

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; *LG1* = 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 lesional 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 (*LG1*)/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). *LG1* 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 *LG1* 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-penetrance 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 *LG11* (Berkovic *et al.*, 2004a) or sodium channel beta-1 subunit gene (*SCN1B*; Scheffer *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 $P_{affected}=0.4$. 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 $P_{affected}=0.3$), 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 ≥ 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

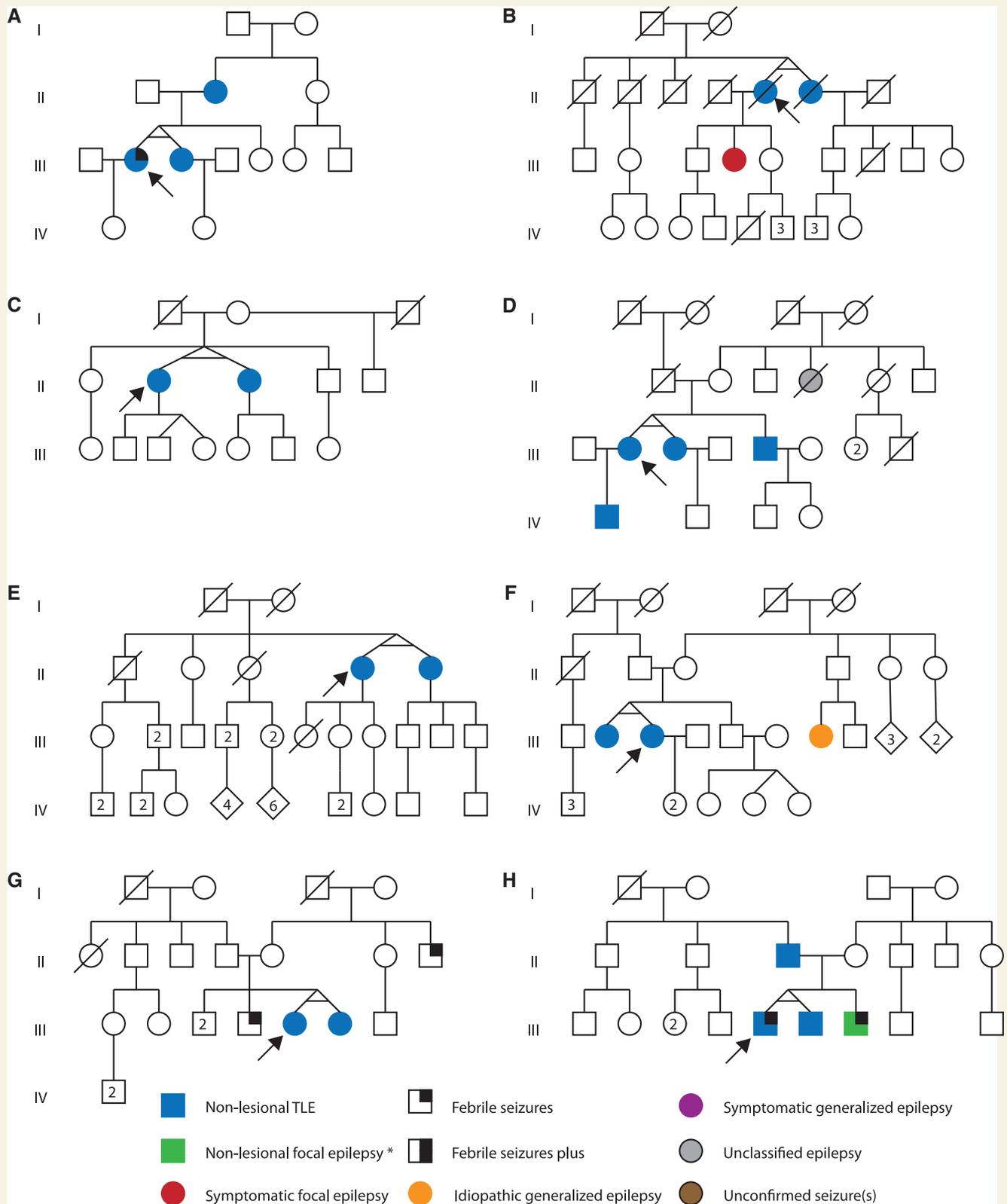


Figure 1 Mesial temporal lobe epilepsy family pedigrees of monozygotic twin probands. Family A (**A**) is not previously reported. Five families were originally reported by Berkovic *et al.* (1996) as follows. Current designation (**B**), 1996 designation Family C; (**C**), Family D; (**D**), Family 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.

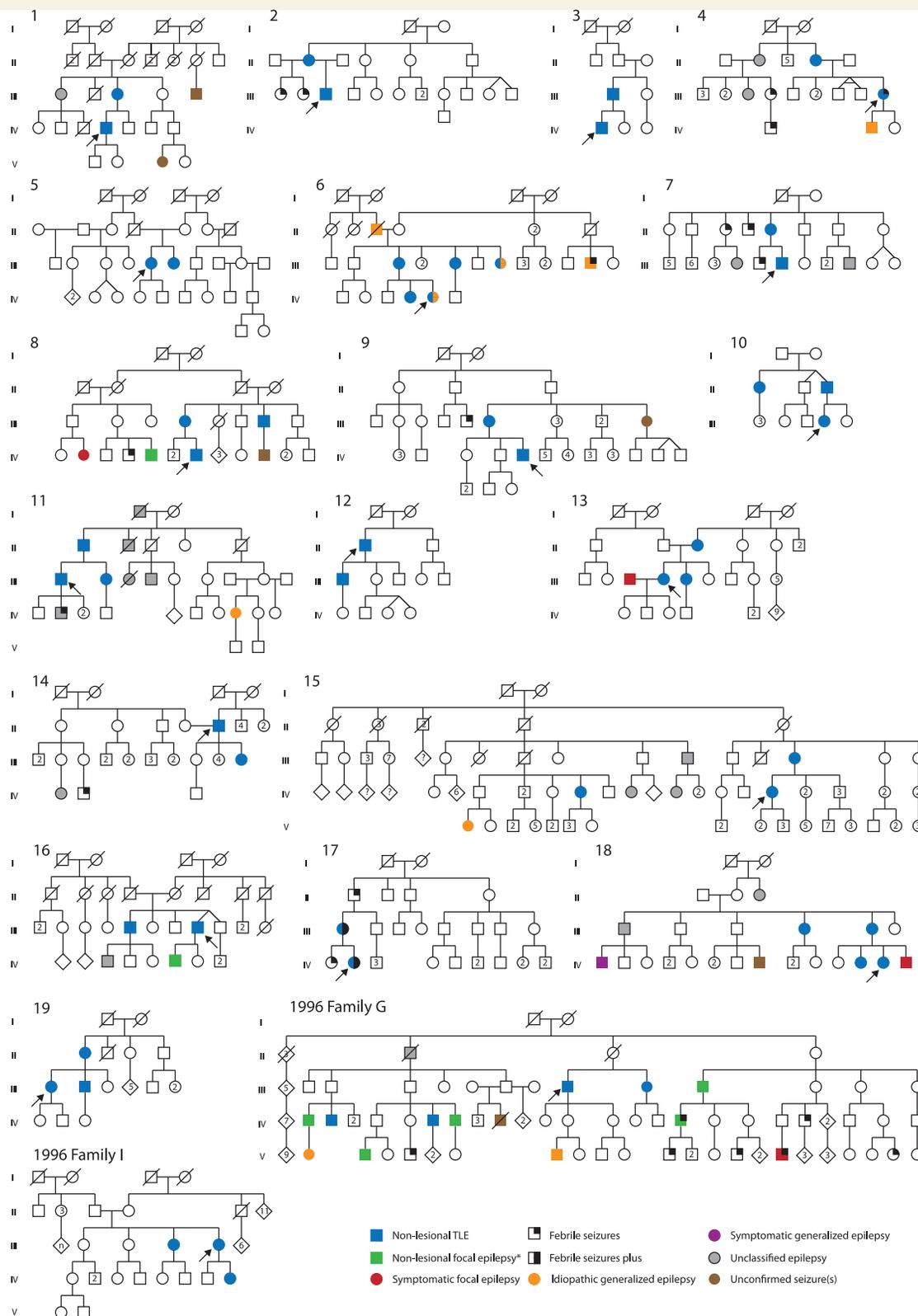


Figure 2 Pedigrees of families of non-twin probands with mesial temporal lobe epilepsy. Of the 21 families shown, 1–19 are not previously reported. Families B, G, I, J, K, L and M from Berkovic *et al.* (1996) are also included in the current segregation analysis. In families G and I, the affected status 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.

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

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

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

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

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

Epilepsy treatment	Number
Previously treated with AED	9 ^a
Previous diagnosis without treatment	2 ^a
Undiagnosed prior to study, untreated	8 ^a
1 AED	28
>1 AED	4
Epilepsy Surgery	1 (right-anterior temporal lobectomy)

a Total not on treatment = 19.

AED: Anti-epileptic drug.

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 photoepileptiform 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.

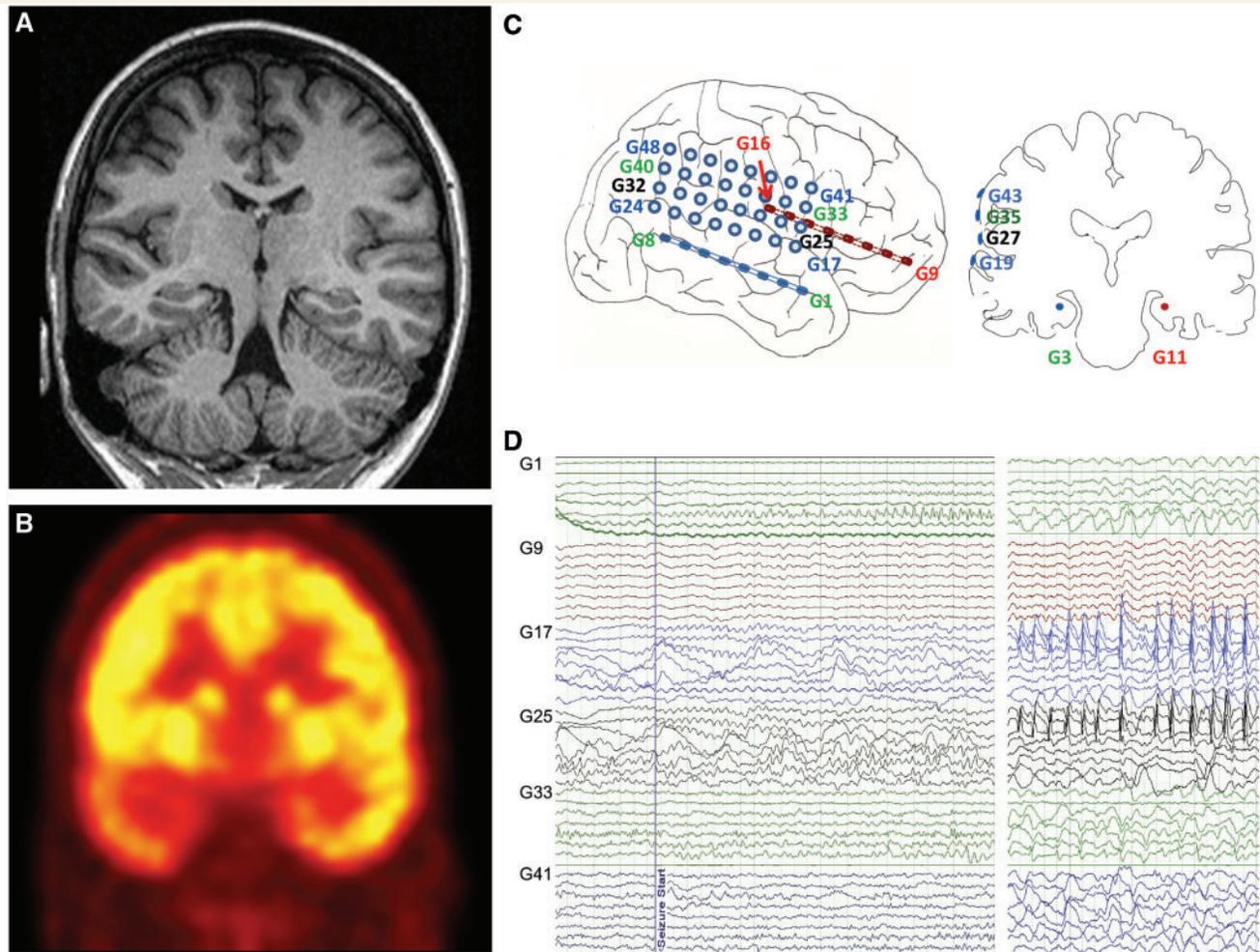


Figure 3 MRI, PET and EEG of a refractory patient with familial mesial temporal lobe epilepsy who underwent right anterior temporal lobectomy with Engel class 1 outcome. (A) T₂ weighted coronal MRI section demonstrating normal mesial temporal structures, without hippocampal atrophy or increased T₂ signal; 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 (G25–48) 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 (G25–48) 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.

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

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

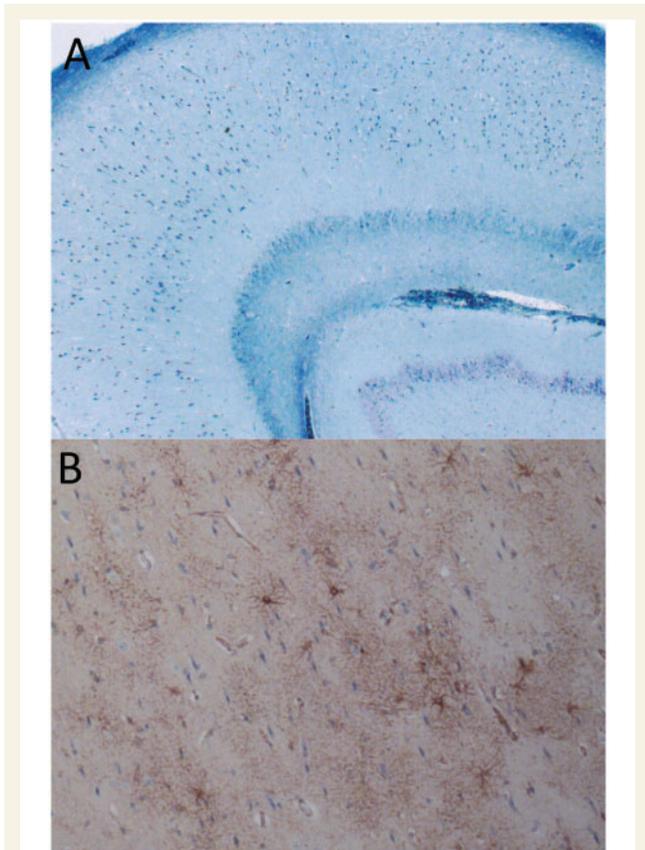


Figure 4 Histopathology of resected right-anterior-temporal lobe from Individual III-6 of Family 5 who had refractory seizures. (A) Low power magnification of cornu ammonis showing no evidence of loss of neurons in the pyramidal cell layer or dentate gyrus (Luxol Fast Blue $\times 20$). (B) Temporal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

Table 3 Segregation of temporal lobe epilepsy and other epilepsies

Family set	Model	Eligible relatives ^a	Relatives with TLE	Relatives with other epilepsy	Expected number of affected relatives	P-value (accept model)
Monozygotic twin families	A	64	4	NA	25.6	1.5×10^{-9}
	B	64	4	NA	19.2	6.6×10^{-6}
	C	65	4	5	25.6	5.9×10^{-6}
	D	65	4	5	19.5	0.0041
Non-twin families	A	266	45	NA	106.4	5.1×10^{-16}
	B	266	45	NA	79.8	1.2×10^{-6}
	C	266	45	19	106.4	5.6×10^{-8}
	D	266	45	19	79.8	0.038
Combined families	A	330	49	NA	132	$<2.2 \times 10^{-16}$
	B	330	49	NA	99	1.9×10^{-10}
	C	331	49	24	132.4	6.4×10^{-12}
	D	331	49	24	99.3	0.0014

^a 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 (Reutens *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 *LG11* 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 (Poza *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.*, 2007; Helbig *et al.*, 2009), may unlock the majority of the genetic basis of mesial temporal lobe epilepsy.

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References

- Aguglia U, Gambardella A, LePiane E, Messina D, Olivieri RL, Russo C, et al. Mild, non-lesional temporal lobe epilepsy. *Can J Neurol Sci* 1998; 25: 282–6.
- Al-Asmi A, Jansen AC, Badhwar A, Dubeau F, Tampieri D, Shustik C, et al. Familial temporal lobe epilepsy as a presenting feature of choreoacanthocytosis. *Epilepsia* 2005; 46: 1256–63.
- Baulac S, Picard F, Herman A, Feingold J, Genin E, Hirsch E, et al. Evidence for digenic inheritance in a family with both febrile convulsions and temporal lobe epilepsy implicating chromosomes 18qter and 1q25–q31. *Ann Neurol* 2001; 49: 786–792.
- Beck-Mannagetta G, Janz D. Syndrome-related genetics in generalized epilepsy. *Epilepsy Res Suppl* 1991; 4: 105–11.
- Beckmann JS, Estivill X, Antonarakis SE. Copy number variants and genetic traits: closer to the resolution of phenotypic to genotypic variability. *Nat Rev Genet* 2007; 8: 639–46.
- Berkovic SF, Hay DA, Hopper JL. Epilepsies in twins. In: Wolf P, editor. *Epileptic seizures and syndromes*. London: John Libby; 1994. p. 157–64.
- Berkovic SF, Howell RA, Hay DA, Hopper JL. Twin birth is not a risk factor for seizures. *Neurology* 1993; 43: 2515–9.
- Berkovic SF, Howell RA, Hay DA, Hopper JL. Epilepsies in twins: genetics of the major epilepsy syndromes. *Ann Neurol* 1998; 43: 435–45.
- Berkovic SF, Izzillo P, McMahon JM, Harkin LA, McIntosh AM, Phillips HA, et al. *LG11* mutations in temporal lobe epilepsies. *Neurology* 2004a; 62: 1115–9.
- Berkovic SF, McIntosh A, Howell RA, Mitchell A, Sheffield LJ, Hopper JL. Familial temporal lobe epilepsy: a common disorder identified in twins. *Ann Neurol* 1996; 40: 227–35.
- Berkovic SF, Serratosa JM, Phillips HA, Xiong L, Andermann E, Diaz-Otero F, et al. Familial partial epilepsy with variable foci: Clinical features and linkage to chromosome 22q12. *Epilepsia* 2004b; 45: 1054–60.
- Cendes F, Lopes-Cendes I, Andermann E, Andermann F. Familial temporal lobe epilepsy: a clinically heterogeneous syndrome. *Neurology* 1998; 50: 554–7.
- Chabrol E, Gourfinkel-An I, Scheffer IE, Picard F, Couarch P, Berkovic SF, et al. Absence of mutations in the *LG11* receptor *ADAM22* gene in autosomal dominant lateral temporal epilepsy. *Epilepsy Res* 2007; 76: 41–8.
- Claes L, Audenaert D, Deprez L, Van Paesschen W, Depondt C, Goossens D, et al. Novel locus on chromosome 12q22–q23.3 responsible for familial temporal lobe epilepsy associated with febrile seizures. *J Med Genet* 2004; 41: 710–4.
- Conover WJ. *Practical nonparametric statistics*. New York: John Wiley & Sons; 1971. p. 97–104.
- Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. *Brain* 1992; 115: 1001–15.
- Cossette P, Liu L, Brisebois K, Dong H, Lortie A, Vanasse M, et al. Mutation of *GABRA1* in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat Genet* 2002; 31: 184–9.
- Currie S, Heathfield KW, Henson RA, Scott DF. Clinical course and prognosis of temporal lobe epilepsy. A survey of 666 patients. *Brain* 1971; 94: 173–90.
- Depondt C, Van Paesschen W, Matthijs G, Legius E, Martens K, Demaerel P, et al. Familial temporal lobe epilepsy with febrile seizures. *Neurology* 2002; 58: 1429–1433.
- Gambardella A, Messina D, Le Piane E, Oliveri RL, Annesi G, Zappia M, et al. Familial temporal lobe epilepsy autosomal dominant inheritance in a large pedigree from southern Italy. *Epilepsy Res* 2000; 38: 127–32.
- Gambardella A, Labate A, Giallonardo A, Aguglia U. Familial mesial temporal lobe epilepsies: clinical and genetic features. *Epilepsia* 2009; 50 (Suppl. 5): 55–7.
- Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. *Epilepsia* 1975; 16: 1–66.
- Hedera P, Blair MA, Andermann E, Andermann F, D'Agostino D, Taylor KA, et al. Familial mesial temporal lobe epilepsy maps to chromosome 4q13.2–q21.3. *Neurology* 2007; 68: 2107–12.
- Helbig I, Mefford HC, Sharp AJ, Guipponi M, Fichera M, Franke A, et al. 15q13.3 microdeletions increase risk of idiopathic generalized epilepsy. *Nat Genet* 2009; 41: 160–2.
- Hempelmann A, Taylor KP, Heils A, Lorenz S, Prud'homme JF, Nabbout R, et al. Exploration of the genetic architecture of idiopathic generalized epilepsies. *Epilepsia* 2006; 47: 1682–90.

- Jack CR Jr, Theodore WH, Cook M, McCarthy G. MRI-based hippocampal volumetrics: data acquisition, normal ranges, and optimal protocol. *Magn Reson Imaging* 1995; 13: 1057–64.
- Jackson GD, Berkovic SF, Duncan JS, Connolly A. Optimizing the diagnosis of hippocampal sclerosis using MR imaging. *AJNR Am J Neuroradiol* 1993; 14: 753–62.
- Kalachikov S, Evgrafov O, Ross B, Winawer M, Barker-Cummings C, Martinelli Boneschi F, et al. Mutations in *LG1* cause autosomal-dominant partial epilepsy with auditory features. *Nat Genet* 2002; 30: 335–41.
- King MA, Newton MR, Jackson GD, Fitt GJ, Mitchell LA, Silvapulle MJ, et al. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* 1998; 352: 1007–11.
- Kobayashi E, Lopes-Cendes I, Guerreiro CA, Sousa SC, Guerreiro MM, Cendes F. Seizure outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy. *Neurology* 2001; 56: 166–72.
- Labate A, Ventura P, Gambardella A, Le Piane E, Colosimo E, Leggio U, et al. MRI evidence of mesial temporal sclerosis in sporadic “benign” temporal lobe epilepsy. *Neurology* 2006; 66: 562–5.
- Morante-Redolat JM, Gorostidi-Pagola A, Piquer-Sirerol S, Saenz A, Poza JJ, Galan J, et al. Mutations in the *LG1*/Epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. *Hum Mol Genet* 2002; 11: 1119–28.
- Mullen SA, Crompton DE, Carney PW, Helbig I, Berkovic SF. A neurologist’s guide to genome-wide association studies. *Neurology* 2009; 72: 558–65.
- Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. *Pediatrics* 1978; 61: 720–7.
- Ottman R. Analysis of genetically complex epilepsies. *Epilepsia* 2005; 46 (Suppl. 10): 7–14.
- Ottman R, Risch N, Hauser WA, Pedley TA, Lee JH, Barker-Cummings C, et al. Localization of a gene for partial epilepsy to chromosome 10q. *Nat Genet* 1995; 10: 56–60.
- Ottman R, Winawer MR, Kalachikov S, Barker-Cummings C, Gilliam TC, Pedley TA, et al. *LG1* mutations in autosomal dominant partial epilepsy with auditory features. *Neurology* 2004; 62: 1120–6.
- Picard F, Baulac S, Kahane P, Hirsch E, Sebastianelli R, Thomas P, et al. Dominant partial epilepsies. A clinical, electrophysiological and genetic study of 19 European families. *Brain* 2000; 123: 1247–62.
- Poza JJ, Saenz A, Martinez-Gil A, Cheron N, Cobo AM, Urtasun M, et al. Autosomal dominant lateral temporal epilepsy: clinical and genetic study of a large Basque pedigree linked to chromosome 10q. *Ann Neurol* 1999; 45: 182–8.
- Reutens DC, Howell RA, Gebert KE, Berkovic SF. Validation of a questionnaire for clinical seizure diagnosis. *Epilepsia* 1992; 33: 1065–71.
- Reutens DC, Stevens JM, Kingsley D, Kendall B, Moseley I, Cook MJ, et al. Reliability of visual inspection for detection of volumetric hippocampal asymmetry. *Neuroradiology* 1996; 38: 221–5.
- Scheffer IE, Phillips HA, O’Brien CE, Saling MM, Wrennall JA, Wallace RH, et al. Familial partial epilepsy with variable foci: a new partial epilepsy syndrome with suggestion of linkage to chromosome 2. *Ann Neurol* 1998; 44: 890–9.
- Scheffer IE, Harkin LA, Grinton BE, Dibbens LM, Turner SJ, Zielinski MA, et al. Temporal lobe epilepsy and GEFS+ phenotypes associated with *SCN1B* mutations. *Brain* 2007; 130: 100–9.
- Striano P, Gambardella A, Coppola A, Di Bonaventura C, Bovo G, Diani E, et al. Familial mesial temporal lobe epilepsy (FMTLE): a clinical and genetic study of 15 Italian families. *J Neurol* 2008; 255: 16–23.
- Thomas R, Favell K, Morante-Redolat J, Pool M, Kent C, Wright M, et al. *LG1* is a Nogo receptor 1 ligand that antagonizes myelin-based growth inhibition. *J Neurosci* 2010; 30: 6607–12.
- Vadlamudi L, Scheffer IE, Berkovic SF. Genetics of temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2003; 74: 1359–61.
- Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I—Prevalence and recurrence in the first five years of life. *Br Med J (Clin Res Ed)* 1985; 290: 1307–10.
- Xiong L, Labuda M, Li D-S, Hudson TJ, Desbiens R, Patry G, et al. Mapping of a gene determining familial partial epilepsy with variable foci to chromosome 22q11-q12. *Am J Hum Genet* 1999; 65: 1698–1710.
- Zarrelli MM, Beghi E, Rocca WA, Hauser WA. Incidence of epileptic syndromes in Rochester, Minnesota: 1980–1984. *Epilepsia* 1999; 40: 1708–14.
- Zhou YD, Lee S, Jin Z, Wright M, Smith SE, Anderson MP. Arrested maturation of excitatory synapses in autosomal dominant lateral temporal lobe epilepsy. *Nat Med* 2009; 15: 1208–14.