FAME 3

A novel form of progressive myoclonus and epilepsy

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ABSTRACT **Background:** Familial adult myoclonic epilepsy (FAME) is associated with myoclonus, tremor, and rare seizures, and is a nonprogressive disorder linked to the FAME 1 locus. A similar disorder has been linked to the FAME 2 locus. **Methods:** Seventeen patients from two families with myoclonus and epilepsy were evaluated clinically and underwent EEG, EMG, jerk-locked averaging, and MRI scanning. Three had responses to magnetic stimulation assessed. Linkage was assessed for microsatellite markers across the FAME 1 and 2 loci. **Results:** The median age at onset was 20 years, with many patients having frequent seizures, cognitive impairment, and cerebellar dysfunction. Electrophysiologic features of cortical myoclonus were typically present, but photosensitivity was uncommon. MRI frequently demonstrated cerebellar atrophy. Pathology of a single case showed Purkinje cell loss, dentate atrophy, and neuronal loss and gliosis in the olives and pallidum. Analysis of genotypes for markers at the FAME 1 and FAME 2 loci excluded these as the region containing the same locus in one family, but only the FAME 2 locus was excluded in the other family. **Conclusions:** This form of familial adult myoclonic epilepsy does not show linkage to either of the known familial adult myoclonic epilepsy loci, and is characterized in some members by frequent seizures, cerebellar ataxia, dementia, and progression of the disease. This may represent a new form of progressive myoclonus and epilepsy, which we have termed familial adult myoclonic epilepsy type 3. **NEUROLOGY 2007;68:1382–1389**

Familial adult myoclonic epilepsy (FAME) has autosomal dominant inheritance and often presents in early adulthood, as may progressive myoclonic epilepsy (PME). However, in PME, dominant inheritance is only seen in dentatorubral pallidoluysian atrophy (DRPLA),[1] a single family with Kufs disease,[2] and mutations in the neuroserpin gene.[3] FAME was described in families from Japan and is characterized by myoclonic jerks in the arms and legs, tremulous finger movements, rare generalized tonic-clonic seizures (GTCS), and has been linked to chromosome 8q24.[4,5] Families with a clinical phenotype similar to FAME have been described from Spain in which linkage to FAME 1 was excluded, indicating genetic heterogeneity.[6] A similar condition, autosomal dominant cortical myoclonus and epilepsy (ADCME), has features of a primary generalized seizure disorder, complex partial seizures and mental retardation in some affecteds, and maps to chromosome 2p11.1-q12.2,[7] a locus termed FAME 2. Three other families with FAME have been linked to the same region, but did not have mental retardation or complex partial seizures, suggesting that the disorders may be allelic.[8,9] It has been proposed that FAME 1 is seen in Japanese families linked to 8q24 and FAME 2 in European families linked to 2p11.1-q12.2.[9] However, a family from the Netherlands has been described in which the loci responsible for both FAME 1 and FAME 2 were excluded.[10]

We report a novel form of epilepsy, characterized by the presence of GTCS, myoclonic jerks, and associated in some individuals with progressive neurologic deficit, which we have termed familial adult myoclonic epilepsy 3 (FAME 3).[11] Two families were identified from the Western Cape Province of South Africa, and are of mixed ancestry, predominantly resulting from intermarriage between the original inhabitants of the area, the Khoi-San, and early settlers of European origin.

Supplemental data at www.neurology.org

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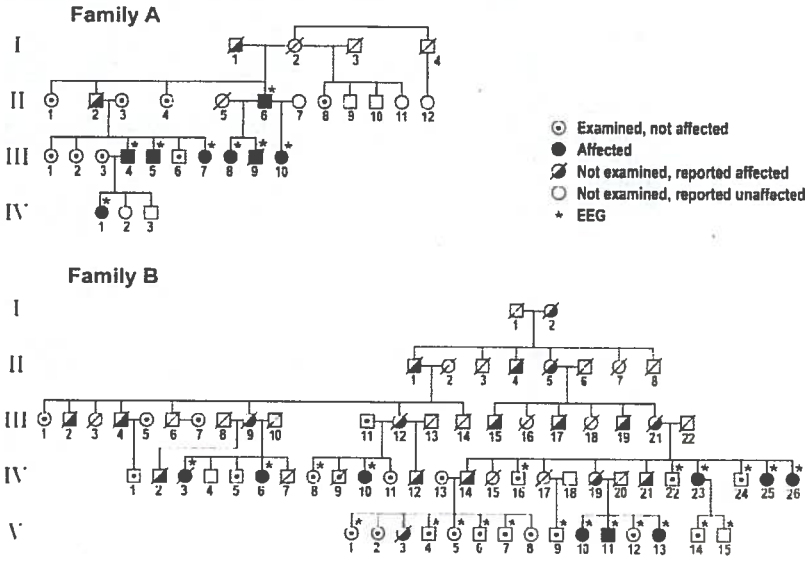
Figure 1 Family trees of the two affected families



METHODS The proband of Family A (A-III-8) was identified from a search for patients with idiopathic generalized epilepsies (IGE), and that for Family B (B-IV-3) was referred with epilepsy from a psychiatric ward in our hospital (figure 1). Patients were examined and underwent MRI and routine neurophysiologic investigations including EEG, visual evoked potentials (VEP), and somatosensory evoked potentials (SEP) and nerve conduction studies. In addition, jerk locked averaging was performed, and the response to magnetic stimulation was determined. Pathology of the fixed brain of subject A-III-9 was obtained.

Neurophysiology. EEGs were obtained after the application of electrodes and conducting jelly, using the International 10-20 system. Standard techniques for nerve conduction studies were used,[12] peroneal and tibial motor responses and sural sensory responses were recorded. For SEPs, the median nerve at the wrist was stimulated, and upper limb SEPs were recorded at the contralateral scalp (C3′ and C4′: 2 cm posterior to C3 and C4 on the international 10-20 system). Stimulation rate was 3 Hz, with a duration of 0.2 msec. Digital averaging was performed using 200 rectified samples; the filters were set at a high cut of 500 Hz, and a low cut of 10 Hz. The latencies of the N20, P25, and N33 peaks, and the interpeak amplitudes of N20-P25 and P25-N33 were recorded, as were the N20 amplitudes. Averaging was typically performed three times to ensure reproducibility. For VEPs, responses were measured using checkerboard pattern-reversal stimuli. The stimulation frequency was 2 Hz, with filters set to a high cut of 50 Hz and low cut of 20 Hz. Digital averaging was performed using 100 rectified samples. Long-loop reflexes were obtained by stimulation of the median nerve while recording over the thenar muscle, with EMG monitoring to ensure that the muscle was relaxed. Jerk-locked averaging was performed on a Neuropack electromyograph (Nihon Koden, Japan). EEG recordings were obtained from the C4[1]-Cz derivation with filter settings of 50 Hz and 0.05 Hz for high and low cut. EMG filter settings were 3 KHz and 5 Hz for high and low cut. Some patients had additional derivations recorded, such as C4-Fz. Recordings were obtained from the thenar eminence, a site where regular myoclonic jerks occurred, and where jerks could be obtained regularly and reliably at rest. Jerks occurred frequently but were well defined. Movement artifact did not present problems since the jerks were of low amplitude. For magnetic stimulation surface EMG was recorded from the right abductor pollicis brevis muscle. The study was performed at rest, silence being monitored on the EMG. A Magstim 200 stimulator (The Magstim Company, Dyfed, UK) was used with a double circular 7 cm coil. Based on handedness, the dominant cortex was stimulated in the region of the hand area. The threshold for motor stimulation was determined from a trial of 10, being the minimum percentage of the stimulator output required to produce a response in half the trials, at a sensitivity of 200 μV/div. The trigger input socket of the Magstim was synchronized to the electromyograph, the trigger mode of which was set to random. Paired stimuli were administered to the median nerve, with a stimulus interval of 8 msec, with the duration of the first and second stimuli being 0.5 msec.[13] The strength of the stimulus was maintained at a point which was subthreshold for evoking a compound muscle action potential (CMAP). MEPs were recorded with filter settings of 3 KHz and 2 Hz for the high and low cut. The delay to the time of triggering the Magstim varied from 10 msec through to 70 msec in increments of 10, with the delay being measured from the first of the two paired stimuli. For each time period, eight shocks were administered, and between shocks the MEP amplitude was measured from onset to peak. At each stimulus interval from 10 to 70 msec, two runs were done, one at 20% above threshold (termed low level stimulus), and one at maximum power (termed high level stimulus), this being defined as that power which was determined to give the maximum motor evoked potential (MEP). Three patients were examined and compared with a control group of 28 subjects.

Magnetic resonance imaging. MRI was obtained in 10 subjects, using standard sagittal and axial T1, axial T2/proton density and coronal T2, and in more recent studies, FLAIR sequences.

Pathology. Patient A-III-9 was reported to have died at night following a seizure. The precise cause of death is unknown.

Table 1 Clinical features of Families A and B

Patient	Onset age, y	MMSE	Seizure frequency	Nystagmus	Dysarthria	Ataxia	Hyperreflexia/Babinski
A-II-6	22	16	Rare	−	+	+	+
A-III-4	20	28	Rare	−	−	+	−
A-III-5	18	9	2-3/mo	−	−	+	−
A-III-7	14	ND	1/mo	+	+	−	+
A-III-8	18	27	2/mo	−	−	+	−
A-III-9	20	ND	1/mo	−	+	+	+
A-III-10	23	26	Rare	+	−	+	+
A-IV-1	13	30	None	−	−	−	−
B-IV-3	31	ND	Seldom	−	−	−	−
B-IV-6	20	28	2-3/mo	−	−	+	+
B-IV-10	25	ND	2-3/mo	−	−	+	+
B-IV-23	17	15	1-2/y	−	+	+	+
B-IV-25	19	16	Rare	−	−	+	+
B-IV-26	30	9	Rare	−	−	−	+
B-V-10	25	Unable	Very frequent	+	+	+	+
B-V-13	19	18	Rare	−	−	−	+

MMSE = Mini-Mental State Examination, + = present, − = absent, ND = not done

Postmortem was obtained approximately 14 hours after death, limited to the brain.

Ethical approval was obtained from the University of Stellenbosch for extraction and analysis of DNA and for neurophysiologic investigations.

Genotyping and linkage analysis. We collected eight blood samples from Family A, including II-3, II-4, II-6, III-4, III-5, III-7, III-8, III-10, and 19 blood samples from Family B, including III-1, III-11, IV-3, IV-5, IV-6, IV-8, IV-9, IV-10, IV-11, IV-16, IV-23, IV-24, IV-25, IV-26, V-9, V-10, V-12, V-13, V-14. Formal informed consents were given by all the recruited individuals before they entered the present study. Genomic DNA was extracted from peripheral blood leukocytes by a standard phenol extraction method. We studied three microsatellite markers (D21S2040, D21S1912, and D21S1959) from the *EPM1* locus (chromosome 21q22.3),[14] a CAG repeat in the *DRPLA* gene (chromosome 12p13.31),[15] seven microsatellite markers (D8S1784, D8S1830, D8S1779, D8S547, D8S1694, D8S342, and D8S1826) across the *FAME1* locus (chromosome 8q23.3-q24.1), and 10 microsatellite markers (D2S139, D2S2180, D2S1387, D2S2333, D2S2161, D2S388, D2S2216, D2S2264, D2S135, and D2S1897) from the *FAME2* locus (chromosome 2p11.1-q12.2). The markers on *FAME1* and *FAME2* loci were selected from those listed on the genetic map at the Marshfield Medical Clinic Web site (http://research.marshfieldclinic.org/genetics/home/index.asp). The microsatellite markers were amplified by PCR with one primer pair for each microsatellite marker. PCR products were separated by electrophoresis on a CEQ 8000 Genetic Analysis System and analyzed with Fragment Analysis software (Beckman Coulter, CA) per the manufacturer's instructions. MLINK program was used to run the two-point linkage analysis with the following model: autosomal dominant inheritance, frequency of the dominant allele of the causative gene being 0.0001, and penetrance being 0.9.

RESULTS Clinical characteristics. During the study, 17 affected individuals were identified, with the oldest affected at the age of 31 (B-IV-3), and the youngest at 13 years (A-IV-1), with a median age at onset of 20 years. The core syndrome of the illness consisted of GTCS and myoclonus. Myoclonus comprised both positive and negative myoclonus of the whole body, predominantly involving the upper limbs and trunk, as well as tremulousness of the hands, brought out by posture holding. Although myoclonic jerks were observed in the legs these were considerably less than in the arms. Blepharospasm was also noted, but no other jerks of the face were seen. Additional features, such as nystagmus, abnormal pursuit, dysarthria, and hyperreflexia, were observed (table 1). Eleven patients had combinations of truncal and limb ataxia. Eleven patients had hyperreflexia, an extensor plantar response, or both. Two patients (B-IV-25 and B-V-10) were observed to have prominent, high amplitude positive and negative myoclonus resulting in occasional falls, in both of whom myoclonus responded to valproate and clonazepam (video 1 on the *Neurology* Web site at www.neurology.org). Seven patients reported runs of myoclonus prior to a generalized tonic-clonic seizure. In four patients myoclonus was either very slight or absent, although tremor was present in all except B-V-11, whose status was determined by generalized spike discharges on EEG.

Table 2 Results of investigations

Patient	Abnormal EEG	Photic response	Enlarged SEP	Abnormal C response	Symmetric myoclonus	JLA waves	Cerebellar atrophy
A-II-6	+	−	+	+	Rare	−	+
A-III-4	+	−	+	+	ND	ND	+
A-III-8	+	−	+	+	At times	+	−
A-III-9	+	−	ND	+	At times	+	ND
A-III-10	+	−	ND	ND	No	+	ND
B-IV-3	+	−	−	+	Variable	+	ND
B-IV-6	+	−	ND	+	ND	+	+
B-IV-10	+	−	+	+	Frequent	+	+
B-IV-23	+	−	+	+	At times	+	+
B-IV-25	+	+	+	+	At times	ND	+
B-IV-26	+	−	ND	+	No	ND	+
B-V-10	+	−	+	+	No	ND	+

SEP = somatosensory evoked potentials, + = present, − = absent, ND = not done

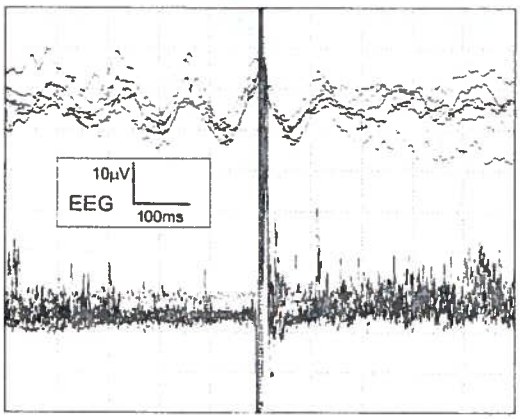
Patient A-III-9 died following a seizure at the age of 31, B-IV-3 died at the age of 39, and B-V-10 died at the age of 35 years. The disorder may affect life expectancy for the usual reasons seen in poorly controlled epilepsy. It is unclear whether, in addition, as a result primarily of an associated neurodegenerative process, there is increased mortality. It appears that similarly to Unverricht-Lundborg disease, this condition may have been worsened by phenytoin.[16] Certainly, in all patients in whom reasonable compliance occurred and response could be assessed (six patients), there was considerable improvement on valproate.

A number of patients were noted at the time of presentation to have cognitive impairment. The father of the proband of Family A, who was severely disabled, answered questions slowly and with difficulty, and had a Mini-Mental State Examination score (MMSE) of 16. In addition, Patient B-V-10 was severely demented, Patient B-IV-26 had an MMSE of 9, although she also had a history of severe alcohol abuse and had callosal agenesis, and her two affected sisters had MMSE scores of 15 and 16. A number of patients had considerable neurologic disability at the time of presentation, or were observed to have a decline in function during the course of the study. The proband of Family B, who developed the disease relatively late at the age of 31, felt that the illness was progressive, and led to impaired functioning at home, to the extent that she was no longer able to care for herself. She died 8 years after onset of her illness. Patient B-IV-23 was noted to become forgetful and developed dysarthria. Patient B-V-10 was noted to be demented and ataxic at the time of her initial presentation at the age of 29 (video 2), and both conditions deteriorated over the next 5 years. Patient A-II-6 had prominent dysarthria, ataxia, and cognitive impairment when initially assessed at the age of 46, and reported progression of his condition, particularly truncal ataxia. His nephew, A-III-5, was noted to have a clear decline in coordination with gait ataxia. A number of patients also reported that their affected parents were neurologically impaired and died young: B-III-9 and B-III-12 were reported to have been affected in their early 30s and died in their late 30s. B-IV-19 died at the age of 45 following a seizure, had frequent seizures, unsteadiness of gait, and confusion at times. Patient II-1 had tremor, many seizures, and drowned after he ran into a farm dam following a seizure. Patient B-III-21 had seizures every 2 to 3 weeks and walked as though she were intoxicated. Detailed case histories are provided (appendix E-1).

Electrophysiology. Patients A-III-5, A-IV-1, B-V-11, and B-V-13 only underwent EEG studies (table 2). Sixteen patients had a total of 26 recordings. All of the patients had at least one abnormal study, except for one (A-III-7), who did not have an EEG. In Family A, seven patients had either an abnormal background or intermittent bursts of slow activity (theta and delta bursts). Four patients had polyspike and wave activity (PSW), and the remainder had clear epileptogenic activity (one each independent focal spike, single burst of PSW, and left frontal spike). In Family B, seven patients had an abnormal background or intermittent bursts of slowing. Two had a normal background (both with recurrent bursts of PSW). Six patients had abundant PSW activity and one had brief frontal spike discharges. One patient (B-V-13) had no spike or PSW discharges (total of

Seven superimposed averages from Patient B-IV 23, each of 100 averages

Figure 2 Jerk locked averaging



three EEGs), but had a markedly abnormal background. Patient B-V-11, with no history of myoclonus or epilepsy, had a normal EEG on one occasion, and a second EEG that showed a single burst of polyspike and wave. Subsequent long-term recordings showed abundant generalized spike and wave activity. With regard to photic responses, one patient, B-IV-25, had a photoparoxysmal response associated with clinical myoclonus, although three other subsequent EEGs did not show this response. Another patient, B-V-10, had jerks associated with photic stimulation, and the study was terminated. Two further EEGs in this patient did not show a photoparoxysmal response.

Among unaffected family members, Individual B-V-9 had right temporal spikes and right temporal delta, a normal neurologic examination, and seizures that were controlled with phenytoin, and was classified as unaffected. Ten unaffected family members had 16 EEGs, which were normal.

Eleven patients were examined for late responses by stimulation of the median nerve. At low stimulation currents late responses were easily evoked and replicated, with latencies of between 36.2 and 46.6 msec. With regard to evoked potentials, of eight patients examined, seven had enlarged SEPs (N20-P25 $> 5\ \mu V$; P25-N33 $> 10\ \mu V$); latencies of SEPs were normal. VEPs were normal in amplitude and latency. Eleven patients had nerve conduction studies: in nine, the sural, peroneal, and tibial latencies, amplitudes, and velocities were normal, and in two, only the sural was examined and was normal. Myoclonic jerks were examined in nine patients, and the duration of the EMG discharge was less than 50 msec in all. In the majority of patients studied, jerk-locked averaging showed 8- to 10-Hz frequency spindle time locked to the jerk (figure 2). Recording from the right upper limb showed that this activity phase reversed at C3-P3, with some waves exhibiting electronegative phase-reversal at C3 on parasagittal and coronal montages and the C3-P3 derivation being relatively isoelectric (figure E-1). For magnetic stimulation, a comparison was performed between 3 patients and 28 controls, recruited from staff and medical students. Using the package Statsgraphics (Manugistics, Inc.), men and women in the control group overall showed no significant differences, although at individual duration times, there were significant differences; therefore the male controls were removed from subsequent analyses used to examine differences between the 10 female controls and the 3 female patients. Repeated measures analysis of variance for low level stimuli and high level stimuli showed effects for group and duration and the group × duration interaction which were highly significant.

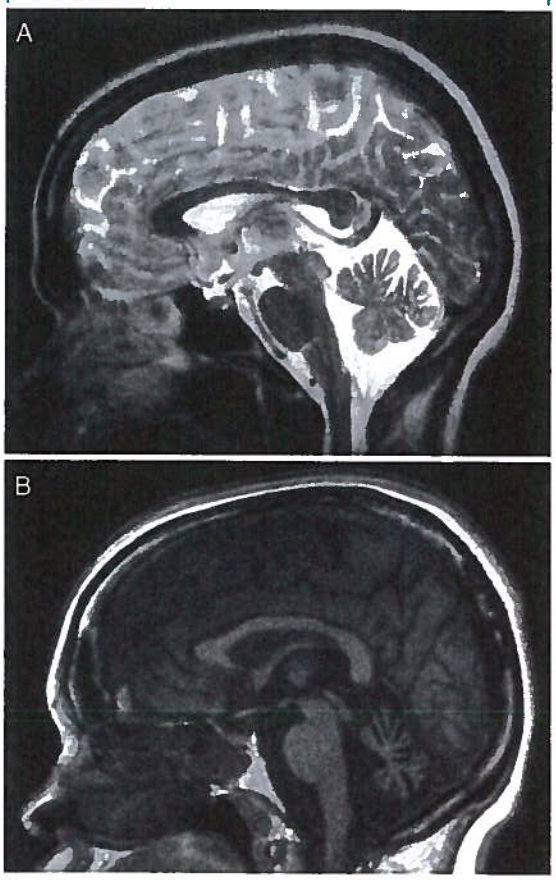
Pathology. In Patient A-III-8, biopsies of the axillary apocrine glands and palmar eccrine glands did not show any abnormal storage material or evidence of neuronal ceroid lipofuscinosis on routine histology or electron microscopy. A muscle biopsy was normal.

In Patient A-III-9, in examination of brain macroscopically, the gyral pattern was within normal limits and there was no cerebral atrophy. Sections showed normal sized ventricles, a well-defined cortical ribbon, and unremarkable central gray matter. The substantia nigra and the locus ceruleus appeared well pigmented, and the mamillary bodies and red nuclei appeared normal. The brainstem structures did not appear atrophic and there was no evidence of cerebellar atrophy, involving either the lateral lobes or vermis. Regarding histology, the brain was extensively sampled in an attempt to assess the presence of neuronal loss and gliosis. The most obvious changes were seen in the sections of the cerebellum where there was focal Purkinje cell loss, with early Bergman gliosis and the presence of torpedoes (especially evident in silver stains) (figure E-2). In addition, the dentate nucleus showed patchy neuronal loss and neuronal atrophy, with occasional ghost cells and neurons with large eosinophilic, hyaline cytoplasmic inclusions. The hilus showed some myelin pallor and scattered microglial clusters were noted in the middle cerebellar peduncle. The superior cerebellar peduncles appeared atrophic. The olives showed mild neuronal loss and some evidence of astrocytosis on glial fibrillary acid protein stain.

Sections of the basal ganglia show mild neuronal loss and astrocytic gliosis in the pallidum, while there was probable atrophy of large striatal neurones and lipofuscin accumulation. The subtha-

(A) Sagittal T2-weighted MRI of Patient B-IV-6 (age 36) (B) Sagittal T1-weighted MRI of Patient B-V-10 (age 30)

Figure 3 Sagittal weighted MRIs



lamic nucleus showed no obvious neuronal loss, but a single microglial cluster was noted. The substantia nigra was normal. Sections of the neocortex from many areas show no obvious neuronal loss and normal lamination appeared to be maintained. The centrum semiovale showed some pallor of myelin staining.

Imaging. Eight of the 10 patients showed cerebellar atrophy, varying from mild to severe in the oldest patient (figure 3). The atrophy was typically characterized by widening of major fissures and vermal atrophy.

STIR sequences were performed in Patients B-V-10, B-IV-23, and B-IV-26 and showed normal hippocampal formations. In addition, Patient B-IV-26 also had partial callosal agenesis of the genu and body of the corpus callosum. Patient A-II-6 had bilateral T2/FLAIR hyperintense signal change in the basis pontis, a focal cortical defect in the left opercular cortex, and lacunar infarctions in the right striatum and thalami. Patient B-IV-23 had periventricular T2 and FLAIR signal change, with multiple basal ganglia lacunes, and a single brainstem lacune (figure E-3). Patient B-V-10 had an area of T2/FLAIR hyperintense signal in the periventricular white matter. Two studies were normal (A-III-8, B-V-13).

Genetics. In Family A, the generation of strongly negative two-point lod scores at three markers tightly linked to the EPM1 locus excluded this candidate locus from involvement with FAME 3 (table E-1). The DRPLA locus was also eliminated as a candidate locus in this family, both by the generation of a strongly negative lod score and the absence of expansion of the triplet repeat in the atrophin gene (table E-1). These loci were not analyzed in Family B.

Analysis of genotypes for markers at the FAME 1 and FAME 2 loci on chromosomes 8 and 2 excluded these as the region containing the same locus in Family B (table E-2). In the smaller Family A the chromosome 2 locus was excluded, however, the chromosome 8 locus could not be excluded in Family A since there was a shared haplotype among the five affected samples that were available for genotyping (table E-3).

DISCUSSION In comparison to patients with FAME, the two families described in this report have a more severe disease. The affected members had an earlier age at onset and had more frequent seizures than is usually associated with FAME, in which seizures are typically infrequent. Other features which suggest that this condition is unique compared to more benign forms of familial myoclonic epilepsy include dementia and corticospinal and cerebellar dysfunction. Furthermore, two patients already had marked neurologic impairment at the time of presentation and showed increasing disability, and three other patients developed neurologic dysfunction subsequent to diagnosis. Three of the patients died during this study, at age 31, 35, and 39, and early death and disability were reported in a number of affected family members. Further distinctive features included MRI findings of cerebellar atrophy and pathologic changes of Purkinje cell loss, dentate atrophy, and neuronal loss and gliosis in the pallidum and olives. An additional radiologic feature was that three patients had lacunar infarctions in the basal ganglia, brainstem, and white matter changes, notably in the absence of a history of hypertension. Linkage analysis excluded several plausible candidate loci as causes of FAME 3 in the families studied. In Family B, both FAME 1 and FAME 2, the most likely candidate loci, were eliminated from involvement with the South African disease. In the smaller Family A, FAME 2, EPM1, and DRPLA were excluded from disease development, although it was not possible to exclude FAME 1. However, the fact that this family shares the same phenotype as Family B, in which this locus has been excluded, and the progressive nature of FAME 3 in

contrast to FAME 1, makes linkage to FAME 1 unlikely. Taken together, these data demonstrate that a novel locus is responsible for the epilepsy in Family B, at least. This is consistent with the unique phenotype that we have characterized in these families.

In contradistinction, FAME appears to be a fairly uniform and relatively benign syndrome, characterized by myoclonus and rare seizures and mild or no progression of disease, and without associated neurologic features except tremor.[4,6,8,9,17] Compared with the disease in the South African families, the seizures associated with FAME may occur at a later age.[6,8,17] The EEG background is normal in ADCME and some family members with FAME have normal EEGs,[6,9,18] whereas abnormal EEG backgrounds and abundant polyspike discharges were the rule in the patients described in this report. However, as opposed to our findings in the South African patients, photosensitivity appears to be common in both FAME and ADCME.[4,5,7,9] In FAME, MRI is generally reported to be normal,[6,9] whereas cerebellar atrophy, ranging from mild to severe, was found in 8 of 10 patients from the two families reported here. Mild cerebellar atrophy on MRI was seen in two of four patients in a Dutch family with FAME, and a 68-year-old patient from this family had cerebellar degeneration at autopsy.[19] However, this family had typical features of FAME in other respects, with mean age at onset of seizures at 43 years, and no other features of neurologic disease other than mild cognitive impairment.[10,18]

The EEG findings of generalized spike and wave, high amplitude evoked potentials, and enhanced late responses suggest that the abnormal discharges arise from abnormally excitable cortex. This is supported by the results of the magnetic stimulation, which demonstrated enhanced responses in the patients compared with controls. Jerk-locked averaging showed a series of waves, a similar pattern to that described initially in primary generalized epileptic myoclonus and also described as a manifestation of ADCME, and in familial myoclonus epilepsy.[7,20,21]

The condition described in this report, which we have termed FAME 3, appears different from FAME, and does not link to the FAME 1 locus for Family B. We cannot completely rule out the FAME 1 locus in Family A, but the FAME 2 locus has been excluded in both families. We therefore believe that FAME 3 is a unique condition, and since it is frequently characterized by frequent seizures, dementia, and there is clinical and MRI evidence of cerebellar impairment, it falls on the spectrum of the progressive myoclonic epilepsies, occupying a place between FAME and more severe forms of PME.

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