

CHANNELING INTO THE EPILEPSIES

The Spectrum of SCN1A-Related Infantile Epileptic Encephalopathies. Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, Sadleir LG, Andermann E, Gill D, Farrell K, Connolly M, Stanley T, Harbord M, Andermann F, Wang J, Batish SD, Jones JG, Seltzer WK, Gardner A; Infantile Epileptic Encephalopathy Referral Consortium, Sutherland G, Berkovic SF, Mulley JC, Scheffer IE. *Brain* 2007;130(Pt 3):843–852. The relationship between severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome) and the related syndrome SMEI-borderlands (SMEB) with mutations in the sodium channel alpha 1 subunit gene *SCN1A* is well established. To explore the phenotypic variability associated with *SCN1A* mutations, 188 patients with a range of epileptic encephalopathies were examined for *SCN1A* sequence variations by denaturing high performance liquid chromatography and sequencing. All patients had seizure onset within the first 2 years of life. A higher proportion of mutations were identified in patients with SMEI (52/66; 79%) compared to patients with SMEB (25/36; 69%). By studying a broader spectrum of infantile epileptic encephalopathies, we identified mutations in other syndromes including cryptogenic generalized epilepsy (24%) and cryptogenic focal epilepsy (22%). Within the latter group, a distinctive subgroup designated as severe infantile multifocal epilepsy had *SCN1A* mutations in three of five cases. This phenotype is characterized by early onset multifocal seizures and later cognitive decline. Knowledge of an expanded spectrum of epileptic encephalopathies associated with *SCN1A* mutations allows earlier diagnostic confirmation for children with these devastating disorders.

COMMENTARY

An increasing number of human neurological diseases have been identified that are due to brain ion channel dysfunction, the neurological channelopathies. Often after the first discovery that a particular phenotype is associated with a dysfunctional channel, further work leads to the recognition of a wider range of phenotypic variation. Appreciation of the full phenotypic spectrum can be very important clinically and can shed light on fundamental disease mechanisms. The present study reveals a wider phenotypic range of diseases linked to neuronal sodium channel dysfunction.

The epileptic encephalopathies are a group of devastating disorders that encompass both idiopathic conditions, such as West syndrome (infantile spasms), and genetic disorders, such as severe myoclonic epilepsy of infancy (SMEI). Patients undergo a relentless neurological decline and their seizures often are difficult to treat. SMEI (also known as Dravet syndrome) is a rare disorder characterized by generalized tonic, clonic, and tonic-clonic seizures, which are initially induced by fever and develop during the first year of life. Later, other seizure types develop, including absence, myoclonic, and simple or complex partial seizures, which culminate in a malignant epileptic syndrome. Psychomotor development becomes abnormal during the second year. Those patients who do not fulfill the entire diagnostic criteria for SMEI have been referred to as SMEI-borderland or SMEB.

Mutations in the sodium channel α_1 subunit gene, *SCN1A*, were first identified in patients with generalized epilepsy with febrile seizures plus (GEFS+) syndrome, a relatively benign in-

herited epilepsy syndrome (1). *SCN1A* encodes the α_1 subunit of the neuronal voltage-gated sodium channel $\text{Na}_v1.1$, which is responsible for propagation of action potentials. Since the initial report, mutations in the sodium channel α_1 subunit have also been identified in patients with SMEI (2) and other epileptic encephalopathies, such as infantile spasms (3) and more recently postvaccine encephalopathy (4). These sporadic and autosomal dominant epilepsy syndromes are now thought to represent different ends of the phenotypic spectrum of *SCN1A* mutations. Confusingly, epilepsy-associated mutations can lead to both a loss and a gain of function of $\text{Na}_v1.1$ in vitro (5). Thus, the downstream result of opposite alterations in sodium currents presumably has different effects on inhibitory and excitatory neuronal networks, leading to the common final pathway of epileptogenesis.

Many *SCN1A* mutations have been identified in patients with SMEI, usually these occur de novo (6,7). In this comprehensive study, Harkin et al. have analyzed a cohort of 188 patients with various epileptic encephalopathies and have provided extensive clinical and EEG phenotypes (8). Patients were screened for mutations in *SCN1A*, mainly by direct DNA sequencing. Mutations were identified in 48% of patients. Of the 90 mutations, 72 were novel, all affecting conserved parts of the channel protein, and 96% occurred de novo. No patients with West syndrome, infantile spasms, myoclonic encephalopathies, progressive myoclonic epilepsy, alternating hemiplegia, or unclassified epilepsy syndromes had a *SCN1A* mutation. However, mutations were not restricted to those with typical epileptic encephalopathy. Interestingly, six patients (24%) with cryptogenic generalized epilepsy, three (8%) with cryptogenic focal epilepsy, two (20%) with myoclonic-astatic, and one (8%) with Lennox-Gastaut syndrome also carried mutations. Some of these patients had a normal intellect and/or no

associated neurological deficit. The majority of mutations were found in patients with SMEI or SMEB. Pooling the cases in their study gives a detection rate of 75.4% for SMEI/SMEB, which is comparable to a recent report of 71% in SMEI/SMEB, of which 82% were de novo (9). The mutation types also were in keeping with the published literature, with SMEI more often associated with nonsense or splice site mutations (61%) and SMEB a result of missense mutations (52%). In both SMEI and SMEB, missense mutations clustered in the transmembrane segments of the protein, as has been shown previously.

This important paper widens the phenotypic spectrum of *SCN1A* mutations: GEFS+ and a recent report of a family with febrile seizures and TLE (10) represent the milder side; intractable childhood epilepsy with generalized tonic-clonic seizures (5) and some patients with cryptogenic epilepsies (8) now are included in the middle ground; while added to the severe end of the spectrum with the epileptic encephalopathies of SMEI/SMEB, are Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, and postvaccine encephalopathy (4). Providing a definitive genetic diagnosis for these children can be helpful, both by directing appropriate treatment (for example, lamotrigine and carbamazepine may make seizures worse) but also by avoiding further unnecessary and invasive investigations. Although there are currently no gene-specific anticonvulsants, such treatments may be available in the future.

While many different *SCN1A* mutations have been identified in patients with SMEI, most of which are unique to individuals, several recurrent mutations have also been found (7). Mutations are spread throughout the gene and, therefore, have different predicted functional effects on the protein (11). However, it is apparent that wherever and whatever the functional effects of these mutations are, they all lead to a similar seizure phenotype. Collating the available functional data on such mutations does not lead to an obvious explanation of the shared epilepsy phenotype; however, mathematical modeling has predicted an increased excitability via augmented action potential firing (12). Mutations in *SCN1A* are the most numerous genetic cause of epilepsy; hence further efforts to clarify their precise pathophysiology are likely to be important to the fundamental understanding of epileptogenesis.

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