Familial Adult Myoclonic Epilepsy

Recognition of Mild Phenotypes and Refinement of the 2q Locus

Douglas E. Crompton, MA, MBBS, PhD, MRCP(UK); Lynette G. Sadleir, MBChB, MD; Catherine J. Bromhead, BSc(Hons); Melanie Bahlo, PhD; Susannah T. Bellows, BA(Hons); Todor Arsov, PhD; Rosemary Harty, BBMedSci(Hons); Kate M. Lawrence, BSc(Hons); John W. Dunne, MBBS, FRACP; Samuel F. Berkovic, MD, FRACP, FRS; Ingrid E. Scheffer, MBBS, FRACP, PhD

**Background:** Familial adult myoclonic epilepsy (FAME) is an autosomal dominant syndrome characterized by a core triad of cortical tremor, multifocal myoclonus, and generalized tonic-clonic seizures.

**Objectives:** To expand the phenotypic spectrum of FAME, to highlight diagnostic pointers to this under-recognized disorder, and to refine the FAME2 genetic locus.

**Design:** Observational family study.

**Setting:** The study was coordinated in a tertiary academic hospital, with data acquired in diverse primary, secondary, and tertiary care settings.

**Participants:** Consenting members of a single large family.

**Results:** A 6-generation FAME kindred of European descent was ascertained in New Zealand and Australia. Affected family members (N=55) had fine hand tremor, with onset typically in adolescence (median age, 15 years; age range, 4-60 years). Proximal myoclonus was present in 44 of 55 (80%), arising later than hand tremor (median age, 17 years; age range, 5-60 years). Generalized tonic-clonic seizures occurred in 8 of 55 (15%), with a median age at onset of 43.5 years (age range, 18-76 years).

**Conclusions:** The most common FAME phenotype in this large family is mild postural hand tremor resembling essential tremor, combined with subtle proximal myoclonus. Generalized tonic-clonic seizures are uncommon and occur around sleep onset following severe generalized myoclonus.

Arch Neurol. 2012;69(4):474-481

**Familial Adult Myoclonic Epilepsy**

Familial adult myoclonic epilepsy (FAME) is an autosomal dominant syndrome characterized by a core triad of cortical tremor, multifocal myoclonus, and generalized tonic-clonic seizures. Cortical tremor is a jerky postural and action tremor of the hands, usually with adolescent or adult onset, accompanied by neurophysiological features of cortical reflex myoclonus. Photosensitivity is common. FAME is typically slowly progressive and is usually nondisabling.

Some families with cortical tremor, myoclonus, and GTCS have additional clinical features, including cognitive impairment,3,5 partial seizures,4 migraine,6 and night blindness.7 Different investigations with varying emphases have led to multiple syndromic labels for comparable clinical conditions.8,9

In 1999, linkage to chromosome 8 (8q23.3-8q24.11 [FAME1 locus]) was demonstrated in Japanese families with FAME.10,31 European families with similar phenotypes were subsequently described.12-18 In 2001, Guerrini and colleagues4 demonstrated linkage to a second locus in the pericentromeric region of chromosome 2 (2p11.1-2q12.2 [FAME2 locus]) in an Italian family. Overlapping linkage intervals were defined, and allelism was inferred in subsequent studies.12,16,19,20 of other European families. Evidence of further genetic heterogeneity comes from 2 European families13,15 and a Chinese family,21 which do not map to either locus. Linkage to chromosome 5p15 has recently been demonstrated in one of these families.22

Herein, we report clinical, neurophysiological, and molecular genetic data from a large family of European descent with FAME living in New Zealand and Australia.
lia. These data allow refinement of the clinical spectrum and the FAME2 locus.

**METHODS**

**CLINICAL DATA COLLECTION**

Two distantly related consultands were referred simultaneously. This enabled ascertainment of a 6-generation pedigree, comprising 390 individuals (Figure 1). Family members for whom any tremor, myoclonus, or seizure symptoms were reported personally, or by close relatives, were viewed as potentially affected. For such individuals, a validated epilepsy questionnaire and a systematic tremor and myoclonus questionnaire were administered. Forty-five affected individuals were examined by one of us (D.E.C., L.G.S., J.W.D., or I.E.S.). Clinical data are also presented for 10 family members who were geographically inaccessible but whose characteristic description by telephone of tremor, myoclonus, or seizures demonstrated their affected status. A few individuals, particularly adolescents and young adults, had very mild hand tremor, not definitely outside the physiological range, and their disease status was coded as uncertain (gray symbols in Figure 1). Their clinical data and those of all deceased individuals were excluded.

Source medical records and investigation results, including neuroimaging, were reviewed wherever possible, and blood or saliva samples were collected for DNA extraction. Partners and parents were routinely interviewed to obtain eyewitness histories and to help exclude phenocopies due to bilineal inheritance of tremor, myoclonus, or seizures. Written informed consent was obtained from all participants or from their guardians in the case of minors. The study was approved by the Human Research Ethics Committee of Austin Health, Heidelberg, Victoria, Australia, and the multicenter New Zealand Medical Research Ethics Committee, Wellington.

**ELECTROPHYSIOLOGICAL STUDIES**

Electroencephalogram (EEG), multichannel electromyogram (EMG), EEG-EMG back averaging, and somatosensory evoked potentials were recorded using standard techniques. The protocol is given in the eAppendix (http://www.archneurol.com).

**LINKAGE ANALYSIS**

Linkage analysis was performed among 45 affected individuals. We initially selected 11 affected individuals from multiple branches of the pedigree to allow adequately powered testing of known FAME loci or identification of a novel locus. Single-nucleotide polymorphism (SNP) genotyping was performed using an SNP platform (Affymetrix 250K). Linkage data files were prepared using LINKDATAGEN by selecting a set of highly polymorphic SNPs in linkage equilibrium. Data analysis was performed under a fully penetrant, rare autosomal dominant model (disease allele [A] frequency of 0.0001, penetrance [affected | aa or Aa] of 0.999, and phenocopy rate [affected | AA] of 0.001). Exact parametric multipoint linkage analysis and haplotype inference were performed using an available program (MERLIN; http://www.sph.umich.edu/csg/abecasis/Merlin) on subsets of the pedigree. Approximate parametric linkage analysis was performed using another program (HAPLOPAINTER; http://haplopainter.sourceforge.net). Subsequent fine mapping was performed among 45 affected individuals genotyped for multiple microsatellite markers spanning the linkage region (Affymetrix).

**RESULTS**

The family (Figure 1) descended from an affected Austrian ancestor who emigrated to New Zealand in the mid-19th century. Segregation was consistent with autosomal dominant inheritance. There were no instances of affected offspring from unaffected parents, suggesting 100% penetrance in this family. Detailed clinical information was available for 55 affected individuals (29 male and 26 female). Age range at the time of study was 13 to 90 years (median age, 49.5 years).

**FAME PHENOTYPE**

**Tremor**

The median age at tremor onset was 15 years (age range, 4-60 years). Tremor was present in all affected individuals and had mixed components. All individuals had a fine rhythmic, although slightly irregular, finger and hand tremor (individuals IV-39, V-24, V-12, and V-46 [video]). In addition, many had more prominent low-amplitude jerks of fingers or wrists admixed with the fine tremor (eg, individuals IV-30, V-18, IV-6, and V-57 [video]). Tremor was exacerbated by action and fixed postures and was reduced or absent at rest. Tremor always affected the hands and was usually symmetrical (in 51 of 55 [93%]). Other body parts were variably involved, with fine semirhythmic movements and with higher-amplitude jerks (discussed more in the “Myoclonus” subsection). Tremulous movements were particularly evident in the eyelids (individuals IV-47, IV-39, and III-24 [video]), perioral region, neck, and leg muscles. The mixture of tremor and jerking sometimes resembled shivering.

**Myoclonus**

Multifocal proximal predominant myoclonus was present in 44 of 55 individuals (80%). Onset was later than for tremor (median age, 17 years; age range, 5-60 years) (Figure 2). The most frequently and severely affected body part was the proximal upper limbs (video). Myoclonus could be accentuated during examination by maneuvers, including closing the eyes (exacerbating eyelid tremor and widespread multifocal myoclonus) and standing on tiptoes. Family members were often unaware of having widespread tremulous movements and myoclonus, despite their prominence on examination.

Myoclonus varied in severity from asymptomatic focal jerks to generalized myoclonus causing drop attacks; 19 of 55 individuals (35%) reported photic induction of myoclonus. Tactile stimuli evoked myoclonus in 14 of 45 individuals (31%) examined. Six individuals experienced myoclonus causing falls, often with momentary impairment of awareness; all 6 reported photic or pattern sensitivity precipitating their drop attacks.
Figure 1. Pedigree of family with familial adult myoclonic epilepsy. Black quadrant indicates affected with tremor or finger myoclonus; blue quadrant, affected with proximal myoclonic jerks; red half filled, affected with focal seizures or generalized tonic-clonic seizures and gray, clinical affected status is uncertain. The 2 consultands (referred independently) are marked with arrows. A square represents a male individual; a circle, a female individual; and a diamond, an individual whose sex is unknown. Multiple individuals are indicated by a number inside the shape. A slash mark indicates a deceased individual.
Multiple factors were reported to exacerbate tremor and myoclonus, the most common being stress (in 33 of 55 [60%]) and sleep deprivation (in 27 of 55 [49%]). Fine tasks, such as performing needlework or using a screwdriver, were frequently associated with worse symptoms. Hunger worsened tremor or myoclonus in 20 of 55 individuals (36%). Improvement was reported at the time of alcohol ingestion in 18 of 55 individuals (33%), with worsening of tremor and myoclonus consistently described the day after alcohol excess.

In 7 of 8 individuals who experienced GTCS, these seizures followed a prodrome of severe myoclonus. This myoclonus was usually generalized (focal, involving the right leg only, in a single individual) and would persist for minutes or hours with further exacerbation on eye closure when trying to sleep. Myoclonic status would then progress to GTCS within 2 hours of sleep onset (in 7 of 8 individuals).

Both tremor and myoclonus worsened slightly with advancing age (Figure 3). Affected individuals would avoid carrying cup and saucer or dishes of soup and would partly fill mugs of coffee to avoid spillage. Four individuals volunteered difficulty in climbing ladders, which would exacerbate leg tremor. Public speaking was widely reported to be difficult because of voice tremor and exacerbation of multifocal tremor and myoclonus.

Most affected individuals never sought medical attention, perceiving their involuntary movements to be mild and due to the “family condition.” Individuals seeking medical advice had most often received a diagnosis of essential tremor, leading to prescriptions of β-blockers or primidone. β-Blockers were helpful in 4 of 5 individuals. Primidone caused marked improvement in one, modest benefit in another, and intolerable sedation in a third individual. Seven family members reported improvement in proximal myoclonus with antmyoclonic drugs, 3 with sodium valproate, 2 with clonazepam, and 1 each with clobazam and diazepam. The effect of antmyoclonic drugs on distal tremor was reported to be minor.

**GTCS and Focal Seizures**

Only 15% (8 of 55) of individuals had GTCS, typically after sleep deprivation, stress, or excitement; GTCS onset was late (median age, 43.5 years; age range, 18-76 years), and seizures were infrequent (range, 1-8 lifetime GTCS days). All 8 individuals received antiepileptic therapy (4 with sodium valproate, 1 with phenytoin and then sodium valproate, 1 with clonazepam, 1 with clobazam, and 1 with lorazepam), although 2 had discontinued treatment before the study. Two of 8 individuals reported further seizures after starting antiepileptic medication; both became seizure free on monotherapy following dosage increments.

Focal seizures with mesiotemporal symptoms occurred in 2 individuals. One described stereotyped episodes of intense déjà vu, nausea, and fear lasting approximately 10 seconds, with onset at age 12 years. The other reported episodes of déjà vu, abdominal lurching sensation, fear, an illusion of time slowing down, and intrusive playback of stereotyped visual memories lasting around 30 seconds, which had occurred since age 18 years. Neither individual had GTCS. Their seizures had not been
diagnosed; hence, EEG and magnetic resonance imaging had not been performed. No family members had significant antecedent brain insults or febrile seizures.

One additional individual described mesiotemporal focal seizures. However, at the time of study, she was 46 years old and had neither tremor nor myoclonus and was considered not to have FAME. No other individuals coded as unaffected had any evidence of tremor, myoclonus, or epilepsy.

**Other Clinical Features**

Migraine was reported by 18 of 55 individuals (33%), of whom 12 reported auras (11 visual and 1 sensory). A history of night blindness was systematically sought but was absent. Individuals were of normal intellect, although formal neuropsychological examination was not performed. No ataxia, dystonia, or spasticity was present on examination of any family members.

**NEUROPHYSIOLOGICAL TESTING**

**Electroencephalogram**

Only 2 of 36 individuals with FAME tested had abnormal EEGs. Generalized polyspike wave discharges (in 1 of 36 [3%]) or irregular, generalized, frontal maximal sharp wave discharges (in 1 of 36 [3%]) were seen. Despite descriptions of clinical photosensitivity, epileptiform photoparoxysmal responses were not seen. In contrast, a photomyogenic response was common on history (in 13 of 36) and on repetitive photic stimulation during EEG. This was not accompanied by EEG change other than muscle artifact.

**Multichannel EMG and Jerk-Locked Back Averaging**

Additional neurophysiological data were acquired for 5 individuals (eFigure) and were compatible with cortical reflex myoclonus. Myoclonus at rest had burst duration of 14 to 30 milliseconds. During voluntary movement and static posture (arms outstretched), EMG showed synchronous bursts in agonist and antagonist muscles at 8 to 12 Hz with burst durations 20 to 65 milliseconds (data not shown).

Premyoclonic cortical potentials had latencies of 20 to 27 milliseconds in 5 of 5 individuals. They were of lower amplitude and consistency in younger individuals.

**Long Loop Reflex (C Reflex)**

Long loop responses (C reflex) at rest, which are not usually detectable at rest in healthy individuals and indicate increased cortical excitability, were present in 3 of 3 individuals in whom this reflex was sought. Latencies were 42.7 to 58.0 milliseconds.

**BRAIN IMAGING**

Brain images (4 magnetic resonance and 4 computed tomography) were available for 8 individuals and were normal in 7. One had magnetic resonance imaging changes that reflected an unrelated diagnosis (superficial siderosis of the central nervous system).

**LINKAGE ANALYSIS**

Significant linkage (logarithm of odds, 3.9-4.5) was established for the pericentromeric region on chromosome 2 using SNP mapping. All affected individuals shared an SNP haplotype within this region. Subsequent fine mapping was performed among 45 affected individuals genotyped for 12 microsatellite markers spanning the identified linkage region (Affymetrix). Three recombinants narrowed the minimal candidate region to 16 cM (13.3 Mb), refining the previously published FAME2 candidate interval; and red lines, refined locus defined herein.

**Figure 4.** Segregation of microsatellite markers refining the FAME2 locus. Right columns (blue text) show microsatellite markers; left columns (black text), marker positions (University of California, Santa Cruz); black lines, previously published FAME2 candidate interval; and red lines, refined locus.
Herein, we present the largest reported family having FAME to date, with 55 affected individuals, and through linkage analysis narrow the \textit{FAME2} locus on chromosome 2 (2p11.1-2q12.2). This family expands our understanding of the phenotypic spectrum and highlights that seizures may be less frequent than reported in previous families. These observations suggest that families with FAME may escape detection because of the predominant tremor phenotype and the low prevalence of seizures.

**Comparing with Previous Families With FAME2**

Comparison of clinical and neurophysiological features of our family with those of other families having FAME (Table 1 and Table 2) demonstrates 2 major differences. The proportion of affected individuals with GTCS or focal seizures is lower than in previous investigations (10 of 55 [18\%] vs 33 of 53 [62\%]) (Table 1), and there are fewer EEG abnormalities herein (2 of 36 [6\%] vs 22 of 32 [69\%]) (Table 2). There are 2 possible explanations. A less severe \textit{FAME2} mutation may be segregating.
ing in our family, leading to a lower incidence of GTCS; however, the age at tremor onset, 4 to 60 years (mean age, 18.5 years), is no older than in other chromosome 2-linked families (Table 1). A weaker allele could correlate with the lower epileptiform EEG rate, although this difference could also reflect that our family members generally underwent a single research EEG compared with multiple or peri-ictal clinical EEG studies in families with active epilepsy. The alternative explanation is that previous families with FAME having prominent seizures have been preferentially ascertained. For example, if the branch descended from individual III0 (Figure 1) had come to research attention because of its density of individuals with GTCS, without knowledge of the wider pedigree, 50% of the family would have been reported as having GTCS. Therefore, this large family in which most (53 of 55) affected individuals were ascertained by family tracing rather than by manifesting striking clinical features might give a more faithful reflection of the usual FAME2 phenotype than smaller families.

Seizures were most commonly GTCS, occurring within 1 to 2 hours of sleep onset. Affected individuals described a vigorous cycle of sleep deprivation and stress or excitement accentuating myoclonus, with further frightening worsening of myoclonus on eye closure when trying to sleep. Although this pattern may rarely be described in idiopathic (genetic) generalized epilepsies, it is uncommon in other epilepsy syndromes and may be a pointer to FAME.

Mesiotemporal focal seizures were observed but were uncommon (in 2 of 55 individuals). Therefore, a predisposition to focal seizures, as reported in another FAME2 kindred, is possible. However, the observation of an otherwise unaffected family member with mesiotemporal seizures raises the possibility that focal seizures might be an incidental finding, unrelated to the FAME2 mutation.

RECOGNITION OF MILD FAME PHENOTYPES AND DIFFERENTIATION FROM ESSENTIAL TREMOR

Our study emphasizes the mild nature of FAME in many affected individuals and highlights the difficulty in differentiating FAME from essential tremor in routine clinical practice. The incorrect essential tremor diagnosis given to most family members who sought medical advice is unsurprising in view of the mild tremor phenotype and the absent or subtle myoclonus in many affected individuals (video). It is notable that β-blockers were helpful in most individuals who tried them, and in one individual (eAppendix, illustrative case history 2), there was unequivocal tremor deterioration with β-blocker withdrawal and subsequent improvement with reinstatement. This is contrary to previous findings among individuals with FAME.

Clinical criteria to distinguish between FAME and essential tremor have been suggested. Discriminators proposed to favor FAME over essential tremor include co-existent epilepsy, lack of benefit from β-blockers, and the absence of head, neck, or voice tremor. However, all these would misclassify a high proportion of affected individuals in this family. Nevertheless, other criteria favoring FAME over essential tremor (age at tremor onset of <50 years and the presence of myoclonus) would correctly classify our family members.

Although a common and important neurological disorder, essential tremor lacks a clinical or diagnostic biomarker. Therefore, it is appropriate to question what proportion of individuals diagnosed as having essential tremor might harbor a FAME mutation. Neurophysiological features of cortical reflex myoclonus, found in FAME, are not seen in essential tremor. However, in our family members with FAME, giant somatosensory evoked potentials were not found, and long loop reflexes at rest, although present, were seen only intermittently in more mildly affected individuals (eFigure, case B). Therefore, even milder FAME alleles might cause a disorder neurophysiologically indistinguishable from essential tremor.

The potential diagnostic gold standard of postmortem neuropathological findings suggests some overlap between FAME and essential tremor. Cerebellar Purkinje cell degeneration was the predominant pathological finding in 2 individuals with FAME studied and in a subset of patients with essential tremor. This large genetically powerful family has enabled refinement of the FAME2 locus, excluding 35 protein-coding genes (National Center for Biotechnology Information hg37 using GeneDistiller; http://www.genedistiller.org). Despite this, the remaining 13.3-Mb interval (harboring 99 known protein-coding genes) is substantial. This reflects infrequent recombination in this pericentromeric region. The same constraint frustrated the identification of genes for other pericentromeric monogenic epilepsy syndromes (eg, infantile convulsions and choreoathetosis), until current methods of next-generation sequencing were used.

The clinical and pathological parallels between FAME in its benign form and essential tremor are striking. In addition to offering important insights into the pathogenesis of cortical tremor, myoclonus, and GTCS, identification of FAME genes will enable the hypothesis of etiological overlap between FAME and essential tremor to be systematically explored.
fer. Administrative, technical, and material support: Sadleir, Bellows, Arsov, Harty, Lawrence, Dunne, and Scheffer. Study supervision: Crompton, Berkovic, and Scheffer. Financial Disclosure: Dr Scheffer has served on scientific advisory boards for UCB and Janssen-Cilag EMEA; serves on the editorial boards of Annals of Neurology and Epileptic Disorders; may accrue future revenue on pending patent WO61/010176 (filed in 2008) for Therapeutic Compound; has received speaker honoraria from Athena Diagnostics, UCB, Janssen-Cilag EMEA, and Eli Lilly and Company; has received funding for travel from Athena Diagnostics, UCB, and Janssen-Cilag EMEA; and receives and has received research support from the National Health and Medical Research Council of Australia, Health Research Council of New Zealand, The University of Melbourne, American Epilepsy Society, the Jack Brockhoff Foundation, the Shepherd Foundation, and the Perpetual Charitable Trustees. Funding/Support: This work was supported by an Educational Fellowship Award from UCB Pharma (Dr Crompton), by a National Health and Medical Research Council of Australia Career Development Award (Dr Bahlo), and by program grants from the National Health and Medical Research Council of Australia (Drs Bahlo, Berkovic, and Scheffer).

Online-Only Material: The eAppendix, eFigure, and video are available at http://www.archneurol.com.

Additional Contributions: Peter Bergin, FRACP, referred the first consultand; Winita Hardikar, PhD, referred the second consultand; Ann-Marie Saunders and Tracey Austin performed EEGs; Elizabeth Walker, FRACP, facilitated clinical study of family members in Auckland, New Zealand; Alice-Ann Sullivan, FRACP, facilitated clinical study of family members in Brisbane, Australia; and Kate Tuck and Bruce Day, FRACP, assisted with EEG-EMG back averaging. We acknowledge the family for their generous participation in the study.

REFERENCES