

THE GENETICS OF TEMPORAL LOBE EPILEPSY AND IMPLICATIONS FOR TREATMENT

Temporal Lobe Epilepsy and GEFS+ Phenotypes Associated with SCN1B Mutations. Scheffer IE, Harkin LA, Grinton BE, Dibbens LM, Turner SJ, Zielinski MA, Xu R, Jackson G, Adams J, Connellan M, Petrou S, Wellard RM, Briellmann RS, Wallace RH, Mulley JC, Berkovic SF. *Brain* 2007;130(Pt 1):100–109. *SCN1B*, the gene encoding the sodium channel $\beta 1$ subunit, was the first gene identified for generalized epilepsy with febrile seizures plus (GEFS+). Only three families have been published with *SCN1B* mutations. Here, we present four new families with *SCN1B* mutations and characterize the associated phenotypes. Analysis of *SCN1B* was performed on 402 individuals with various epilepsy syndromes. Four probands with missense mutations were identified. Detailed electroclinical phenotyping was performed on all available affected family members including quantitative MR imaging in those with temporal lobe epilepsy (TLE). Two new families with the original C121W *SCN1B* mutation were identified; novel mutations R85C and R85H were each found in one family. The following phenotypes occurred in the six families with *SCN1B* missense mutations: 22 febrile seizures, 20 febrile seizures plus, five TLE, three other GEFS+ phenotypes, two unclassified and ten unaffected individuals. All individuals with confirmed TLE had the C121W mutation; two underwent temporal lobectomy (one with hippocampal sclerosis and one without) and both are seizure free. We confirm the role of *SCN1B* in GEFS+ and show that the GEFS+ spectrum may include TLE alone. TLE with an *SCN1B* mutation is not a contraindication to epilepsy surgery.

COMMENTARY

Temporal lobe epilepsy is the most common partial epilepsy. It was once considered to be predominantly an acquired form of epilepsy, and no temporal lobe epilepsy syndrome was listed among the presumably genetic idiopathic epilepsies, even though a genetic element was often recognized (1). However, in the past decade a number of genetic temporal lobe epilepsy syndromes have been described (2–4). First reported was a benign familial temporal lobe epilepsy syndrome identified in twins, with clinical evidence of mesial temporal lobe origin (2). The syndrome was not associated with hippocampal sclerosis. Pedigree analysis was consistent with an autosomal dominant inheritance with incomplete penetrance. Extrapolation from its incidence in monozygotic twins suggested that it was a common epileptic syndrome, perhaps not previously recognized because of its excellent response to medical treatment and its frequently very mild manifestations. It soon became clear that this was not the only genetic temporal lobe epilepsy syndrome and that familial temporal lobe epilepsy is clinically heterogeneous (3,5). Some patients have a history of antecedent febrile seizures or hippocampal sclerosis while others do not; some patients have easily controlled seizures while others have refractory epilepsy, leading to presurgical evaluation and epilepsy surgery. While most familial temporal lobe epilepsy is of mesial temporal origin, familial lateral temporal lobe syndromes with an identified genetic mutation have been recognized. Autosomal dominant partial epilepsy, with auditory

(4) or aphasic (6) manifestations, is related to mutations in the leucine-rich, glioma-inactivated 1 (LGI1) gene.

Mesial temporal lobe epilepsy is much more common than lateral temporal lobe epilepsy and is frequently associated with antecedent childhood complex febrile convulsions, which are considered to have a strong genetic component (7,8). Some evidence suggests that in families with febrile seizures temporal lobe epilepsy may be in part a consequence of febrile status epilepticus (9). One genetic epilepsy syndrome, which includes febrile seizures, is generalized epilepsy with febrile seizures plus (GEFS+) (10,11). GEFS+ most often is due to a mutation in a sodium channel gene and manifests with variable phenotypes, including the typical febrile convulsion syndrome, febrile seizures persisting beyond age 6 years, or coexistent with afebrile generalized tonic–clonic seizures (called febrile seizures plus), as well as other generalized seizure types (8,9). Temporal lobe epilepsy is an occasional phenotype with GEFS+, but published cases thus far had suggested that temporal lobe epilepsy with this condition may be a consequence of febrile status epilepticus, rather than a direct expression of GEFS+ (11,12). In their report, Scheffer and colleagues screened a large number of individuals for mutations in one of the sodium channel genes implicated in GEFS+. In the affected families, they found several individuals with temporal lobe epilepsy that occurred only with one particular mutation and was not necessarily preceded by febrile seizures or associated with hippocampal sclerosis. Scheffer and colleagues concluded that: “GEFS+ phenotypes may include temporal lobe epilepsy in its own right.”

One important impetus for the identification of genetic causes of epilepsy is the expectation that more specific and effective therapy may follow. However, there has not been a clear impact of genetic discoveries on the treatment of temporal lobe

epilepsy. One specific question in the management of epilepsy is whether a genetic basis of epilepsy precludes epilepsy surgery. Intuitively, focal resection does not seem appropriate in genetic epilepsy because the genetic mutation is expected to affect the brain diffusely. However, the data do not support this intuitive conclusion. In a report of epilepsy surgery in 20 patients with familial temporal lobe epilepsy of unspecified genetic basis, surgical outcome was excellent in 85% (13). The three patients in the study with less than excellent outcomes had either absent or symmetrical hippocampal atrophy, while all others had unilateral or asymmetric hippocampal atrophy. Scheffer and colleagues report excellent surgical outcome in two individuals with GEFS+ and temporal lobe epilepsy, including one without hippocampal sclerosis. They confirm that a GEFS+ mutation is specifically not a contraindication to epilepsy surgery when the epileptogenic zone is well localized.

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