-q24.11.

## Patients and Methods

### *Patients and Samples*

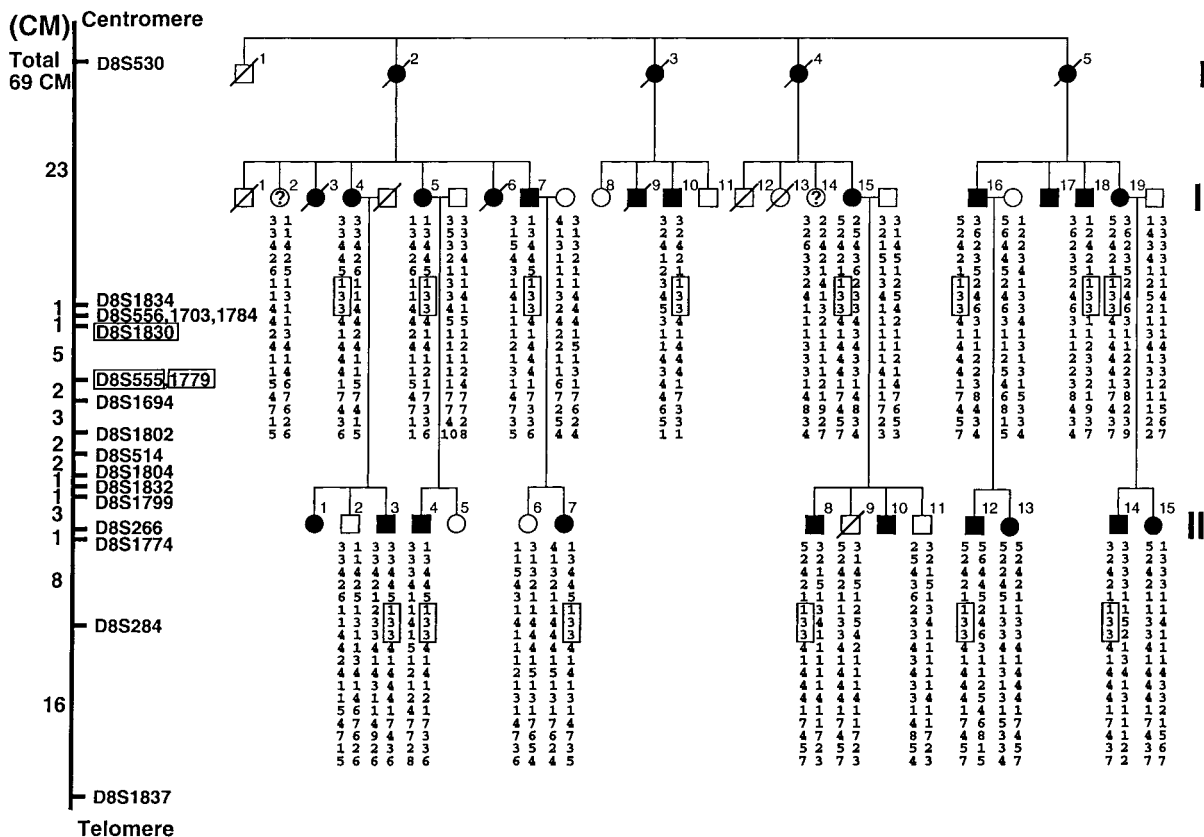
Linkage analysis was performed in a large Japanese family, partly described elsewhere (fig. 1). Altogether, 27

individuals, including 17 affected patients, were studied. From each consenting individual, 10 ml venous blood was collected and used to extract high-molecular-weight DNA.

Following is a brief summary of the clinical features associated with BAFME. Patients developed normally up to adolescence. The onset of symptoms is tremulous finger movement and/or myoclonus of the extremities at an average age of 30.5 years (range 18-45 years). The tremulous finger movements were classified electrophysiologically into two types: one with a relatively stable frequency of ~9-10 Hz, and one with a more variable frequency. There is a variation of symptoms. For instance, myoclonus was limited in the upper extremities in half of the patients, but in the other half myoclonus appeared in both upper and lower extremities. Generalized tonic-clonic convulsions occurred infrequently, often fewer than four times throughout the life span. Epileptic seizures have not yet been observed in two patients (patient II-23 and patient III-7). None of the patients developed either cerebellar ataxia or dementia during the observation period of >10 years. EEGs were abnormal in all patients, and generalized polyspikes and wave complexes were observed in most patients. Photoparoxysmal responses were evoked, and photomyoclonus was induced by photic stimulation in some patients. In the sensory-evoked potentials (SEP) study, the amplitude of the components of SEP (P25 and N33) was increased in all patients. The amplitude of the N75, P100, and/or N145 components was increased by photic stimulation in all seven examined patients in whom visual-evoked potentials were recorded. By use of the jerk-locked-averaging method, with myoclonus of upper extremity as a trigger, positive spikes preceding myoclonus were observed in four patients. A C-reflex was recorded in all patients. Cranial computed tomography showed no particular abnormal findings except mild cerebral-cortex atrophy in three patients. The serum levels of lactate and pyruvate were within the normal range. For treatment, valproate and clonazepam were effective for both myoclonus and epilepsy.

### *Microsatellite-Marker Analysis*

Highly polymorphic microsatellite markers were selected from the Généthon human genetic linkage map (Généthon; Dib et al. 1996). The primer sequences are from the Genome Database. Other trinucleotide-repeat polymorphisms related to neurodegenerative disorders were analyzed. PCR amplification was performed on 50 ng genomic DNA with  $^{32}\text{P}$ -dCTP. PCR conditions were 30 cycles of 94°C for 1 min, specific annealing temperature for each primer for 1 min, and 72°C for 1 min. PCR products were separated onto 6% denaturing



**Figure 1** Pedigree of a large Japanese family with BAFME. Blackened symbols indicate the affected subjects, and unblackened symbols indicate those with no signs or symptoms. A question mark (?) indicates a subject who has not been examined completely. The alleles of the 18 markers are shown under each individual, in the order indicated to the left.

polyacrylamide gels and were visualized by fluorography with the BAS1000 system (FujiFilm).

*LOD-Score Linkage Analysis*

Two-point linkage LOD-score analysis was performed with use of MLINK from the LINKAGE software package version 5.1 (Lathrop et al. 1984). Marker-allele frequencies were derived from 50 Japanese control subjects. The frequency for the disease allele was estimated at ~.00001. LOD scores were calculated at recombination fractions ( $\theta$ ) of .00, .10, .20, .30, .40, and .50. We used an autosomal dominant model with 100% penetrance, assuming the frequency of the affected allele to be 0.00001. Multipoint linkage analysis was performed with the program LINKMAP, using 2 of 16 informative markers each time, from centromere to telomere. Marker order and recombination fractions were obtained from Génethon (Dib et al. 1996).

**Results**

As an initial step, we studied whether BAFME is a variant form of DRPLA, which is a frequent cause of myoclonic epilepsy in the Japanese. The patients with BAFME possess no abnormal expansion of the CAG-tandem repeat in the DRPLA gene and the linkage analysis using the triplet-repeat polymorphism excluded the DRPLA gene as a site for the BAFME mutation (we obtained a two-point LOD score of  $-8$  at  $\theta = .00$ ), which confirm the results obtained by Kuwano et al. (1996). Other trinucleotide-repeat polymorphisms that have been reported to be associated with neurodegenerative diseases were studied. None of them, however, showed abnormal expansion, and negative LOD scores were also obtained. Next, >20 dinucleotide microsatellite markers, including the ones that lie in regions corresponding to previously mapped epilepsies (6p and 21q22.3), were genotyped before linkage was detected (Greenberg et al. 1987; Lehesjoki et al. 1993). Two-point maximum-likelihood calculations were performed after complete ge-

**Table 1**  
Pairwise LOD Scores for BAFME Versus Chromosome 8q Markers

MARKER	LOD SCORE AT $\theta =$						$\theta_{\max}^a$	$Z_{\max}^b$
	.0000	.0050	.0100	.0200	.0300	.04000		
D8S530	$-\infty$	-2.738	-1.233	-.0064	.0292	.0268	.0340	.0318
D8S1834	-1.078	2.110	2.035	1.583	1.030	.0484	.0055	2.298
D8S556	1.961	1.725	1.499	1.083	.0708	.0352	.0000	1.961
D8S1703	-1.631	1.586	1.536	1.166	.0715	.0262	.0061	1.594
D8S1784	-1.660	1.446	1.315	.0739	.0067	-.0297	.0051	1.446
D8S1830	2.092	1.830	1.573	1.085	.0639	.0250	.0000	2.092
D8S555	4.108	3.710	3.295	2.411	1.468	.0556	.0000	4.108
D8S1779	4.314	3.928	3.530	2.688	1.784	.0838	.0000	4.314
D8S1694	-3.437	.0933	.0923	.0617	.0276	.0045	.0070	.0955
D8S1802	1.858	1.672	1.487	1.114	.0734	.0353	.0000	1.858
D8S514	-2.330	1.383	1.340	.0963	.0542	.0206	.0063	1.395
D8S1804	$-\infty$	1.096	1.342	1.194	.0776	.0338	.0118	1.355
D8S1832	$-\infty$	-.0025	.0580	.0767	.0519	.0206	.0174	.0782
D8S1799	-2.848	2.309	2.003	1.602	1.055	.0490	.0065	2.053
D8S266	$-\infty$	1.308	1.619	1.522	1.089	.0539	.0129	1.651
D8S1774	$-\infty$	-1.102	.0036	.0775	.0833	.0552	.0261	.0860
D8S284	$-\infty$	-.0718	-.0108	.0208	.0180	.0074	.0229	.0218
D8S1837	$-\infty$	-.0715	.0129	.0660	.0682	.0422	.0255	.0714

<sup>a</sup> Maximum  $\theta$ .

<sup>b</sup> Maximum LOD score.

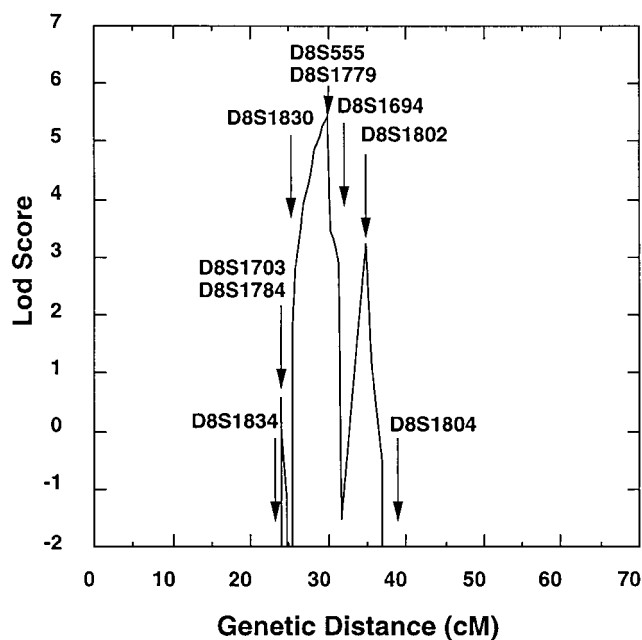
notyping with one marker. We detected preliminary evidence for linkage with D8S284 (we obtained a maximum two-point LOD score of 0.214 at  $\theta = .25$ ), which was associated with BFNC2. This prompted us to study additional markers on chromosome 8q. On the

basis of the positions reported, 17 other markers on chromosome 8q were studied. The results of two-point LOD scores between the disease phenotype and each marker loci and haplotype analysis for these markers are shown in table 1 and figure 1, respectively.

The maximum LOD score obtained was 4.314 at  $\theta = .00$  at D8S1779 in a two-point analysis. For D8S555 and D8S1830, no recombinations were observed ( $\theta = .00$ ), with maximum LOD scores of 4.108 and 2.092, respectively. Results of the three-point analysis confirm linkage between the disease phenotype and this region, since a maximum multipoint LOD score of 5.42 for the interval between D8S555 and D8S1779 was observed (fig. 2). The proximal recombination site is between D8S1784 and D8S1830, as observed in six affected members comprising patient I-2's offspring (patients II-4, II-5, II-7, III-3, III-4, and III-7), and the distal site is between D8S1779 and D8S1694, which occurred in an affected family member (patient II-18). These results suggest the susceptibility area of this disease to be within the 8-cM interval between D8S1784 and D8S1694.

## Discussion

After examining >20 microsatellite markers lying in the regions corresponding to the previously mapped loci for epilepsies and excluding them as a site for mutation, we obtained strong evidence for the localization of a gene for BAFME, which maps to chromosome 8q23.3-24.11, with a maximum multipoint LOD score of 5.42



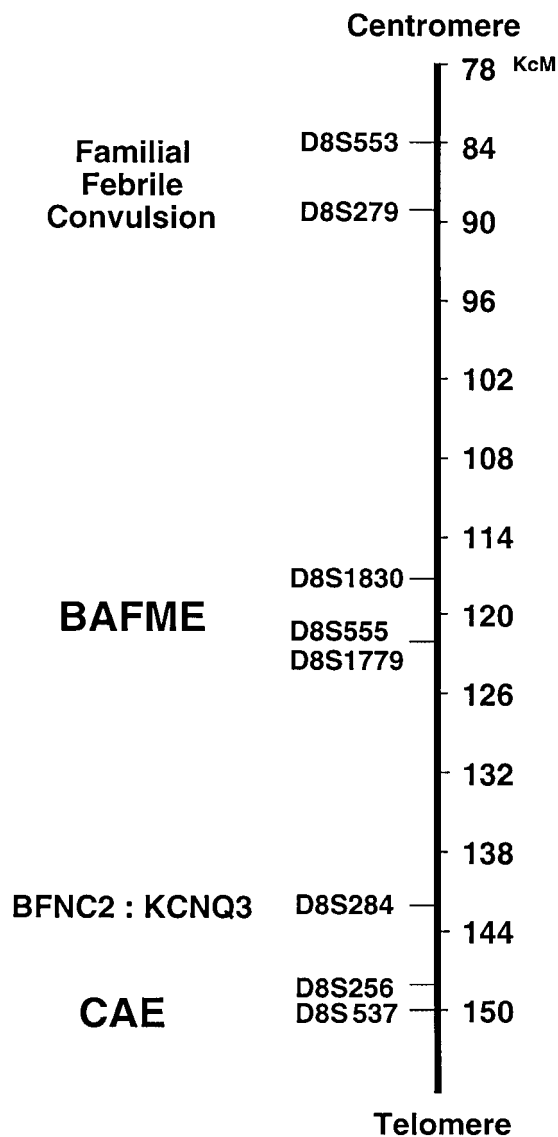
**Figure 2** Multipoint LOD scores for genetic location on chromosome 8q. Genetic distances from D8S530 are in centimorgans. The telomere is to the right. Arrows indicate the markers that provide each LOD score.

for the interval between D8S555 and D8S1779. Three other epilepsy syndromes have been mapped to chromosome 8q. The gene locus for familial febrile convulsions was mapped to the region flanked by markers D8S553 and D8S279 (chromosome 8q13-21; Wallace et al. 1996), and this region is ~30 cM centromeric to our BAFME locus. Lewis et al. (1993) reported the linkage of BFNC2 to markers D8S284 and D8S256, localized on chromosome 8q24.13-qtel, and the same region was implicated in families with an idiopathic generalized epilepsy syndrome (Zara et al. 1995). Our BAFME locus is 23 cM centromeric from D8S284, with which we obtained a maximum two-point LOD score of 0.214 at  $\theta = 0.25$ . The locus for childhood absence epilepsy (CAE) was mapped to 8q24 (Fong et al. 1998), further telomeric, by several centimorgans, from D8S256. Present results, together with the above reports, indicate that the locus for BAFME assigned here is distinct from other loci for epilepsy syndromes mapped to chromosome 8q (fig. 3).

We cannot estimate the proportion of BAFME that can be attributed to alleles at this locus, since our analysis was restricted to a single family. Study of additional families is required to further investigation of the effects of the allele and locus heterogeneity. It is interesting that BAFME and similar cases have been reported only from Japan, as far as we know, which indicates the possibility of the existence of a founder effect in this disorder.

Recent progress in molecular genetics in epilepsy has shed light on the understanding of the basic mechanisms of epileptogenesis. A mutation in the gene *CHRNA4*, encoding the  $\alpha 4$  subunit of the ionotropic-type neuronal nicotinic-acetylcholine receptor (nAChR) was recently identified in ADNFLE (Steinlein et al. 1995). In vitro studies have demonstrated that the mutation results in reduced permeability to calcium (Kuryatov et al. 1997; Bertrand et al. 1998). The gene for BAFME may be a gene for a type of nAChR subunit, and human genes encoding the  $\alpha 2$  and  $\beta 3$  subunits of the nAChR (*CHRNA2* and *CHRNA3*) have been mapped to chromosome 8. However, the precise location of both genes recently has been found to be chromosome 8p (Koyama et al. 1994; Wood et al. 1995). The glutamate-binding subunit of another ionotropic receptor, the NMDA receptor (*GRINA*), was mapped to 8q24.3 (Lewis et al. 1996), which is distal to the region defined for BAFME. Causative mutations in *KCNQ2* and *KCNQ3* in BFNC1 and BFNC2, and a sodium-channel gene (*SCN1B*) in febrile seizures and generalized epilepsies, have been demonstrated (Biervert et al. 1998; Charlier et al. 1998; Singh et al. 1998; Wallace et al. 1998). Although these genes locate differently from the loci for BAFME, as mentioned above, these findings may suggest a gene search for other ion channels or ion channel-related molecules as the candidate. Finally, we would like to

## Chromosome 8q



**Figure 3** Genetic map of chromosome 8q region near BAFME, on the basis of the CEPH/G n thon chromosome 8 linkage map (G n thon). Relative positions of the BAFME locus and of the other three loci for epilepsy-related syndromes, familial febrile convulsions, BFNC2, and CAE are indicated.

emphasize that BAFME is a novel entity, as shown by its clinical picture and the distinct locus assigned here.

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## Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Généthon, <http://genethon.fr/> (for markers)

Genome Database, <http://gdbwww.gdb.org/> (for primer sequence)

Online Mendelian inheritance in man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for BAFME [MIM 601068])

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