Familial mesial temporal lobe epilepsy: a benign epilepsy syndrome showing complex inheritance

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Temporal lobe epilepsy is the commonest partial epilepsy of adulthood. Although generally perceived as an acquired disorder, several forms of familial temporal lobe epilepsy, with mesial or lateral seizure semiology, have been described. Descriptions of familial mesial temporal lobe epilepsy have varied widely from a benign epilepsy syndrome with prominent déjà vu and without antecedent febrile seizures or magnetic resonance imaging abnormalities, to heterogeneous, but generally more refractory epilepsies, often with a history of febrile seizures and with frequent hippocampal atrophy and high T2 signal on magnetic resonance imaging. Compelling evidence of a genetic aetiology (rather than chance aggregation) in familial mesial temporal lobe epilepsy has come from twin studies. Dominant inheritance has been reported in two large families, though the usual mode of inheritance is not known. Here, we describe clinical and neurophysiological features of 20 new mesial temporal lobe epilepsy families including 51 affected individuals. The epilepsies in these families were generally benign, and febrile seizure history was infrequent (9.8%). No evidence of hippocampal sclerosis or dysplasia was present on brain imaging. A single individual underwent anterior temporal lobectomy, with subsequent seizure freedom and histopathological evidence of hippocampal sclerosis was not found. Inheritance patterns in probands’ relatives were analysed in these families, together with 19 other temporal lobe epilepsy families previously reported by us. Observed frequencies of epilepsies in relatives were lower than predicted by dominant Mendelian models, while only a minority (8/39) of families could be compatible with recessive inheritance. These findings strongly suggest that complex inheritance, similar to that widely accepted in the idiopathic generalized epilepsies, is the usual mode of inheritance in familial mesial temporal lobe epilepsy. This disorder, which appears to be relatively common, and not typically associated with hippocampal sclerosis, is an appropriate target for contemporary approaches to complex disorders such as genome-wide association studies for common genetic variants or deep sequencing for rare variants.

Keywords: family study; epileptology; temporal lobe epilepsy; genetics
Abbreviations: FDG = fluorodeoxy glucose; LG11 = leucine rich glioma-inactivated gene 1; SCN1B = sodium channel beta-1 subunit gene

Introduction

Temporal lobe epilepsy is the commonest partial onset epilepsy of adulthood (Zarrelli et al., 1999). Research in this disorder has historically been skewed towards surgical series of medically refractory temporal lobe epilepsy, often associated with congenital or acquired temporal lobe lesions on MRI and histopathological abnormalities in post-surgical specimens. This has engendered a widespread perception of temporal lobe epilepsy as a predominantly lesion disorder, though several forms of non-lesional, familial temporal lobe epilepsy have now been described (Vadlamudi et al., 2003). The relative contributions of genetic and acquired aetiological factors in the common and important clinical entity of sporadic, radiologically non-lesional temporal lobe epilepsy is largely unknown, although a positive family history has been noted in some series (Currie et al., 1971; Aguglia et al., 1998).

Familial temporal lobe epilepsy can be classified by predominant seizure semiology into mesial and lateral/neocortical subtypes. Familial mesial temporal lobe epilepsy was first recognized in a study of epilepsies in twins, and the high concordance in monozygotic twin pairs compared with dizygotic twins provided compelling evidence of a genetic aetiology (Berkovic et al., 1994, 1998). The same syndrome was subsequently appreciated in non-twin families (Berkovic et al., 1996). This form of familial mesial temporal lobe epilepsy is a relatively benign epilepsy syndrome with adolescent or adult onset, often with prominent ictal déjà vu, dreamlike state, fear and nausea, with simple partial and complex partial seizures and infrequent secondary generalization. An antecedent history of febrile seizures was uncommon (2.7%) and no different from background population estimates (2.3–3.9%) (Hauser and Kurland, 1975; Nelson and Ellenberg, 1978; Verity et al., 1985). MRI, where available, was normal. More recently, a further 15 small families with comparable clinical features were reported by a multicentre Italian collaboration (Striano et al., 2008).

A clinically heterogeneous but generally more severe group of familial mesial temporal lobe epilepsy has also been described (Cendes et al., 1998; Kobayashi et al., 2001). Affected individuals in these families had variable ages of onset, commonly in the first decade of life. Hippocampal atrophy with high T2 signal was common (30 and 57% in these series, respectively) as was medication refractoriness. Kobayashi and colleagues also reported somewhat different seizure semiology, with visceral/epigastric auras predominating and déjà vu being rare (7%).

An autosomal dominant form of temporal lobe epilepsy with lateral/neocortical semiology (often featuring auditory auras of ringing or ‘machinery-like humming’, with early ictal aphasia) was first described in 1995 (Ottman et al., 1995). Linkage to chromosome 10q was demonstrated (Ottman et al., 1995), with subsequent identification of leucine rich glioma-inactivated gene 1 (LGI1)/epitempin as the responsible gene (Kalachikov et al., 2002; Morante-Redolat et al., 2002). Mutations in this gene are now believed to account for around half of families where ≥2 individuals have temporal lobe epilepsy with auditory features (Berkovic et al., 2004a; Ottman et al., 2004). LG11 has an important role in post-natal maturation and dendritic pruning of glutamatergic synapses in mouse hippocampus, suggesting that persistence of hyperexcitable glutamatergic circuits may be the underlying cause of the epilepsy (Zhou et al., 2009). Very recently LG11 has also been shown to function as a Nogo receptor 1 ligand, antagonizing growth cone collapse normally induced by myelin and promoting neuronal growth on (inhibitory) myelin substrates (Thomas et al., 2010).

In contrast to dominant mutations frequently causing lateral temporal lobe epilepsy, the genetic architecture of benign mesial temporal lobe epilepsy is less clear. Understanding genetic architecture is crucial as the appropriate methodology for gene discovery depends on this (Mullen et al., 2009). One large benign mesial temporal lobe epilepsy family (11 individuals with temporal lobe epilepsy) has been reported from the USA with linkage to chromosome 4q (Hedera et al., 2007), thus implicating a dominant mutation, though the gene is not yet known. Another apparently dominant family from southern Italy has also been described, but without linkage data (Gambardella et al., 2000). In contrast, the majority of families described with this disorder are small, typically two to five affected individuals, and although low-penetration dominant inheritance was initially suggested by us (Berkovic et al., 1996), other inheritance patterns are not excluded. Large dominant families may be the exception rather than the rule, as is the case for the idiopathic generalized epilepsies, where very rare large dominant families have been highly informative (Cossette et al., 2002) but the common genetic architecture is polygenic (Beck-Mannagetta and Janz, 1991; Ottman, 2005; Hempelmann et al., 2006).

In this study, we present clinical and family history data on 20 new families. In our combined families, including 100 individuals with temporal lobe epilepsy, only a single individual required epilepsy surgery. We present EEG, MRI, fluorodeoxyglucose(FDG)-PET and histopathology from this medically refractory familial mesial temporal lobe epilepsy case, who underwent anterior temporal lobectomy with Engel class 1 outcome. We critically reappraise the genetic architecture of benign familial temporal lobe epilepsy, including an analysis of our eight concordant monozygotic twin families and our total of 31 non-twin pedigrees. We conclude that in the majority of kindreds, familial temporal lobe epilepsy has complex (either polygenic or multifactorial) inheritance.

Patients and methods

Inclusion and exclusion criteria

Families with multiplex temporal lobe epilepsy were ascertained according to the following criteria: first, two or more first-degree
relatives have a history of temporal lobe epilepsy, with clear mesial ictal semiology in at least one. The following features occurring at seizure onset were accepted as strongly supportive of mesial temporal localization: déjà vu, stereotyped flashbacks of a past event, a rising epigastric/visceral sensation or stereotyped (and usually noxious) olfactory or gustatory hallucination. Two or more such symptoms were frequently present simultaneously or in rapid succession. Features such as a dreamlike sensation, fear, nausea, warmth, sweating, flushing and pallor were frequent accompaniments but in the absence of at least one of the strongly supportive mesial temporal features they were not felt to be sufficiently localizing. Second, no other likely aetiology of epilepsy is known i.e. no potentially epileptogenic abnormality detectable on MRI. Hippocampal sclerosis was not an exclusion criterion though hippocampal sclerosis was not seen in this series. Third, no identified genetic cause [such as mutation in LGI1 (Berkovic et al., 2004a) or sodium channel beta-1 subunit gene (SCN1B; Scheffler et al., 2007)] has been found. Diagnosis of temporal lobe epilepsy was made on clinical and electrographic grounds. Temporal epileptiform EEG abnormality was not required for diagnosis where there was a clear clinical history of a temporal lobe aura.

Ascertainment of families with temporal lobe epilepsy

Families with mesial temporal lobe epilepsy were ascertained from our private and hospital practices (S.F.B. and I.E.S.), referrals from other neurologists and from community-based volunteer twin registers as described earlier (Berkovic et al., 1993). A small minority of multiplex families had been derived from probands with epilepsy syndromes that were non-temporal lobe epilepsy. In such cases, the temporal lobe epilepsy proband was assigned as the person with temporal lobe epilepsy who was the closest relative to the original proband. Where two individuals with temporal lobe epilepsy had identical relatedness to the original proband, the temporal lobe epilepsy proband was assigned at random (www.random.org coin-flip simulation).

Written informed consent was obtained from all participants, or their guardians in the case of minors. The study was approved by the Human Research Ethics Committee of Austin Health, Melbourne, Australia.

Epilepsy evaluation

Epilepsy probands underwent detailed historical evaluation. This included completion of a validated structured questionnaire (Reutens et al., 1992) comprehensively detailing antenatal and birth history, early development, educational history, general medical history and a detailed family pedigree. All available first- and second-degree relatives of epilepsy probands were interviewed, irrespective of whether epilepsy was suspected. All putatively affected and many unaffected individuals were also interviewed by a neurologist experienced in the assessment of epilepsy (S.F.B., I.E.S., D.E.C. or I.T.), with particular attention paid to antecedents to epilepsy, age of seizure onset, seizure semiology, seizure types, epilepsy syndrome and response to treatment. Informant interviews were routinely sought both to aid in diagnosis of seizures and, in the case of parents and grandparents, to corroborate early life details, notably the presence or absence of febrile seizures. Every effort was made to obtain all previous EEG and neuroimaging data, in addition to clinical notes from treating specialists and hospital records. In several cases EEG and MRI were performed or repeated at Austin Health, Melbourne, Australia, but wide geographical dispersion of family members made it impossible to acquire these data in all cases. MRIs were evaluated by visual inspection for evidence of hippocampal sclerosis (Jackson et al., 1993); quantitation of hippocampal volume was not routinely performed but was carried out in the surgically treated case as described earlier (Cook et al., 1992).

Analysis of goodness of fit to Mendelian models

Goodness of fit to four simple dominant Mendelian models was assessed separately in twin \( n = 8 \) and non-twin proband families \( n = 31 \), and in the combined data set. All models assume a zero new mutation rate and no effect on reproductive fitness conferred by the hypothesized epilepsy-causing allele. Model A is an 80% penetrant dominant model in which only temporal lobe epilepsy (but not other epilepsies, possible epilepsies or special syndromes of febrile seizures or solitary seizures) is considered as the resulting phenotype. According to this model, for first-degree relatives \( P_{\text{affected}} = 0.4 \). The probability that the observed number of affected relatives conforms to this model is assessed using two-tailed exact binomial tests (Conover, 1971). Model B is a dominant model with 60% penetrance (hence for first-degree relatives \( P_{\text{affected}} = 0.3 \)), again with only temporal lobe epilepsy accepted as the phenotype. Because familial temporal lobe epilepsy typically has onset in adolescence, only first- and second-degree relatives of \( \geq 13 \) years were considered eligible in these segregation analyses. This did not lead to exclusion of any relatives affected with temporal lobe epilepsy. In models C and D, we consider any epilepsy, possible epilepsy, or special epilepsy syndrome as a phenotype arising from the putative dominant mutation, with 80 and 60% penetrance, respectively. Because of the varied phenotypes being accepted in these models, including infantile febrile seizures, all first- or second-degree relatives over 6 months of age were considered eligible for an epilepsy syndrome or special syndrome and thus were included in analyses for Models C and D. Symptomatic epilepsies arising only after acquired brain injuries \( n = 2 \) were assumed to be non-genetic and were not counted in segregation analyses.

Second-degree relatives were divided into antecedent relatives (grandparents, uncles, aunts) and descendant relatives (grandchildren, nephews, nieces). Segregation in antecedent second-degree relatives was analysed in the affected (maternal or paternal) lineage only, with affected probabilities of 0.4% for 80% penetrant and 0.3% for 60% penetrant models. For families in which neither maternal nor paternal relatives were affected, the mean of the paternal and maternal eligible antecedent second-degree relatives was used. In some families where only epilepsies that were non-temporal lobe epilepsy were seen in antecedent relatives, a mean was used in calculations for models A and B, with the affected (non-temporal lobe epilepsy) lineage used in models C and D.

Results

Clinical and electrographic features of twenty new families with temporal lobe epilepsy

New mesial temporal lobe epilepsy pedigrees are shown in Fig. 1 (Family A) and Fig. 2 (Families 1–19). These families include 51 individuals (34 females, 17 males) affected with temporal lobe epilepsy. Mean seizure onset age was 18±9.6 years (range 3–46 years, median 15 years). Antecedent febrile seizures occurred
Figure 1. Mesial temporal lobe epilepsy family pedigrees of monozygotic twin probands. Family A (A) is not previously reported. Five families were originally reported by Berkovic et al. (1996) as follows. Current designation (B), 1996 designation Family C; (C), Family D; (D), Family A; (E), Family E; (F), Family F. Two further families were first reported by Chabrol et al. (2007) as follows: (G), AUS6; (H), AUS9. Note that some members of the AUS9 family previously coded as affected with temporal lobe epilepsy on the basis of prominent déjà vu have, on the basis of further clinical data, been reclassified as having physiological déjà vu only. Asterisk indicates non-lesional focal epilepsy: this group includes extra-temporal partial epilepsies and partial epilepsies where seizure onset is not possible to localize.
Figure 2 Pedigrees of families of non-twin probands with mesial temporal lobe epilepsy. Of the 21 families shown, 1–19 are not previously reported. Families B, G, I, J, K, L and M from Berkovic et al. (1996) are also included in the current segregation analysis. In families G and I, the affected status of some individuals has evolved during follow-up, so these pedigrees are shown here in updated form. Five further families first reported in Chabrol et al. (2007) (AUS1, AUS2, AUS3, AUS4 and AUS8) are also included in the segregation analysis. Other families with temporal lobe epilepsy presented in these earlier reports do not fulfil inclusion criteria for the current study (see ‘Patients and methods’ section). Asterisk indicates non-lesional focal epilepsy: this group includes extra-temporal partial epilepsies and partial epilepsies where seizure onset is not possible to localize.
in five individuals with subsequent temporal lobe epilepsy (9.8%) including a single episode of febrile status epilepticus in one individual at the age of 5 years. No other antecedent factors predisposing to brain injury (birth trauma, central nervous system infections, significant head trauma, etc.) were present.

Partial seizure symptoms in these individuals are summarized in Table 1. Psychic/dysmnestic features predominated (particularly déjà vu, present in 37/51, 73%), with autonomic phenomena also commonly seen (nausea 16/51, 31%; rising visceral/epigastric sensation 14/51, 27%; sweating, flushing or pallor 11/51, 22%). Forty-five of 51 individuals (88%) had simple partial seizures, including 10 who had no other seizure types. Thirty-two had complex partial seizures (63%) and 23 (45%) had infrequent generalized tonic clonic seizures.

The epilepsy was usually mild and responsive to medication (Table 2). Nineteen of 51 (37%) individuals were on no treatment at the time of the study. Of these, eight individuals (16%) had not received a diagnosis of epilepsy prior to the study. The majority (28/51, 55%) had good seizure control with a single anti-epileptic drug, while only four individuals (8%) required more than one drug. Only a single individual (Fig. 2, Family 5, Individual III-6) underwent epilepsy surgery (see below).

### Brain imaging and electroencephalography

Brain MRI was available for 34/51 affected individuals (67%) and was normal in 32 (94% of available MRIs). One (Fig. 2, Family 18, Individual III-1) showed mild global atrophy with no focal temporal lobe abnormality. In another (Fig. 2, Family 3, Individual IV-1), a 2 mm simple cyst of the hippocampal head was seen. This was suspected to be incidental, but was noted to be ipsilateral to the patient’s mesial temporal seizure onset. MRI correlates of hippocampal sclerosis (qualitative hippocampal atrophy and/or increased T2 signal) were not seen in any individual. Two affected family members who had not had MRI had normal brain CT.

EEG data were available for 38/51 affected individuals (75%). Focal temporal epileptiform changes were seen in 15 (39% of available results; 8 left, 6 right and 1 bi-temporal). Twenty-two (58%) had EEGs that were normal or showed only minor, non-specific slowing. One patient (Fig. 2, Family 6, Individual IV-5), with a coexisting diagnosis of an idiopathic generalized epilepsy (juvenile myoclonic epilepsy), had generalized epileptiform EEG changes (generalized spike-wave and polyspike-wave discharges, and positive photoplejiform response).

Only one individual underwent epilepsy surgery. This female (Fig. 2 Family 5, Individual III-6), aged 57 years at the time of study, described onset at the age of 12 years of simple partial seizures with initial déjà vu and a subsequent rising epigastric aura. She began to have complex partial seizures in her early 20s, which initially responded to medication adjustments. During her 40s, however, her attacks became refractory to treatment. Routine EEG showed right temporal sharp waves and sharp-slow complexes. MRI was normal to visual inspection and on quantitative hippocampal volumetry [right 2.95 cm³, left 3.01 cm³, normal female volume 3.01 ± 0.3 cm³ mean ± SD (Jack et al., 1995)], Fig. 3A]. She was assessed for epilepsy surgery at the age of 50. It was not possible to unequivocally localize ictal EEG onset using scalp electrodes, prompting intracranial EEG monitoring, which demonstrated right mesial temporal ictal onset spreading to the right lateral cortex (Fig. 3C and D). FDG-PET (Fig. 3B) clearly demonstrated right-temporal hypometabolism. The patient underwent a standard right anterior-temporal lobectomy at the age of 51. She had two simple partial seizures around 1 year post-operatively, but then became seizure free after medication adjustment and has remained seizure free since, with a further 5 years of follow-up. Histopathology of the resected anterior temporal lobe specimen (Fig. 4) showed a normal density of neurons in the cornu ammonis, with moderate gliosis of hippocampus, amygdala and temporal neocortex. Changes of hippocampal sclerosis were not seen.

### Table 1 Simple partial seizure symptoms in 51 individuals with familial mesial temporal lobe epilepsy

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number affected</th>
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<tbody>
<tr>
<td>Psychic/dysmnestic</td>
<td></td>
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<tr>
<td>Total affected individuals</td>
<td>43</td>
</tr>
<tr>
<td>Déjà vu</td>
<td>37</td>
</tr>
<tr>
<td>Derealization/depersonalization</td>
<td>16</td>
</tr>
<tr>
<td>dreamlike state/slow motion</td>
<td></td>
</tr>
<tr>
<td>Fear/panic/anxiety</td>
<td>6</td>
</tr>
<tr>
<td>Forced thoughts</td>
<td>4</td>
</tr>
<tr>
<td>Euphoria</td>
<td>3</td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
</tr>
<tr>
<td>Total affected individuals</td>
<td>30</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
</tr>
<tr>
<td>Visceral/epigastric</td>
<td>14</td>
</tr>
<tr>
<td>Sweating/flushing/pallor</td>
<td>11</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Special Sensory</td>
<td></td>
</tr>
<tr>
<td>Total affected individuals</td>
<td>21</td>
</tr>
<tr>
<td>Olfactory</td>
<td>8</td>
</tr>
<tr>
<td>Auditory (simple)</td>
<td>6</td>
</tr>
<tr>
<td>Gustatory</td>
<td>5</td>
</tr>
<tr>
<td>Auditory (complex)</td>
<td>4</td>
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<tr>
<td>Tingling</td>
<td>4</td>
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</tbody>
</table>

a Features listed are those described by two or more subjects.

### Table 2 Treatment of 51 new patients with familial temporal lobe epilepsy

<table>
<thead>
<tr>
<th>Epilepsy treatment</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously treated with AED</td>
<td>9</td>
</tr>
<tr>
<td>Previous diagnosis without treatment</td>
<td>2</td>
</tr>
<tr>
<td>Undiagnosed prior to study, untreated</td>
<td>8</td>
</tr>
<tr>
<td>1 AED</td>
<td>28</td>
</tr>
<tr>
<td>&gt;1 AED</td>
<td>4</td>
</tr>
<tr>
<td>Epilepsy Surgery</td>
<td>1 (right-anterior temporal lobectomy)</td>
</tr>
</tbody>
</table>

a Total not on treatment = 19.

AED: Anti-epileptic drug.
Genetic architecture of familial temporal lobe epilepsy

Overall inheritance patterns
Segregation analyses were performed using data from the 20 new families, pooled with 19 Australian families with temporal lobe epilepsy previously reported by us (Berkovic et al., 1996; Chabrol et al., 2007). In these 39 families, comprising 100 individuals with temporal lobe epilepsy, 33 instances of parent–child transmission were seen. There were 21 transmitting females and 12 transmitting males. These proportions do not significantly differ from the gender distribution of the overall data set (40 males, 60 females; $P = 0.76$), thus there is no evidence to suggest mitochondrial inheritance of temporal lobe epilepsy. Male to male transmission was seen in six instances, excluding exclusive X-linked inheritance.

Goodness of fit to dominant inheritance models
Testimony of twins revisited
Seven monozygotic twin pairs with temporal lobe epilepsy ascertained at this centre have been described in previous reports (Berkovic et al., 1996; Chabrol et al., 2007). All have been concordant for temporal lobe epilepsy. The eighth is unreported (Family A, Fig. 1). All eight monozygotic twin proband pedigrees are shown in Fig. 1, including two (Families F and G) where further individuals have become affected during follow-up since their

Figure 3 MRI, PET and EEG of a refractory patient with familial mesial temporal lobe epilepsy who underwent right anterior temporal lobectomy with Engel class 1 outcome. (A) T$_2$ weighted coronal MRI section demonstrating normal mesial temporal structures, without hippocampal atrophy or increased T$_2$ signal; normal hippocampal volumes were confirmed quantitatively. (B) FDG-PET demonstrating marked hypometabolism in the right temporal lobe, including the mesial structures. (C and D) Intracranial EEG. (C) Right-lateral surface and coronal section diagrams showing positioning of right mesial temporal depth electrodes (G1–G8), left mesial temporal depth electrodes (G9–G16), superior temporal (G17–G24) and parietal (G25–G48) sub-dural grid electrodes. (D) Left: average reference intracranial EEG showing right-mesial temporal ictal onset first evident in the G6 and G7 depth electrodes; early ictal spread to the superior temporal (G17–G24) and parietal (G25–G48) sub-dural grid electrodes is also seen. (D) Right: later in seizure evolution a clear ictal rhythm is seen in superior temporal and parietal subdural grid electrodes.
original publication (Berkovic et al., 1996). Table 3 summarizes temporal lobe epilepsy and other epilepsy phenotypes observed in the first-degree and antecedent second-degree relatives of the proband twin pair. It can be seen from Table 3 that the observed frequencies of affected relatives are significantly lower than predicted by Mendelian dominant models (see ‘Patients and methods’ section) in every case. This includes \( P = 0.0041 \) for Model D, allowing confident rejection of even this most accommodating Mendelian model.

**Segregation in non-twin families**

Observed frequencies of temporal lobe epilepsy and other epilepsies in 31 non-twin proband families with temporal lobe epilepsy are also summarized in Table 3. When these are compared with the expected Mendelian dominant frequencies, (Models A–D, see ‘Patients and methods’ section) observed frequencies are significantly lower than predicted by all models, even for the most relaxed Model D (\( P = 0.038 \)). When twin and non-twin data sets are merged this is highly significant (Model D, \( P = 0.0014 \), Table 3).

**Discussion**

**Clinical features of familial mesial temporal lobe epilepsy**

We present 20 new families with mesial temporal lobe epilepsy, ascertained as two first-degree relatives having temporal lobe epilepsy without evidence of an acquired cause. Previously published familial temporal lobe epilepsy cohorts have varied considerably (Berkovic et al., 1996; Cendes et al., 1998; Kobayashi et al., 2001; Striano et al., 2008, Gambardella et al., 2009), notably in age of onset, frequency of antecedent febrile seizures, ictal semiology, medication refractoriness and in MRI surrogates of hippocampal sclerosis (hippocampal atrophy and/or high hippocampal \( T_2 \) signal). The clinical features of the cohort of 20 new families with temporal lobe epilepsy presented here is congruent with our previous description (Berkovic et al., 1996) and that of a recent multicentre Italian series (Striano et al., 2008). Females were affected more often than males (34 females, 17 males). While this could simply reflect a greater likelihood for female probands to consent to research or to admit to psychic/experiential phenomena, this gender bias is consistently seen, and thus could be a

![Figure 4](http://brain.oxfordjournals.org/)

**Figure 4** Histopathology of resected right-anterior-temporal lobe from Individual III-6 of Family 5 who had refractory seizures. (A) Low power magnification of cornu ammonis showing no evidence of loss of neurons in the pyramidal cell layer or dentate gyrus (Luxol Fast Blue \( \times 20 \)). (B) Temporal neocortex showing patchy mild gliosis (GFAP \( \times 100 \)).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Segregation of temporal lobe epilepsy and other epilepsies</th>
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<tbody>
<tr>
<td>Family set</td>
<td>Model</td>
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<tr>
<td>Monozygotic twin families</td>
<td>A</td>
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<td></td>
<td>B</td>
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<td></td>
<td>C</td>
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<td>D</td>
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<tr>
<td>Non-twin families</td>
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<td></td>
<td>C</td>
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<td></td>
<td>D</td>
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<tr>
<td>Combined families</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
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<tr>
<td></td>
<td>C</td>
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<td></td>
<td>D</td>
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</table>

*First-degree relatives and antecedent second-degree relatives from affected side of family are combined (see ‘Patients and methods’ section). These non-temporal lobe epilepsy individuals are not considered under Models A and B. NA = not applicable; TLE = temporal lobe epilepsy.
biological phenomenon rather than a research artefact. Our individuals with familial mesial temporal lobe epilepsy have a generally benign epilepsy syndrome with predominant simple or complex partial seizures, frequent déjà vu, medication responsiveness and normal MRI. In contrast with our previous description, the rate of febrile seizures in the new families was higher than estimates of background population frequency (5/51, 9.8% versus 3.5%, \( P = 0.035 \); Nelson and Ellenberg, 1978) though this may be a sampling artefact as the rate in our whole cohort (6/100, 6%) is not significantly different from this background estimate (\( P = 0.17 \)).

We did not observe the frequent medication refractoriness and high rates of overt hippocampal sclerosis reported by other investigators (Cendes et al., 1998; Kobayashi et al., 2001), though whether this is due to a real regional variation in disease profile or is a consequence of different ascertainment strategies, is not clear. In cohorts where more individuals are ascertained due to medication refractoriness and assessment for epilepsy surgery, a higher frequency of hippocampal sclerosis might be seen. Our cohort is ascertained from a combination of routine office and hospital practice, referrals on the basis of multiple relatives with epilepsies and twin probands. Moreover, in our ‘first seizure clinic’, where new onset cases routinely have MRIs (King et al., 1998) we regularly observe individuals with normal MRI and familial temporal lobe epilepsy, but not familial hippocampal sclerosis (D. E. Crompton, M. Newton and S. F. Berkovic, unpublished data). It should, however, be noted that one family with a mixture of temporal lobe epilepsy, febrile seizures and febrile seizures plus, including one member with bilateral hippocampal sclerosis and another with seizure freedom post-temporal lobectomy in the absence of hippocampal sclerosis, was excluded from this report in view of a known causative mutation in \( SCN1B \) (Family A (Scheffer et al., 2007)). While we cannot exclude subtle degrees of hippocampal atrophy detectable by volumetrics, overt hippocampal sclerosis that is reliably detected by visual inspection (Reuts et al., 1996) was absent, as further confirmed pathologically in our surgical case (Fig. 3). One study has demonstrated MRI features of hippocampal sclerosis in 38.6% of sporadic individuals with longstanding benign mesial temporal lobe epilepsy (Labate et al., 2006). Although many individuals with temporal lobe epilepsy presented here had initial or repeat MRI many years after their seizure onset, the formal possibility that hippocampal sclerosis features could emerge in a subset of our patients in years to come cannot be excluded.

Genetic architecture of familial temporal lobe epilepsy

It is clear that temporal lobe epilepsy can, in some instances, be inherited as a dominant Mendelian trait, both in autosomal dominant partial epilepsy with auditory features, where mutations in \( LGI1 \) are causative, and probably in rare large families with mesial temporal lobe epilepsy (Gambardella et al., 2000; Picard et al., 2000; Hedera et al., 2007). Familial temporal lobe epilepsy can also coexist with other partial onset epilepsy phenotypes in the syndrome of familial partial epilepsy with variable foci (Scheffer et al., 1998, Xiong et al., 1999, Berkovic et al., 2004b). Additionally, temporal lobe epilepsy can occur in rare families with dominant inheritance of febrile seizure syndromes including genetic epilepsy with febrile seizures plus. These are genetically heterogeneous with a variety of loci being reported and, in some families, the sodium channel gene \( SCN1B \) has been implicated (Baulac et al., 2001; Depondt et al., 2002; Claes et al., 2004; Scheffer et al., 2007). Our results argue strongly against dominant inheritance being usual in families with mesial temporal lobe epilepsy. We applied four dominant models that varied in penetrance assumptions (80% versus 60%) and in the epilepsy phenotypes accepted as resulting from the hypothetical dominant mutation (temporal lobe epilepsy alone versus all epilepsies, possible epilepsies, solitary seizures or febrile seizures). A model with 80% penetrance was chosen, as this has been reported in autosomal dominant partial epilepsy with auditory features (Ottman et al., 1999). Exclusion of probands and first-degree relatives yields a lower penetrance estimate for families with autosomal dominant partial epilepsy with auditory features (Ottman et al., 2004), but no such adjustment was used here. A model with 60% penetrance was also considered, as this was the penetrance estimate in our first description of familial temporal lobe epilepsy (Berkovic et al., 1996).

Assumptions inherent in our dominant models were that the epilepsy allele did not significantly reduce reproductive fitness and that the new mutation rate was zero. Given the generally benign nature of the disorder, this fitness assumption seems reasonable. Incorrect assumption of a zero new mutation rate could account in part for the lower than expected frequencies of temporal lobe epilepsy in antecedent relatives and it is impossible to confirm this zero mutation assumption on the basis of currently available data. It is, however, notable that in descendant second-degree relatives temporal lobe epilepsy was not seen at all (0/41), and this observation is not compatible with de novo dominant mutations, though it is wholly compatible with a polygenic genetic architecture. We cannot exclude the possibility that recessive inheritance is occurring in some small families, though vertical transmission is seen in 31 of 39 families demonstrating that recessive inheritance occurs in only a small minority, if at all. Familial temporal lobe epilepsy has been reported as part of the phenotype of the recessive trait neuroacanthocytosis, but none of our families had the features of that rare condition (Al-Asmi et al., 2005).

Our estimates of proportions of affected relatives in multiplex families are likely to be over-estimates because we selected families with two or more members affected, without other clinical or laboratory markers of genetic mesial temporal lobe epilepsy being available for sporadic cases. However, the twin analyses avoid this problem, and the observed frequency of affected relatives of twin probands (Table 3) is less than anticipated in any dominant model, giving powerful, unbiased and highly statistically significant evidence against dominant inheritance being usual in familial temporal lobe epilepsy.

Acquiring reliable evidence as to the genetic architecture in such families is confounded by multiple factors. First, familial mesial temporal lobe epilepsy may run a very benign course such that affected individuals are frequently unaware that they are affected.
Second, family members often choose not to share information about their epilepsy with their relatives. We have endeavoured to negate the under-ascertainment bias that could be created by these effects by meticulously interviewing at-risk relatives, irrespective of their perceived affected status, and excluding sets of first- or (more commonly) second-degree relatives in families where comprehensive, reliable clinical data excluding or confirming the presence of seizures could not be obtained.

Familial temporal lobe epilepsy was first recognized in twin families where its strong genetic basis was demonstrated by high concordance in monozygotic twins. Although dominant inheritance can be seen in mesial temporal lobe epilepsy, our analyses of frequencies in affected family members demonstrate that this situation is likely to be exceptional. An alternative hypothesis of polygenic inheritance in most familial mesial temporal lobe epilepsy neatly marries the observations of high heritability (as shown in twins) but absence of dominant segregation. Moreover, this hypothesis predicts that the common, apparently sporadic cases of benign temporal lobe epilepsy beginning in adolescence or adulthood (Currie et al., 1971; Aguglia et al., 1998; Labate et al., 2006) may share the genetic determinants underlying the familial cases described here. The proposal of common polygenic and rare dominant inheritance in familial mesial temporal lobe epilepsy predicts the allelic structure of mesial temporal lobe epilepsy to be similar to that of idiopathic generalized epilepsies. It implies that Mendelian linkage analysis will reveal only a small proportion of the genetic variation causing mesial temporal lobe epilepsy. Instead, genome-wide association studies to search for common genetic variants and deep re-sequencing methodologies to identify causative rare variants, in combination with copy number variation screening (Beckmann et al., 2009; Helbig et al., 2009), may unlock the majority of the genetic basis of mesial temporal lobe epilepsy.

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References


