SCN1A IN SMEI, ICEGTC, AND GEFS+: ALPHABET SOUP OR EMERGING GENOTYPIC–PHENOTYPIC CLARITY?

Mutations of Sodium Channel α-Subunit Type 1 (SCN1A) in Intractable Childhood Epilepsies with Frequent Generalized Tonic–clonic Seizures

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A group of infant-onset epilepsies manifest very frequent generalized tonic–clonic seizures (GTCs) intractable to medical therapy, which may or may not be accompanied by minor seizures such as myoclonic seizures, absences, and partial seizures. They include severe myoclonic epilepsy in infancy (SMEI) and intractable childhood epilepsy with GTCs (ICEGTC). They are commonly associated with fever sensitivity, family history of seizure disorders, and developmental decline after seizure onset. Mutations of the neuronal voltage-gated sodium channel α-subunit type 1 gene (*SCN1A*) were recently reported in SMEI patients. To clarify the genotypic differences in this group of epilepsies, we searched for *SCN1A* abnormalities in 25 patients with SMEI and 10 with ICEGTC, together with the family members of 15 patients. Frameshift mutations in *SCN1A* were observed in four patients, nonsense mutations in five patients, missense mutations in 21 patients, other mutations in two patients, and no mutation in five patients. SMEI patients showed nonsense mutations, frameshifts, or missense mutations, whereas ICEGTC patients showed only missense mutations. Study of both parents of 11 patients revealed that the mutations in these patients were de novo. However, two mothers had the same missense mutations as their ICEGTC children, and they had generalized epilepsy with febrile seizures plus. Here we suggest that SMEI and ICEGTC represent a continuum with minor phenotypic and genotypic differences.

COMMENTARY

Currents flowing through the family of voltage-gated sodium channels play a critical role in the regulation of neuronal excitability. Fast sodium currents are responsible for action-potential generation, whereas a variety of persistent sodium currents govern subthreshold neuronal excitability. Several anticonvulsants (AEDs), including phenytoin (PHT) and carbamazepine (CBZ), target sodium channels. Therefore it is not surprising that mutations in genes for numerous sodium channel subunits have been described in epilepsies and other disorders of neuronal excitability (1).

In particular, the gene for the voltage-gated sodium channel α-subunit type 1 (*SCN1A*) has been implicated in a rapidly expanding variety of epilepsy syndromes. In generalized epilepsy with febrile seizures plus (GEFS+), mutations in *SCN1A* as well as other sodium channel subunits (e.g., *SCN1B*, *SCN2A*) are found in a high percentage of cases. Two other epilepsy syndromes have been associated with *SCN1A* mutations as well: severe myoclonic epilepsy of infancy (SMEI) and idiopathic childhood epilepsy with generalized tonic–clonic seizures (ICEGTC). These syndromes are both epileptic encephalopathies, afflicting children in the first year of life with recalcitrant seizures and cognitive decline.

SMEI, or Dravet syndrome (for a review, see reference 2), is a particularly refractory brand of childhood epilepsy. Seizures begin in the first year of life, frequently with prolonged febrile status epilepticus. Seizures in SMEI are GTCs or unilateral motor (hemiclonic) episodes; later, other seizure types emerge, such as absence, complex partial, atonic, and myoclonic. After age 1 year, affected children develop motor abnormalities and developmental regression. In a study of seven children with SMEI, Claes et al. (3) found that all seven children had de novo mutations in *SCN1A*. Subsequent studies from Japan have found such mutations in more than 75% of affected children, whereas European and Australian figures hover around 35% (4,5). Half of children with SMEI have a family history of epilepsy, usually mild generalized seizures or a history of febrile seizures. In addition to the de novo cases, familial cases of SMEI associated with *SCN1A* mutations have now been reported (5), suggesting that this disorder is genetically heterogeneous and can be inherited as well as sporadic. In familial cases, the transmitting individuals are asymptomatic or afflicted with less severe epilepsy.

Many of the features of ICEGTC overlap those of SMEI, including age at onset, association with fever, intractability, and cognitive decline (6). Indeed, ICEGTC is considered in

the "borderland" of SMEI. However, in ICEGTC, seizures are predominantly GTC in type, and myoclonic seizures are not present. This article evaluates the hypothesis that SMEI and ICEGTC share molecular genetic features as well as clinical ones.

Fujiwara et al. searched for *SCN1A* abnormalities in 35 patients with SMEI or ICEGTC and also studied family members of some of those patients. *SCN1A* mutations were found in 23 of 25 patients with SMEI and in seven of 10 patients with ICEGTC. Patients with SMEI had missense, nonsense, and frameshift mutations, whereas those with ICEGTC showed only missense mutations. These results support the hypothesis that SMEI and ICEGTC share a common genetic and phenotypic basis, with some minor clinical and genetic differences. Two mothers of children with ICEGTC had missense mutations identical to those of their affected children; the mothers had mild forms of GEFS+. The authors conclude that ICEGTC represents a disorder at the severe end of the GEFS+ spectrum. Whether SMEI shares a position along this continuum is uncertain at present but is supported by the familial *SCN1A* mutations in the study of Nabbout et al. (5). The tendency of seizures (at least initial ones) to occur with fever in each of these syndromes might also implicate the *SCN1A* gene, but fever has not been proven as a necessary or sufficient physiological stimulus.

The reliability of any genotype–phenotype correlation depends on the accuracy of the phenotype assignment. That is, ascertainment bias can alter the ultimate number of cases determined to have the genetic mutation and may account for the widely varying *SCN1A* mutation rates among children with clinically defined GEFS+, SMEI, and ICEGTC.

How do the various *SCN1A* mutations lead to altered neuronal physiology and, hence, to the epilepsy phenotype? Different *SCN1A* mutations seem to alter sodium-channel kinetics in different ways. So far, mutations have been reported to enhance slow inactivation, accelerate recovery from inactivation, and shift the voltage dependence of activation and inactivation. Recent studies, using human *SCN1A* mutant channels transfected into HEK293 cells, showed that the mutant sodium channels bearing SMEI missense or nonsense mutations were markedly deficient in passing sodium current, suggesting a loss of function in the aberrant channels (7). An important remaining goal is to identify molecular pathologies that can be specifically targeted with pharmaceuticals or alternative treatments in these devastating epileptic encephalopathies of infancy associated with *SCN1A* mutations.

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