Generalized epilepsy with febrile seizures plus
A genetic disorder with heterogeneous clinical phenotypes

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Summary
The clinical and genetic relationships of febrile seizures and the generalized epilepsies are poorly understood. We ascertained a family with genealogical information in 2000 individuals where there was an unusual concentration of individuals with febrile seizures and generalized epilepsy in one part of the pedigree. We first clarified complex consanguineous relationships in earlier generations and then systematically studied the epilepsy phenotypes in affected individuals. In one branch (core family) 25 individuals over four generations were affected. The commonest phenotype, denoted as 'febrile seizures plus' (FS+), comprised childhood onset (median 1 year) of multiple febrile seizures, but unlike the typical febrile convulsion syndrome, attacks with fever continued beyond 6 years, or afebrile seizures occurred. Seizures usually ceased by mid childhood (median 11 years). Other phenotypes included FS+ and absences, FS+ and myoclonic seizures, FS+ and atonic seizures, and the most severely affected individual had myoclonic–astatic epilepsy (MAE). The pattern of inheritance was autosomal dominant. The large variation in generalized epilepsy phenotypes was not explained by acquired factors. Analysis of this large family and critical review of the literature led to the concept of a genetic epilepsy syndrome termed generalized epilepsy with febrile seizures plus (GEFS+). GEFS+ has a spectrum of phenotypes including febrile seizures, FS+, and the less common MAE. Recognition of GEFS+ explains the epilepsy phenotypes of previously poorly understood benign childhood generalized epilepsies. In individual patients the inherited nature of GEFS+ may be overlooked. Molecular genetic study of such large families should allow identification of genes relevant to febrile seizures and generalized epilepsies.

Keywords: generalized epilepsy; febrile seizures; genetics

Abbreviations: FS+ = febrile seizures plus; GEFS+ = generalized epilepsy with febrile seizures plus; GTCS = generalized tonic–clonic seizure; HLA = human leucocyte antigens; MAE = myoclonic–astatic epilepsy

Introduction
The international classification of epilepsy syndromes (Commission, 1989), which describes epilepsy phenotypes based on seizure type, age of onset, EEG patterns and other features has been an important advance in epileptology. In this paper we describe a large family with generalized epilepsy that highlights two problems with the classification of the generalized epilepsies. First, the classification does not presently incorporate all phenotypes commonly observed; in particular, generalized epilepsy associated with febrile seizures. Secondly, as opposed to the undoubted value of the classification in diagnosing individuals, when families are evaluated, heterogeneous phenotypes are observed. Understanding the familial inter-relationships of phenotypes is a critical prerequisite for molecular genetic studies. We introduce these two problems below and the value of rare large multiplex families in clarifying these issues.

Febrile seizures and generalized epilepsy
Febrile seizures affect 2–5% of all children. In the well-recognized febrile convulsion syndrome, seizures are confined to early childhood (<6 years) and are associated with a low overall risk of later epilepsy (Nelson and Ellenberg, 1976; Commission, 1989).

A number of generalized epilepsy syndromes may begin with a febrile seizure (Commission, 1989). Initially it may be impossible to distinguish such disorders from the febrile convulsion syndrome (O'Donohoe, 1992). Children suffering
febrile seizures extending beyond 6 years, with or without associated afebrile generalized tonic–clonic seizures (GTCS), who do not have one of the recognized syndromes are frequently seen. We describe this phenotype as ‘febrile seizures plus’ (FS+).

**Genetics of febrile seizures and generalized epilepsies**

Family studies of febrile seizures and of the common syndromes of generalized epilepsy suggest that their inheritance is complex rather than monogenic (Andermann, 1991). Complex inheritance is suggested not only by genetic analyses, but also by the observations that specific syndromes described in the classification have considerable nosological overlap and different syndromes are frequently found within one family (Italian League, 1993; Reutens and Berkovic, 1995). Genetic linkage studies in disorders following complex inheritance are considerably more difficult than in monogenic disorders (Lander and Schork, 1994).

**Value of large multigenerational families**

Large multigenerational families are an invaluable resource in studying disorders with complex inheritance. Such families with generalized epilepsy are extremely rare but can be used in two important ways. First, they are ideal for clarifying the inter-relationships of epilepsy syndromes, as they allow analysis of the phenotypic variation deriving from a relatively homogeneous genetic pool. Secondly, because of their relative genetic homogeneity they provide the best approach for molecular genetic studies, as shown by successful molecular genetic studies in a variety of other complex disorders (Lander and Schork, 1994).

Here we describe a large multiplex family with a variety of generalized epilepsy phenotypes. We characterized the epilepsy phenotypes of all available affected family members and analysed their genetic relationships. The most frequent phenotype was FS+. This large family provides a unique perspective on the clinical spectrum and genetics of FS+ and related phenotypes, a common, but hitherto neglected, group of generalized epilepsies. Insights from study of this family also have important implications for understanding clinical genetics and planning molecular genetic studies of the epilepsies. In particular, we introduce the concept of a genetic epilepsy syndrome where a single major gene may be associated with diverse individual epilepsy phenotypes.

**Methods**

**Ascertainment of the family**

The proband (VIII-7; Fig. 1) was referred to S.F.B. for evaluation of severe epilepsy. He is a dizygous twin and was included in our large twin study of epilepsy (Berkovic et al., 1993, 1994). We were independently informed of this family by Dr Lloyd Shield, Royal Children’s Hospital, Melbourne who had treated individual VIII-20 (Fig. 1) for multiple seizures with fever and noted an extensive family history of seizures. Initial evaluation of the family during our twin study of epilepsy suggested that there were a large number of affected individuals. We therefore embarked on an extensive study of the genealogy and clinical epileptology of this family.

**Genealogical documentation**

The family originated in Skelmanthorpe, Yorkshire, UK. Using records held by various family members we obtained genealogical information on 2000 family members dating back to the mid-1700s. These 2000 individuals were the descendants of I-4 and I-5 (Fig. 1).

Consanguineous marriages were known to have occurred a number of times in the family tree, but their exact nature was uncertain. I.E.S. performed extensive genealogical research and field work in Australia and Britain to clarify the family relationships.

The branch of the family with multiple affected individuals descended from II-7 who immigrated to Australia. V-7 and V-8 and their descendants were designated the ‘core family’. Most members lived in a small sheep-raising and grape-growing town 180 km north west of Melbourne, 72 km from the provincial city of Ballarat. The town is in the goldfields region of Victoria and was settled in the 1850s with the core family living there from that period.

**Clinical epileptology**

We obtained clinical information on 289 descendants of II-7 by personal or telephone interview. We successfully traced all the descendants of generation IV except those of IV-9. The initial interview was designed to establish the occurrence of seizures or possible seizures prior to detailed clinical evaluation.

Detailed clinical evaluation was subsequently performed on 53 living individuals in the core family plus 14 spouses regardless of whether or not they had a clinical history of a seizure disorder, and on other living individuals outside the core family with a history of seizures or possible seizures. These evaluations were principally performed in the local town involving field trips by the two investigators, a research nurse and an EEG technologist. A temporary EEG laboratory was established in the local Bush Nursing Hospital. A few individuals were studied at the Austin and Repatriation Medical Centre and in other parts of Australia. Only two individuals (VIII-1 and VIII-12) from the core family were unavailable for evaluation; both were unaffected and detailed histories were obtained from their parents.

The clinical evaluation protocol involved a structured interview using a validated questionnaire (Reutens et al., 1992) designed to elicit seizure history, seizure types according to the international classification of seizures (Commission, 1981), as well as a birth and general medical
Genetics of generalized epilepsy

Fig. 1 Pedigree of the family showing three levels of consanguinity (double solid or dotted lines) where Family H married into Family F. All branches shown here were traced with the exception of the descendants of IV-9. Genealogical data on an additional 1700 individuals descending from I-4 and I-5 was obtained (not shown).

Classification of epilepsies

Following the clinical evaluation, we attempted to classify the epilepsy phenotypes of all affected individuals according to the international classification of epilepsies and epileptic syndromes (Commission, 1989). A number of epilepsy phenotypes were not found in the international classification and these are described in the results. Defined syndromes relevant to this study were myoclonic–astatic epilepsy (MAE) and febrile convulsion syndrome.

MAE usually begins between 2 and 5 years of age with seizure types of myoclonic, astatic (tonic), myoclonic–astatic, absence and tonic–clonic seizures. The EEG usually shows irregular generalized fast spike-and-wave or polyspikes but where astatic seizures are prominent, 2–3 Hz spike-and-wave complexes may occur. Early seizures are often with fever and the clinical course is variable (Commission, 1989; Doose, 1992a).

The febrile convulsion syndrome comprises generalized seizures (usually generalized tonic–clonic) occurring during an acute febrile illness. Seizures are confined to early childhood (Commission, 1989) which we defined as 6 years or under. We used the term ‘febrile seizure’ to refer to any convulsion with fever irrespective of age, and ‘febrile convulsion syndrome’ to refer to the phenotype conforming to the international classification (Commission, 1989).

The study was approved by the Austin Hospital Ethics Committee, and all participating individuals, or their parents in the case of minors, gave informed consent.

Results

Genealogical data

The pedigree of the family is shown in Fig. 1. The ancestors were derived from two Yorkshire families designated F and H. In the first generation shown (Fig. 1), a brother (I-4) and sister (I-3) from the F family married a sister (I-5) and brother (I-6) from the H family. The seventh child of the second generation (II-7: born 1812 in Skelmanthorpe) immigrated to Australia in 1857 and had 289 descendants. Three consanguineous marriages occurred. The first involved his son (III-3) who married his ‘double second cousin’ (III-4). Their son (IV-2) then
Table 1 Clinical details of subjects in this study

<table>
<thead>
<tr>
<th>Pedigree reference</th>
<th>Age* (years)</th>
<th>Number of GTCS</th>
<th>Onset year</th>
<th>Fever</th>
<th>Offset year</th>
<th>Other seizure types (years)</th>
<th>Neurological examination</th>
<th>Previous EEG studies (age, years)</th>
<th>Study EEG</th>
<th>Epilepsy phenotype†</th>
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<tr>
<td>Core family</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>VI-3</td>
<td>78</td>
<td>1</td>
<td>9</td>
<td>9</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VI-4</td>
<td>78</td>
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<td>10</td>
<td></td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>UNW</td>
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<tr>
<td>VI-5</td>
<td>77</td>
<td>1-2 UNW</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>UNW</td>
<td></td>
</tr>
<tr>
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<td>&lt;5</td>
<td></td>
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<td>Normal</td>
<td>Normal</td>
<td>UNW</td>
<td></td>
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<td>VI-8</td>
<td>72</td>
<td>Many</td>
<td>Infancy</td>
<td></td>
<td>13</td>
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<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
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<td>Normal</td>
<td>Normal</td>
<td>UNW</td>
<td></td>
</tr>
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<td>VII-1</td>
<td>44</td>
<td>1 UNW</td>
<td>2</td>
<td>Never</td>
<td>2</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>UNW</td>
<td></td>
</tr>
<tr>
<td>VII-4</td>
<td>49</td>
<td>45</td>
<td>0.75</td>
<td>Never</td>
<td>43</td>
<td>Atonic (11–14)</td>
<td>Normal</td>
<td>Moderate DS</td>
<td>FS+, atonic sz</td>
<td></td>
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<td>VII-8</td>
<td>38</td>
<td>100</td>
<td>0.5</td>
<td>&gt;50%</td>
<td>16</td>
<td>Absences (9–10)</td>
<td>Normal</td>
<td>Mild DS</td>
<td>FS+, absences</td>
<td></td>
</tr>
<tr>
<td>VII-9</td>
<td>33</td>
<td>15</td>
<td>1</td>
<td>&gt;50%</td>
<td>25</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VII-10</td>
<td>47</td>
<td>10</td>
<td>0.75</td>
<td>Always</td>
<td>12</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VII-2</td>
<td>7</td>
<td>22</td>
<td>0.5</td>
<td>Always</td>
<td>&gt;9</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VII-3</td>
<td>5</td>
<td>13</td>
<td>0.9</td>
<td>Never</td>
<td>&gt;6</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VII-6</td>
<td>20</td>
<td>50</td>
<td>5</td>
<td>&lt;50%</td>
<td>8</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VII-7</td>
<td>20</td>
<td>100s</td>
<td>3</td>
<td>50%</td>
<td>&gt;20</td>
<td>Atonic, myoclonic, absences (&lt;5)</td>
<td>Moderate ID</td>
<td>GSW background slowing</td>
<td>2.5 Hz GSW marked DS</td>
<td>Myoclonic-astatic epilepsy</td>
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<tr>
<td>VII-11</td>
<td>21</td>
<td>20</td>
<td>0.8</td>
<td>Always</td>
<td>3</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VII-14</td>
<td>19</td>
<td>6</td>
<td>1</td>
<td>Always</td>
<td>11</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VII-16</td>
<td>12</td>
<td>50</td>
<td>0.6</td>
<td>&gt;50%</td>
<td>11</td>
<td>Myoclonic (0.6–3)</td>
<td>Normal</td>
<td>Mld background slowing (4)</td>
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<td>VII-17</td>
<td>9</td>
<td>30</td>
<td>0.4</td>
<td>&gt;50%</td>
<td>8</td>
<td>Absences (3–4)</td>
<td>Normal</td>
<td>3 Hz GSW (3)</td>
<td>FS+, absences</td>
<td></td>
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<tr>
<td>VII-19</td>
<td>6</td>
<td>18</td>
<td>0.75</td>
<td>&gt;50%</td>
<td>5</td>
<td>Absences (2–3)</td>
<td>Normal</td>
<td>Normal</td>
<td>GSW</td>
<td>FS+, absences</td>
</tr>
<tr>
<td>VII-20</td>
<td>4</td>
<td>13</td>
<td>0.9</td>
<td>Always</td>
<td>&gt;4</td>
<td>Absences (2–3)</td>
<td>Normal</td>
<td>Normal</td>
<td>Not done</td>
<td>FS+, absences</td>
</tr>
<tr>
<td>VII-23</td>
<td>14</td>
<td>20</td>
<td>1</td>
<td>&gt;50%</td>
<td>12</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS+</td>
<td></td>
</tr>
<tr>
<td>VII-24</td>
<td>9</td>
<td>3</td>
<td>0.7</td>
<td>&gt;50%</td>
<td>0.9</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>FS</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V–1</td>
<td>–</td>
<td>Recurrent</td>
<td>60</td>
<td>–</td>
<td>69</td>
<td>Complex partial (50–+)</td>
<td>–</td>
<td>–</td>
<td>Partial epilepsy</td>
<td></td>
</tr>
<tr>
<td>VI-2</td>
<td>60</td>
<td>100s</td>
<td>12</td>
<td>&lt;50%</td>
<td>49</td>
<td>Myoclonus (11)</td>
<td>Normal</td>
<td>Normal</td>
<td>Juvenile myoclonic epilepsy</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis in generation VI was difficult: living witnesses were available for seizures of VI-3 and VI-8 allowing diagnosis. *Age = age at start of study. † FS = febrile seizures, FS+ = febrile seizures plus, UNW = unwitnessed, sz = seizures, DS = diffuse slowing, GSW = generalized spike wave; ID = intellectual disability.

married his first cousin (IV-12). Their daughter (V-7: born 1889) then became the wife of her biological uncle (V-8: born 1887). This couple (V-8,V-7) were the patriarch and matriarch of the branch of the family with multiple affected individuals (‘core family’). No further consanguinity occurred in the subsequent generations.

Seizures occurred in 25 members of the ‘core family’ including the proband (VIII-7) and in three other individuals in the wider family (Fig. 1).

Clinical evaluation of the core family

In the core family, 25 of 60 members spanning four generations had seizures. A history of seizures was present in 67% of individuals in generation VI, 33% of generation VII and 36% of generation VIII. The matriarch (V-7) and patriarch (V-8) of the family were both reputed to have had seizures, but no specific information was available and they have not been included in the main analysis. The second wife of VII-1 had breathholding attacks and suspected but unconfirmed epileptic seizures in early childhood and she was not included in the main analysis. None of the other 13 spouses studied had seizures.

The remaining 23 affected members (Table 1) had seizure disorders beginning in childhood (mean onset 1.6 years, median 0.8 years, range 0.4–9 years) with a variety of seizure types. All 23 had GTCS. These could occur with or without fever, both asleep and awake. In addition, four individuals also had absence seizures, one had myoclonic seizures, one had atomic seizures and one (the proband) had multiple seizure types including atomic, myoclonic seizures and absence seizures.

Neurological examination and intellect were normal in all individuals except the proband who had moderate intellectual disability and required institutional care.

EEG recordings were normal in 41 family members. In three individuals (VII-8, VIII-17 and VIII-19) studied during the active phase of their epilepsy, generalized epileptiform activity was found (Figs 2 and 3). Four of the more severely affected individuals (VII-4, VII-8, VII-7 and VIII-16) had mild or moderate diffuse background slowing (Table 1).

Recognized epilepsy phenotypes in the core family

Three individuals had phenotypes consistent with epilepsy syndromes described in the international classification (Commission, 1989).
Fig. 2 Interictal and ictal EEG of the 20-year-old proband (VIII-7) with myoclonic–astatic epilepsy. Interictal recording shows moderate diffuse background slowing with generalized spike-and-wave discharges. The ictal recording of a generalized tonic-clonic seizure (GTCS) shows a generalized discharge and then movement artefact.

Fig. 3 Interictal routine EEG of a 6-year-old girl (VIII-19) with FS$^+$ and absence seizures showing generalized spike-and-wave activity with a normal background of 8 Hz activity. The epileptiform activity was activated by hyperventilation and intermittent photic stimulation.
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**Proband: myoclonic–astatic epilepsy**

The 20-year-old proband (VIII-7) had multiple seizure types with GTCS, absence, myoclonic and atonic seizures with moderate intellectual disability typical of MAE (see detailed case history below).

**Febrile convulsion syndrome**

Two children were classified as having febrile convulsions. One (VIII-11) had a classical febrile convulsion syndrome with seizures limited to early childhood (<6 years). The second (VIII-24) had three seizures between 8 and 11 months, one of which may have been afebrile.

**New epilepsy phenotypes in the core family**

**Febrile seizures plus (FS+)**

The most common epilepsy phenotype was FS+ seen in nine individuals (see case histories of VIII-6 and VIII-23). During childhood, these individuals had a benign epilepsy syndrome characterized by frequent GTCS (mean 22, median 13, range 1–100), not always with fever. Mean age of seizure onset was 2.2 years (median 1 year, range 0.5–9 years) and offset was 11.7 years (median 11 years, range 6–25 years). All had normal intellect. EEGs were normal but only two children (VIII-2, VIII-3) had ongoing seizures at the time of their study EEGs.

In addition, four affected individuals in the oldest living generation (VI-4, VI-5, VI-6, VI-10) had childhood seizures but eye witness accounts were not available. For this study their phenotypes were unclassified but we suspect they had FS+ on the basis of the information available (Table 1). VII-1 was also classified as unwitnessed as he was found in a postictal state at 2 years although he probably has FS+ as his mother could not recall him being febrile.

**Febrile seizures plus and absences**

Four individuals (VIII-17, VIII-19, VIII-20 and VII-8) had infrequent absence seizures in addition to FS+ (see case history VIII-19). An EEG from an untreated 6-year-old girl (VIII-19) showed an interictal generalized epileptiform discharge (Fig. 3) and her 9-year-old sister (VIII-17) had previously had active generalized spike-and-wave on EEG but had a normal study EEG while on sodium valproate. The phenotype was not that of childhood absence epilepsy as absence seizures were infrequent and GTCS were frequent.

**Febrile seizures plus and myoclonic seizures**

One 12-year-old boy (VIII-16) had FS+ and myoclonic seizures from 7 months. Both seizure types responded to the introduction of sodium valproate at 3 years. He had 50 GTCS mostly with fever. He did not have the classical phenotype of benign myoclonic epilepsy of infancy where febrile seizures are infrequent (Dravet et al., 1992).

**Febrile seizures plus and atonic seizures**

One man (VII-4) had GTCS from 9 months until 43 years, as well as atonic seizures from 11 to 14 years. These involved predominantly head nods, without falls.

**Relationships of epilepsy phenotypes in the core family**

The epilepsy phenotypes in affected individuals of the core family were heterogeneous, although all had generalized rather than partial epilepsies. None had typical electroclinical phenotypes of other idiopathic generalized epilepsies recognized in the International League Against Epilepsy classification (Commission, 1989) such as childhood absence epilepsy, juvenile absence epilepsy, or juvenile myoclonic epilepsy. Examination of birth records and other medical historical data showed that the large variation in epilepsy severity amongst affected family members was not associated with recognizable acquired factors such as birth trauma, cerebral infection or head injury.

Figure 4 shows the relationships of the epilepsy phenotypes described above within the family. Different phenotypes were distributed throughout the family. Specific phenotypes, such as FS+ or FS− and absences, were not faithfully inherited within nuclear families. For example, a father (VII-4) had FS+ and atonic seizures, one son had FS+ (VIII-6) and his dizygous twin brother (VIII-7) had MAE.

**Mode of inheritance**

Although there was no apparent relationship between specific epilepsy phenotypes, the seizure disorder followed a pattern consistent with autosomal dominant inheritance in generations V–VIII of the core family. Assuming autosomal dominant inheritance, there were three obligate carriers (VII-5, VII-6 and VII-7) where the lack of recognized seizures could be explained by incomplete penetrance. In the cases of two children (VIII-2 and VIII-3), the mode of inheritance may have been more complex as their mother (second wife of VII-1) had questionable seizures as a child.

The severity of epilepsy phenotypes varied throughout the generations. Anticipation was not present. For example, the proband’s twin brother (VIII-6) was more mildly affected than their father (VII-4).

**Epilepsy syndromes in the wider family**

Of the 289 people contacted, two branches other than the core family had a history of seizures. One woman (VI-2) had adolescent onset of frequent GTCS with myoclonic seizures continuing until 49 years. EEG studies were not
done in teenage or young adult life. The clinical history was consistent with juvenile myoclonic epilepsy. Her father (V-1) died at 68 years of cardiorespiratory causes, but his wife and daughters gave a history of complex partial seizures with secondarily generalized tonic–clonic seizures beginning in his fifties suggestive of a late onset symptomatic partial epilepsy. The later ages of onset and distinctly different phenotypes of these two individuals suggested that their epilepsies may not have been related to that of the core family. The second branch involved the brother of the patriarch of the study family. This brother (IV-9) was reputed to have had seizures but no further history could be obtained as his descendants could not be traced.

**Illustrative case histories**

1. **Myoclonic–astatic epilepsy**

   The 20-year-old proband (VIII-7) had seizures from 3.5 years. A series of prolonged convulsions occurred at 5 years and, subsequently, 3 min generalized convulsions occurred twice per week usually associated with fever. Myoclonic–astatic seizures developed in primary school and began with a myoclonic jerk, followed by atonia of the head and body lasting up to 2 s. Absence seizures were also frequent, but by 20 years, had reduced to weekly. In adult life, GTCS were often preceded by a myoclonic jerk and occurred weekly; myoclonic–astatic seizures occurred less often.

   He was the second twin of a pregnancy complicated by hypertension. Normal vaginal delivery occurred at term and he was born in good condition weighing 7 lb 8 oz. His development was behind his twin with slower speech and walking at 16 months. Despite these milestones, his farming family regarded him as quite bright and noted a cognitive decline following his best level of functioning in his early teens. Psychological testing documented a decline from the mildly intellectually impaired range at 11 years to the moderately impaired range at 14 years. He required special school education and worked in a sheltered workshop. Severe behavioural problems occurred with aggression and self-mutilation. Neurological examination was normal.

   Interictal EEG showed generalized sharp and slow wave discharges at 2.5 Hz brought out by hyperventilation (Fig. 2). Moderate background slowing consisting of polymorphic 4–5 Hz rhythms was seen. A GTCS began with a generalized spike wave transient and then was obscured by movement artefact (Fig. 2). CT brain scan was normal.

2. **Febrile seizures plus**

   A 14-year-old girl (VIII-23) had her first febrile convulsion at 1 year, and had 10–20 brief GTCS between 2 and 5 years, mostly associated with fever. Only one later febrile seizure occurred at 12 years. Perinatal and developmental history and examination were normal. Her EEG at 14 years was normal.

3. **Febrile seizures plus**

   A 20-year-old dizygous twin man (VIII-6) had weekly brief GTCS from 5 to 8 years. Seizures often occurred within 2
days of his co-twin’s attacks, although his brother had more frequent seizures. Seizures sometimes occurred with a fever, but stress and fatigue also triggered events. Phenytoin was given from 5 to 12 years. His EEG at 20 years was normal. The twins were dizygous on human leucocyte antigens (HLA) and red cell antigen testing.

4. Febrile seizures plus and absences
A 6-year-old girl (VIII-19) first had febrile convulsions at 9 months, and continued to have two to six brief GTCS per year, many associated with being unwell. In total, she had at least 15 GTCS. She had also had three staring attacks between 2 and 3 years when she was unresponsive, pale and blue without loss of posture. These lasted up to 30 s and no tonic or clonic features were seen. Her perinatal and developmental history were normal. Examination was normal.

Intercital EEG showed frequent generalized spike or double spike-and-wave discharges which were activated by hyperventilation and intermittent photic stimulation at 12, 18 and 20 Hz (Fig. 3). The background activity was normal.

Discussion

Epilepsy phenotypes
This large multiplex family had 25 individuals with generalized epilepsy over four generations. A spectrum of epilepsy phenotypes was seen with most family members having benign self-limited forms of generalized epilepsy such as FS\(^+\), or FS\(^+\) and absences. Less benign epilepsies were seen in two individuals, one had FS\(^+\) and atonic seizures with GTCS persisting to middle age, and his son had severe refractory MAE following initial febrile seizures. Although a number of defined generalized epilepsy syndromes can follow febrile seizures (Commission, 1989), MAE was the only one observed in this family.

The phenotype of FS\(^+\) was documented in nine individuals, and suspected in another five subjects. At onset in early childhood the GTCS were usually brief and associated with fever, thus being clinically indistinguishable from the febrile convulsion syndrome. Later distinguishing features were the persistence of GTCS with fever beyond 6 years, or the occurrence in early or mid childhood of afebrile GTCS. The frequency of seizures in FS\(^+\) subjects in this family (median 13) was greater than that observed in most children with the febrile convulsion syndrome where more than 80% of cases have fewer than four attacks (Nelson and Ellenberg, 1981). Seizures usually did not persist beyond adolescence. All individuals with FS\(^+\) were of normal intellect.

In our opinion, the phenotype of FS\(^+\) probably accounts for many children without a specific epilepsy syndrome diagnosis who have GTCS in childhood with preceding febrile seizures. In the large heterogeneous series of children with GTCS of Oller-Daurella and Oller (1992), 20% cases had isolated febrile seizures which preceded the GTCS and one-third had a family history of epilepsy. GTCS were infrequent with 80% children having fewer than five seizures and some had subsequent absence seizures. We suspect that many of their cases had FS\(^+\), although the frequency of GTCS was less than that seen in our family. Similarly, Aicardi (1994) recognizes that children with febrile seizures and later afebrile GTCS are common, with seizures usually remitting by 10 years, exactly as in our patients with FS\(^+\).

Population-based studies of children with epilepsy show that up to 21% had preceding febrile seizures, with the highest association for GTCS and febrile seizures (Rocca et al., 1987; Camfield et al., 1994). We suggest that many of the cases of febrile seizures evolving to generalized epilepsy have FS\(^+\).

Six patients in the core family of our study had absences, myoclonic seizures or atonic seizures in addition to FS\(^+\), of which the commonest phenotype was FS\(^+\) and absences. The phenotype was not that of childhood absence epilepsy, as absences were infrequent and GTCS dominated the clinical picture. Again, this phenotype is not represented in the international classification (Commission, 1989). These patients resemble those described as having absence epilepsy with tonic–clonic seizures in early childhood (Doose, 1994).

Genetics of febrile seizures and myoclonic–astatic epilepsy
There is an extensive literature on the genetics of phenotypes relevant to this family. Regarding febrile seizures, a family history of seizures occurs in over half of cases (Lennox and Lennox, 1960). Various genetic models have been proposed including autosomal dominant (Frantzen et al., 1970; Lennox-Buchtal, 1973), autosomal recessive (Schuman and Miller, 1966) and polygenic or multifactorial models (Fukuyama et al., 1979; Gardiner, 1990). Based on a complex segregation analysis of 467 families, Rich et al. (1987) found evidence of genetic heterogeneity. They proposed that single febrile seizures were associated with polygenic inheritance whilst three or more febrile seizures followed a single-major-locus model with nearly dominant seizure susceptibility. They defined febrile seizures as beginning before 5 years but did not give a maximum age. In children with febrile seizures, the recurrence risk of seizures is increased with a family history of febrile seizures (Berg et al., 1990; van Esch et al., 1994) or generalized epilepsy (Nelson and Ellenberg, 1978; Annegers et al., 1987; Verity and Golding, 1991). Many of these reported patients could have FS\(^+\). As with our core family, distinction from the classical febrile convulsion syndrome may not be made despite febrile and afebrile seizures occurring well past 6 years of age.

We have observed two clinical patterns of familial febrile seizures consistent with segregation analyses suggesting genetic heterogeneity (Rich et al., 1987). First, families where many individuals have infrequent febrile seizures and one or a few family members have later temporal lobe epilepsy
secondary to mesial temporal sclerosis (Maher and McLachlan, 1995; Wallace et al., 1996). In this group there is suggestive evidence for linkage to chromosome 8q13–21 in one family (Wallace et al., 1996). Secondly, there are families as described here with $FS^+$ and generalized epilepsy where linkage has not yet been found (Cochius et al., 1993; Lopes-Cendes et al., 1995).

In the case of MAE, Doose (1992a) regards inheritance as polygenic with little non-genetic variability with what he termed the 'type A' liability. In 32% of his probands, a family history of seizures was found. It was exceptional for an affected sibling to have a severe seizure disorder such as MAE (Doose, 1992a). Seizures in relatives typically began before 5 years and were most commonly febrile or afebrile GTCS (Doose et al., 1983; Doose, 1992a). Siblings were more commonly affected than parents, and 25% of affected siblings had absence seizures (Doose, 1992a). The epilepsy syndrome in Doose's probands' families was consistent with $FS^-$ and $FS^+$ and absences as described here.

### The genetic syndrome

In this large family there is strong evidence for an autosomal dominant gene segregating with the seizure disorder. Although three consanguineous marriages occurred in the earlier generations (III–V), the high proportion of affected individuals in generations VI–VIII strongly suggests that a major autosomal dominant gene is segregating with the seizure disorder (Fig. 1). Polygenic inheritance is possible but unlikely, because of the high proportion of affected individuals in later generations.

The epilepsy phenotypes were heterogeneous, although all were of generalized type (Fig. 4). Our concept is that there is a single genetic syndrome that we have named 'generalized epilepsy with febrile seizures plus' (GEFS$^+$) depicted in Fig. 5. The phenotypic expression of GEFS$^+$ comprises a spectrum of clinical epilepsy phenotypes including febrile seizures conforming to the febrile convulsion syndrome, $FS^+$, $FS^-$ and absences, $FS^+$ and myoclonic seizures, $FS^+$ and atonic seizures, and MAE. In our own experience of numerous small families with generalized epilepsy and febrile seizures these phenotypic associations are often seen. Only with study of this very large pedigree did the formulation of the concept of a genetic syndrome of GEFS$^+$ become evident.

Doose's data on MAE (see above), and the genetic data of others regarding febrile seizures and generalized epilepsies (Schuman and Miller, 1966; Andermann, 1982) derived from many small families, can be easily re-interpreted and better understood with our concept of GEFS$^+$. MAE is the most severe phenotype seen in the GEFS$^+$ syndrome, with most affected relatives having $FS^+$. Patients with MAE are uncommon, yet families with many members having febrile and afebrile GTCS are relatively common. Not all families with GEFS$^+$ will have an individual severely enough affected to warrant a diagnosis of MAE. There is overlap in the phenotypes of MAE and the Lennox–Gastaut syndrome (Henriksen, 1985; Doose and Baier, 1987; Doose, 1992b). Some cryptogenic cases of Lennox–Gastaut syndrome have a family history of seizures, particularly febrile seizures. We believe that the spectrum of GEFS$^+$ probably includes these cases as well and that their genetic aetiology may often be overlooked. Understanding the relationships of these syndromes and their genetic basis is important for accurate diagnosis and genetic counselling.

The mechanism for the phenotypic variability in this family with GEFS$^+$ is uncertain. There was no clinical evidence for anticipation, nor were recognized acquired factors for epilepsy responsible. In view of the apparent rarity of other families like this, the most likely explanation for the phenotypic variability in GEFS$^+$ is an effect of other modifier genes (Romeo and McKusick, 1994). Modifier genes may have a role in defining the particular phenotype; for example, the two most severely affected individuals (VII-4, VIII-7) were in one nuclear family and two of the four cases of $FS^+$ and absences (VIII-17, VIII-19) were in another.

We hypothesize that in this large family the major gene for GEFS$^+$ was unusually penetrant, accounting for the obvious dominant pattern of inheritance of seizures. In other families ascertained with probands having $FS^+$ or MAE there are also variable phenotypes amongst affected relatives (data not shown), although the family history is rarely as striking as observed here. In such families the major gene may not
be as penetrant, leading to the appearance of polygenic inheritance.

**Epilepsy syndromes and their genetic relevance**

The concept of a genetic syndrome such as GEFS\(^+\), illustrating genotype–phenotype relationships, is fundamental to strategies for studying the genetics of the epilepsies. Until now, the approach has been based on epilepsy syndromes which are very useful for diagnosis of the *individual* with seizures. Because individuals with similar syndromes are generally believed to have a similar biological basis for their condition, the use of syndromes for genetic analysis would seem to be the next logical step. This approach has been successful for some rare syndromes. For example, recognition of a homogeneous syndrome of nocturnal frontal lobe epilepsy in large families (Scheffer et al., 1994, 1995) led to successful linkage studies (Phillips et al., 1995), and identification of the first gene for an idiopathic partial epilepsy in the \(\alpha 4\) subunit of the neuronal nicotinic acetylcholine receptor (Steinlein et al., 1995). Similarly, relatively homogeneous phenotypes are seen in families with benign familial neonatal convulsions where linkage studies have been successful and in Unverricht–Lundborg disease (Leppert et al., 1989; Lehesjoki et al., 1991; Lewis et al., 1993), where linkage and recently, gene identification, has been achieved (Pennacchio et al., 1996).

However, even these rare clinically homogeneous syndromes may be genetically heterogeneous as shown in benign familial neonatal convulsions (Leppert et al., 1989; Lewis et al., 1993) as well as in monogenic mouse generalized epilepsy models (Noebels, 1994). Such genetic heterogeneity is still more likely to exist in the common electroclinical generalized epilepsy syndromes. Thus genetic analyses in these syndromes, based solely on phenotype, are likely to be confounded by genetic heterogeneity.

Examination of phenotypes in small families of probands with the defined syndromes of idiopathic generalized epilepsy, including juvenile myoclonic epilepsy, childhood absence epilepsy and juvenile absence epilepsy, show that these syndromes do not breed true within families (Beck-Mannagetta and Janz, 1991; Italian League, 1993). There may be a similarity of syndromes in close family members but the more distant the genetic relationship the less similar the syndrome. A genetic approach to a specific syndrome thus becomes problematic as, whilst seizure disorders may sometimes be segregating in an apparently mendelian fashion, the specific epilepsy syndrome does not (Beck-Mannagetta and Janz, 1991). The genetic syndrome of GEFS\(^+\) described here comprises an even more diffuse collection of seizure syndromes, the majority of which are not presently recognized by the International League Against Epilepsy classification (Commission, 1989). Most phenotypes in GEFS\(^+\) are broadly described as idiopathic generalized epilepsies, on the basis of normal intellect, normal EEG background, 3 Hz or faster spike-and-wave and benign outcome. In contrast, MAE is regarded as a cryptogenic or symptomatic generalized epilepsy. Thus, this family shows essentially the whole spectrum of the neurobiological continuum of generalized epilepsies (Berkovic et al., 1987), with genetic factors probably being the sole or major determinants of the phenotypic variability.

The insights afforded by this family have major implications for clinical and molecular genetic strategies for the generalized epilepsies. The heterogeneity of generalized epilepsy phenotypes suggests that such families provide more meaningful information regarding the inter-relationships of these syndromes, particularly with respect to their genetic aetiology, than that afforded by analysis of single electroclinical syndromes in multiple disparate families. This is evidenced by the current controversy regarding juvenile myoclonic epilepsy where studies in small families have yielded inconsistent findings regarding the presence and the precise location of linkage in chromosome 6p (Greenberg et al., 1988; Whitehouse et al., 1993), although a stronger case for linkage to 6p in one large family has recently been made (Liu et al., 1995).

The general approach to multi-factorial disorders is a major problem for molecular genetic analysis of common diseases. As pointed out elsewhere (Lander and Schork, 1994), large multigenerational families where the disease appears to be highly penetrant afford a special opportunity to solve the molecular genetic basis of a condition, which may then apply to families where the disease appears to follow a polygenic pattern and even to apparently sporadic cases. Successes in this realm have already been achieved in polygenic diseases such as familial breast cancer and Alzheimer disease, and this family may offer a similar opportunity for generalized epilepsy, in addition to clarifying the phenotypic relationships described here.

**Acknowledgements**

The authors wish to thank Anne Howell, Kathryn Crossland, Jan Barchett and Graeme Cliff for their assistance, Dr Lloyd Shield for referral of the family and Drs Graeme Jackson and Richard Macdonell for critically reviewing the manuscript. We also wish to thank the family in Australia and Britain for their participation in this study. I.E.S and S.F.B. were supported by the National Health and Medical Research Council of Australia, the Ramaciotti Foundation, the Royal Children’s Hospital Research Foundation and Austin Hospital Medical Research Foundation grants, and Dr Scheffer was also the recipient of a Ciba-Geigy (Australia) Epilepsy Fellowship.

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Received May 17, 1996. Revised October 18, 1996. Accepted November 4, 1996.