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Myoclonic occipital photosensitive epilepsy with dystonia (MOPED): A familial epilepsy syndrome

Lynette G. Sadleir[a,*], Sarah Paterson[a], Katherine R. Smith[b,c], Natalie Redshaw[a], Annemarei Ranta[d], Renate Kalnins[e], Samuel F. Berkovic[f], Melanie Bahlo[b,c,g], Michael S. Hildebrand[f], Ingrid E. Scheffer[f,h,i]

[a] Department of Paediatrics, School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand
[b] The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia
[c] Department of Medical Biology, The University of Melbourne, Melbourne, VIC, Australia
[d] Department of Medicine, School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand
[e] University of Melbourne, Austin Health, Pathology, Melbourne, VIC, Australia
[f] Epilepsy Research Centre, Department of Medicine, University of Melbourne, Austin Health, Melbourne, VIC, Australia
[g] Department of Mathematics and Statistics, The University of Melbourne, Melbourne, VIC, Australia
[h] Florey Institute, University of Melbourne, Melbourne, VIC, Australia
[i] Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, VIC, Australia

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ABSTRACT

Purpose: To describe clinical and EEG phenotypes of a family with an unusual familial epilepsy syndrome characterized by myoclonus and dystonia.
Methods: Family members underwent electroclinical phenotyping including review of EEGs and MRI. DNA from family members was genotyped using Illumina OmniExpress genotyping arrays. Parametric and nonparametric linkage analyses were performed using MERLIN.
Results: The disorder followed autosomal dominant (AD) inheritance and affected seven individuals over two generations. Seizures began at a mean of 14.5 years. Six individuals had spontaneous myoclonic seizures, of which five also had photic-induced myoclonus and four had photic-induced occipital seizures. Six individuals had convulsive seizures; generalized in two and focal in four. Photosensitivity was prominent with generalized spike wave and polyspike wave in four individuals of which two also had occipital spikes. MRI scans were normal in the four individuals tested. Extensive metabolic investigation was normal.

Juvenile myoclonic epilepsy (JME) occurred in two; and JME overlapping with idiopathic photosensitive epilepsy (IPOE) in four individuals. All three affected males had a more severe disorder than the four affected females. Two males had a progressive neurological disorder with progressive myoclonus epilepsy and deterioration in their early 30s. They developed episodes of paroxysmal cervical dystonia with cognitive decline during periods of poor seizure control. One plateaued after years of poor seizure control but remained intractable with periods of deterioration. The other deteriorated with episodes of status dystonicus and status epilepticus, ataxia and a progressive ophthalmoplegia before succumbing at 38 years.

Parametric linkage analysis identified three peaks achieving a maximum LOD score of 1.21. Nonparametric analysis identified eight peaks achieving LOD scores above 0.80. These were not statistically significant.
Conclusions: This is a novel autosomal dominant familial epilepsy syndrome. "Myoclonic occipital photosensitive epilepsy with dystonia" (MOPED) involves a spectrum of phenotypes from JME, sometimes with an IPOE overlap, to progressive myoclonus epilepsy with paroxysmal dystonia.

* Corresponding author. Tel.: +64 4 385 5999x6138; fax: +64 4 385 5898.
E-mail address: Lynette.sadleir@otago.ac.nz (L.G. Sadleir).

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Introduction

The syndrome of juvenile myoclonic epilepsy (JME) is the commonest form of genetic generalized epilepsy (GGE). The hallmark feature, myoclonic seizures, develops in neurologically normal individuals during adolescence (Janz, 1985). Generalized tonic clonic seizures (GTCS) are usually experienced and the EEG shows generalized spike (GSW) and polyspike and slow wave (PSW) complexes with a photoparoxysmal response in up to 90% of cases when prolonged photic stimulation is performed (Appleton et al., 2000). Other affected family members of probands with JME have GGE phenotypes with JME seen in 50% of these (Marini et al., 2004).

Idiopathic photosensitive occipital epilepsy (IPOE) is a much less common focal epilepsy beginning in late childhood or adolescence (Guerrini et al., 1995; Taylor et al., 2003). Individuals have a visual aura associated with conscious tonic head and eye version induced by environmental photic stimulation (Guerrini et al., 1995). JME and IPOE share similar features. They have similar age of onset, photosensitivity, GTCS and are genetic in etiology. Family studies have demonstrated phenotypic overlap between these syndromes (Taylor et al., 2004).

The progressive myoclonus epilepsies (PME) are a rare group of disorders often presenting in children and adolescents (de Siqueira, 2010; Genton et al., 2012). Although several seizure types can be seen, myoclonus is the defining feature of this progressive neurological disorder and is typically precipitated by posture, action or photic stimulation (de Siqueira, 2010; Shahwan et al., 2005). In the early stages the clinical features can mimic JME but with time individuals with PME deteriorate with progressive worsening of neurological features and EEG (Shahwan et al., 2005). Occipital seizures and photosensitivity are seen in some PMEs including Lafora's disease (de Siqueira, 2010). Most PMEs are autosomal recessive or have mitochondrial inheritance (de Siqueira, 2010; Genton et al., 2012).

Here we describe a two generation family of European ancestry with likely dominant inheritance of an as yet undescribed familial epilepsy syndrome that we have named MOPED (myoclonic occipital photosensitive epilepsy with dystonia). MOPED involves a spectrum of phenotypes ranging from mild juvenile myoclonic epilepsy, with or without an idiopathic photosensitive occipital epilepsy overlap, to a severe progressive myoclonus epilepsy with associated dystonia.

Methods

Family members with and without a history of seizures underwent a detailed clinical assessment using a validated seizure questionnaire, corroborated by questioning relatives for eyewitness accounts. Previous investigations were obtained from medical records and treating doctors. Family members were personally examined and interviewed. If this was not possible they were interviewed by telephone. EEGs, video-EEG monitoring and MRI were performed where possible. One individual (III-1) had a postmortem examination of his brain. All individuals gave informed consent, or in the case of minors, their parents agreed to their participation. Seizure types were classified according to the International Classification of Epileptic Seizures and epilepsy phenotypes according the International Classification of Epilepsies and Epileptic Syndromes (Commission on Classification and Terminology of the International League Against Epilepsy, 1981, 1989). This study was approved by the New Zealand Health and Disability Ethics committee.

Genomic DNA was isolated from leukocytes of 12 family members (Fig. 1), including all seven affected family members. These samples were genotyped using Illumina OmniExpress genotyping arrays at the Australian Genome Research Facility (Melbourne, Australia).

The Perl script linkdatagen.pl. (Bahlo and Bromhead, 2009) was used to select subsets of markers in approximate linkage equilibrium for linkage analysis and estimation of inbreeding coefficients. SNPs were chosen to have high heterozygosity in the HapMap

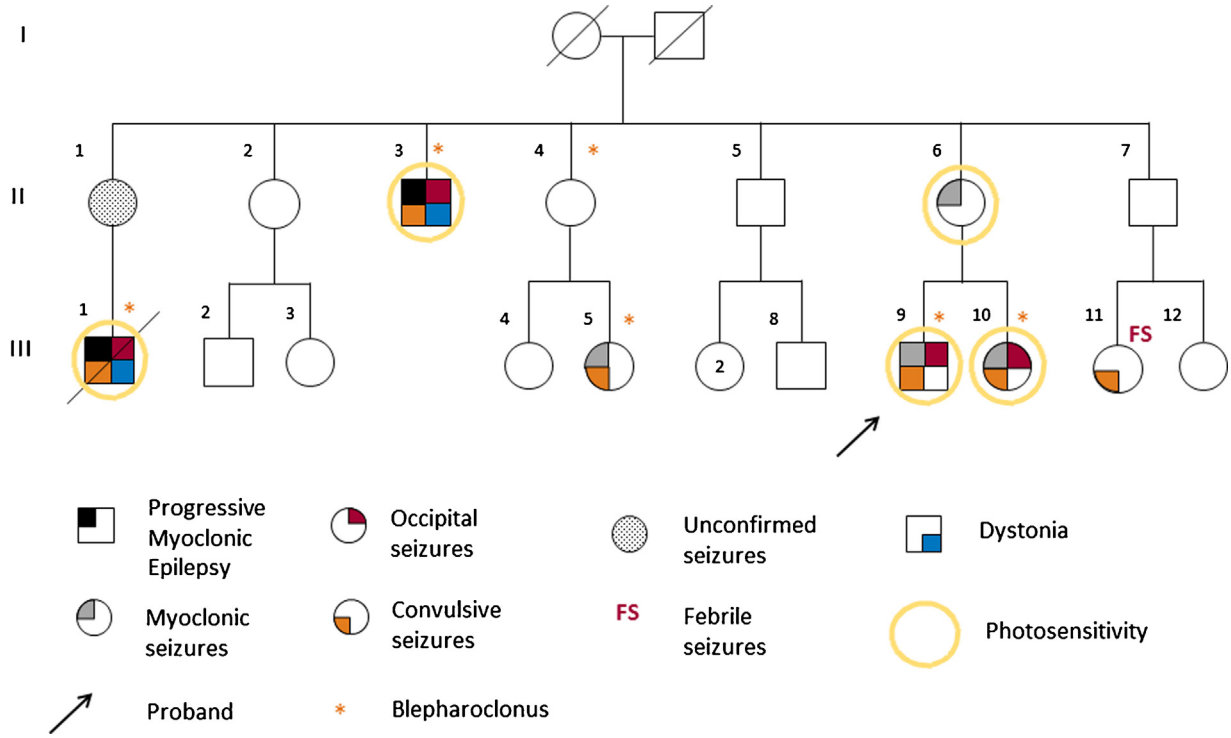

Fig. 1. *Family pedigree.* This New Zealand family of European ancestry had a pattern of likely autosomal dominant inheritance affecting seven individuals with seizures spanning two generations.