Translational Research in Epilepsy Genetics

Sodium Channels in Man to Interneuronopathy in Mouse

Saul A. Mullen, MBBS; Ingrid E. Scheffer, MBBS, PhD

Voltage-gated sodium channels are critical for membrane excitability. Mutations in the genes coding for these proteins cause diseases related to altered excitability of cardiac or skeletal muscle and neurons. Mutations in the central nervous system–specific voltage-gated sodium channel α1 subunit gene (SCN1A) lead not only to seizure syndromes but also to familial hemiplegic migraine. The epilepsies range from benign febrile seizures to the catastrophic epileptic encephalopathy of Dravet syndrome (severe myoclonic epilepsy of infancy). Recently developed animal models of SCN1A mutants recapitulate the human disease. These models exemplify the potential inherent in translational research to debunk preconceived ideas regarding pathogenesis by showing the cellular substrate of Dravet syndrome to be interneurons rather than excitatory cells. This illustrates the key role that basic science plays in the development of targeted novel therapies and, ultimately, in the prevention of devastating genetic disorders.


The key role of sodium channel mutations in disease underscores their importance in membrane excitability whether they are located in brain, heart, nerve, or muscle cells (Table). The sodium channel comprises a pore-forming α subunit with auxiliary β subunits that regulate channel function. The sodium channel α1 subunit gene (SCN1A, OMIM *182389) is now the most clinically significant epilepsy gene with mutational analysis serving as a diagnostic test for specific phenotypes. Mutations in SCN1A were first associated with the familial epilepsy syndrome genetic (generalized) epilepsy with febrile seizures plus (GEFS+).1,2 From this beginning, the spectrum of diseases associated with SCN1A now includes severe infantile epileptic encephalopathy, Dravet syndrome, and familial hemiplegic migraine (FHM). Herein, SCN1A-related disorders will be described before discussion of the new SCN1A animal models and the ways they expand our understanding of the pathogenesis of human epilepsy.

GENETIC (GENERALIZED) EPILEPSY WITH FEBRILE SEIZURES PLUS

Unlike most epilepsy syndromes, where the diagnosis is based on a patient’s seizure syndrome in isolation, GEFS+ is diagnosed by the presence of appropriate phenotypes in 2 or more family members.3,4 The GEFS+ phenotypes are childhood-onset seizure syndromes with a strong tendency toward fever-induced seizures, although persistence of occasional generalized or partial seizures into adulthood may occur. The most common GEFS+ phenotypes are febrile seizures (FS) and febrile seizures plus (FS+). The syndrome FS+ is defined by febrile seizures that occur outside the usual age range of 3 months to 6 years or that are intermixed with afebrile convulsions. Both FS and FS+ may be accompanied by myoclonic, absence, and astatic seizures. Other phenotypes, including partial seizures, are seen as part of the GEFS+ spectrum, as are, rarely, the severe childhood epilep-
sies Dravet syndrome, described in the following subsection, and myoclonic-astatic epilepsy. Although the initial description emphasized the generalized nature of the phenotypes that predominate in GEFS+, the more inclusive term genetic epilepsy with febrile seizures plus better expresses the core features of the syndrome.

Genetic (generalized) epilepsy with febrile seizures plus was initially identified through the study of families with evidence of a gene of dominant effect. With the aid of these rare, large families, first the sodium channel α subunit gene (SCN1A) then SCN1A and the γ-aminobutyric acid (GABA) receptor γ2 subunit gene (GABRG2) were isolated as epilepsy genes. \(^5\text{–}^{11}\) SCN1A is the most frequently implicated gene, although it accounts for only a small proportion of families with GEFS+. Most families with GEFS+ show complex inheritance.

SCN1A is also not causative in most febrile seizures in the community. There is a large family with a pure febrile seizures phenotype with an SCN1A mutation, but this phenomenon can be conceptualized as fitting within the spectrum of GEFS+. \(^8\) Sporadic febrile seizures cases have not shown mutations. \(^9\) Similarly, most tested sporadic FS+ cases also have not shown mutations. \(^10\)

**DRAVET SYNDROME (SEVERE MYOCLONIC EPILEPSY OF INFANCY)**

Dravet syndrome is strongly associated with mutations in SCN1A. To comprehend the evolution in the understanding of this syndrome, it is worth reviewing the history of severe myoclonic epilepsy of infancy (SMEI) and SCN1A mutations.

Severe myoclonic epilepsy of infancy was originally described by Charlotte Dravet et al as an epileptic encephalopathy with onset in the first year of life. \(^11\) The classic syndrome starts with prolonged febrile convulsions at approximately 6 months of age. Even if afebrile initially, sensitivity to temperature-induced seizures is usual. Hemiconvulsion with the affected side varying is characteristic, but generalized convulsions and convulsive status epilepticus are also common. Seizures worsen in the second year of life, with multiple seizure types appearing. Myoclonus was required for diagnosis under the original description and usually was accompanied by a variety of complex partial, absence, tonic, and other seizure types. Spasms were not a feature. Development is initially normal but slows in the second year of life. Unlike in many catastrophic childhood epilepsies, the typical progression of findings via electroencephalogram (EEG) is present. Generalized spike and wave appears at approximately 2 years of age. Paroxysmal fast activity and slow spike and wave suggestive of symptomatic generalized epilepsy are not seen. Seizure-related mortality is high in childhood.

SCN1A was investigated in SMEI owing to the strongly fever-related seizures and the high frequency of GEFS+ in patients’ families. \(^4\) Current estimates are that 80% of patients will harbor a causative SCN1A mutation. \(^12\) \(^13\) There are isolated cases of SMEI associated with GABRG2 mutations. \(^14\)

**THE BORDERLANDS OF SMEI**

The term Dravet syndrome is becoming preferred to SMEI because many patients lack features previously regarded as cardinal. Clinically, the absence of myoclonus, a defining feature of SMEI, does not change the prognosis if onset, temperature sensitivity, and the typical changes on the EEG are present. \(^15\) The more important step has been to look at the spectrum of catastrophic infantile-onset epilepsies that carry a similarly high rate of SCN1A mutations.

In a large cohort of SMEI borderland (SMEB) missing 1 or more features of SMEI, 70% were found to still harbor mutations. \(^15\) The key features of seizure onset be-

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**Table. Voltage-Gated Sodium Channel Genes and Associated Diseases**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Product</th>
<th>Expression</th>
<th>Associated Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>α Subunits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN1A</td>
<td>Na,1,1</td>
<td>Central and peripheral nervous system</td>
<td>Epilepsy (GEFS+ and Dravet syndrome), Familial hemiplegic migraine</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Na,1,2</td>
<td>Central nervous system</td>
<td>Epilepsy (benign familial neonatal-infantile seizures)</td>
</tr>
<tr>
<td>SCN3A</td>
<td>Na,1,3</td>
<td>Central nervous system</td>
<td>None known</td>
</tr>
<tr>
<td>SCN4A</td>
<td>Na,1,4</td>
<td>Skeletal muscle</td>
<td>Periodic paralysis, paramyotonia congenita, infantile-onset myasthenia</td>
</tr>
<tr>
<td>SCN5A</td>
<td>Na,1,5</td>
<td>Cardiac muscle</td>
<td>Long QT syndrome (type 3), Brugada syndrome, progressive familial heart block</td>
</tr>
<tr>
<td>SCN6A</td>
<td>Na,1,6</td>
<td>Central and peripheral nervous system</td>
<td>Cerebellar atrophy</td>
</tr>
<tr>
<td>SCN9A</td>
<td>Na,1,7</td>
<td>Peripheral nervous system</td>
<td>Erythermalgia, paroxysmal extreme pain disorder, insensitivity to pain</td>
</tr>
<tr>
<td>SCN10A</td>
<td>Na,1,8</td>
<td>Peripheral nervous system</td>
<td>None known</td>
</tr>
<tr>
<td>SCN11A</td>
<td>Na,1,9</td>
<td>Peripheral nervous system</td>
<td>None known</td>
</tr>
<tr>
<td>SCN1A</td>
<td>Na,2,1</td>
<td>Cardiac, smooth, and skeletal muscle</td>
<td>None known</td>
</tr>
<tr>
<td>SCN1B</td>
<td>β Subunit type 1</td>
<td>Cardiac and skeletal muscle</td>
<td>Epilepsy (GEFS+)</td>
</tr>
<tr>
<td>SCN2B</td>
<td>β Subunit type 2</td>
<td>Central and peripheral nervous systems</td>
<td>None known</td>
</tr>
<tr>
<td>SCN3B</td>
<td>β Subunit type 3</td>
<td>Central nervous system</td>
<td>None known</td>
</tr>
<tr>
<td>SCN4B</td>
<td>β Subunit type 4</td>
<td>Central and peripheral nervous systems</td>
<td>None known</td>
</tr>
</tbody>
</table>

Abbreviations: GEFS+, genetic (generalized) epilepsy with febrile seizures plus; Na, voltage-gated sodium channels.

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tween the ages of 0 and 1 and developmental slowing were present in all these patients (Figure). Overall, the mutation rate in SMEB is similar to that in classic SMEI, as is the prognosis. The previously described intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) also shows a high mutation rate. It is, in essence, Dravet syndrome in which only convulsive seizures occur. The modern limits of Dravet syndrome are not precisely drawn. These disorders are clinically very similar to SMEI and have a similar mutation rate, suggesting that the term Dravet syndrome should encompass all 3 entities.

In a fourth syndrome associated with SCN1A mutations, severe infantile multifocal epilepsy (SIMFE), early onset of partial seizures, and a multifocal EEG reading precede developmental slowing (Figure). Generalized spike and wave is not seen. The developmental slowing may have a later onset than in Dravet syndrome. Although SIMFE is a catastrophic form of childhood epilepsy carrying a high rate of SCN1A mutation, the difference in clinical presentation from Dravet syndrome is significant. Despite the electroclinical differences, the group of SCN1A-associated childhood epileptic encephalopathies shares the features of onset before 1 year of age and initial normal development (Figure). Scattered cases of other syndromes harbor SCN1A mutations. A few myoclonic-astatic epilepsy cases and some idiopathic Lennox-Gastaut syndrome cases are accounted for by SCN1A mutations.

Dravet syndrome remains recognizable into adulthood. Nocturnal generalized tonic-clonic seizures are seen in all reported cases, and focal, myoclonic, and atonic seizures are seen in some. Unlike the more common Lennox-Gastaut syndrome, tonic seizures are generally not seen. Apart from epilepsy, significant intellectual disability is present in almost all patients with Dravet syndrome, as are, variably, cerebellar ataxia, spasticity, and extrapyramidal dystonia. In addition, Dravet syndrome accounts for so-called vaccine encephalopathy, with a retrospective study showing nearly all patients having the clinical features and 11 of 14 having SCN1A mutations.

**TREATMENT OF DRAVET SYNDROME**

The evidence for therapy in Dravet syndrome has recently been systematically reviewed. Freedom from seizures is rarely achieved, but, as Dravet syndrome is an epileptic encephalopathy, aggressive treatment of seizures has the potential to improve cognitive outcome. Two
randomized trials\textsuperscript{12} of the drug stiripentol show a short- term reduction in seizures when combined with sodium valproate and clobazam. Observational evidence\textsuperscript{3} suggests that this reduction is potentially durable. Topiramate, levetiracetam, and the ketogenic diet have observational evidence\textsuperscript{4-6} to support their use. Lamotrigine therapy may worsen seizures in Dravet syndrome, and there are reports\textsuperscript{7,8} of phenytoin sodium use precipitating chorea.

FHM

Familial hemiplegic migraine (FHM) is a dominant condition in which, in addition to migraine with typical aura, patients experience hemiplegia as an aura symptom, often with stupor. Precipitation of attacks with minor head trauma is not uncommon. Two different mutations in SCN1A have been recently described in 4 families with FHM.\textsuperscript{20-22} SCN1A is an uncommon cause of FHM, with most families with identified genes having mutations in either the calcium channel gene CACNA1A or the sodium/potassium pump gene ATP1A2. There is no difference in the headache phenotype between the SCN1A-related cases and those of other patients with FHM. Although there are FS in a few patients with SCN1A-related FHM, overall there does not seem to be significant clinical crossover between GEFS+ and FHM.

SCN1A MUTATIONS

SCN1A is located on the long arm of chromosome 2 in a cluster of voltage-gated sodium channel genes. SCN1A codes for a brain-specific voltage-gated sodium channel (Na\textsubscript{v}) subunit.\textsuperscript{23} Voltage-gated sodium channels consist of a pore-forming \( \alpha \) subunit, of which there are 4 brain-expressed forms, and 2 \( \beta \) subunits. The protein product of SCN1A, Na\textsubscript{v}1.1, is an \( \alpha \) subunit that forms the transmembrane pore through which sodium ions flow. \( \beta \) Subunits act as regulatory elements, altering the voltage sensitivity and subcellular localization. The gene is large, with 26 exons across a 100-kilobase span of the genome.

Mutations in SCN1A-related disease are spread throughout the gene and are rarely repeated.\textsuperscript{12} Rather than a single, ancestral variant, there are multiple “private” mutations. The mutations described in GEFS+ and FHM are single base changes leading to amino acid substitution (missense mutations). Deletions, mutations that grossly alter transcription (nonsense and frame-shift mutations), and mutations that radically alter the preparation of RNA for translation (splice site mutations) are seen in Dravet syndrome but not in GEFS+ or FHM.\textsuperscript{13} Despite this fact, 40% of Dravet syndrome-related mutations are missense rather than the catastrophic sequence changes mentioned previously herein. This means that the discovery of a missense mutation upon testing a child does not guarantee a benign outcome.

Dravet syndrome is largely associated with de novo mutation without detectable abnormality in the parents (95%). When inherited missense mutations occur, they lead to mild GEFS+ phenotypes in the other family members.\textsuperscript{12} These inherited mutations are an uncommon cause of Dravet syndrome.

FUNCTIONAL CONSEQUENCES OF SCN1A MUTATIONS

Voltage-gated sodium channels are responsible for the initial upstroke of the action potential in neurons and other excitable cells.\textsuperscript{23} Depolarization of the membrane produces opening of the channel at the external surface. As the membrane potential rises, a separate inactivation gate on the inner surface of the channel stops ion flow. This inactivation gate then remains closed to produce a refractory period, preventing further voltage-induced opening of the channel. How the channel performs is related to the function of these gates. Voltage sensitivity, current density, and the refractory period may all vary, as may residual current flow after inactivation. When expressed in model cell lines, the Na\textsubscript{v}1.1 protein products of the SCN1A mutations associated with GEFS+ show diverse alterations in their physiologic features.

Most reported GEFS+ mutations seem to increase excitability, although the opposite also has been found. The results for even a single mutation vary between model systems. A good example of this is the GEFS+-associated missense mutation R1648H, which has been studied in 3 in vitro models. Using the homologous region of human SCN4A, it slowed inactivation and accelerated recovery from inactivation.\textsuperscript{24} With rat Scnla and a Xenopus oocyte model, only accelerated recovery was shown.\textsuperscript{23} Human SCN1A co-expressed with SCN1B in a human kidney cell line showed a third pattern of increased persistent current despite inactivation.\textsuperscript{26} It has been suggested that this increased persistent current is the most prevalent finding, but its relevance to in vivo channel function is unclear.\textsuperscript{23} Overall, the alteration in channel kinetics in GEFS+-related mutations is sufficient to support their pathogenicity but not to make conclusions about the mechanism.

The mutations seen in FHM have been modeled using the homologous sequence in the cardiac sodium channel gene SCN5A rather than the SCN1A-derived channel.\textsuperscript{20} Different FHM mutations produce a similar change in kinetics to that seen with the SCN4A model of the GEFS+ mutation R1648H. The fact that mutations with similar sequence and electrophysiologic changes can result in such different phenotypes as GEFS+ and FHM is remarkable.

In a significant proportion of Dravet syndrome–related mutations, no functional protein is produced. The epilepsy due to SCN1A deletion is identical to that caused by transcribed but untranslated messenger RNA.\textsuperscript{13} This result implies that it is the absence of 1 of the 2 copies of the gene (haploinsufficiency) that causes disease, rather than a dominant negative effect. Haploinsufficiency is, however, insufficient as an explanation for all of Dravet syndrome. Missense mutations account for 40% of Dravet mutations and do not always show complete failure of Na\textsubscript{v}1.1 function. For example, the Dravet-associated mutation R1648C has a different change at the same locus as the GEFS+-associated allele R1648H mentioned previously herein. R1648C shows similar persistent current effects in the human SCN1A model as those mentioned previously herein for R1648H.\textsuperscript{27}
Why missense mutations should produce Dravet syndrome rather than GEFS+ in a patient is not known. Modifier genes, in addition to SCN1A, have been suggested as reasons. This explanation would be supported by the finding of an excess of GEFS+ in the families of patients with Dravet syndrome.4 This frequently reported excess of familial seizures has recently been challenged by an Italian group28 whose study results showed no difference in seizure risk in the relatives of patients with Dravet syndrome compared with controls.

SCN1A MICE

Dravet syndrome–associated haploinsufficiency has recently been modeled in mutant mice. These mice provide a means to investigate Na,1.1 function in vivo. This allows the effects of the mutation to be seen at a range of levels, from subcellular localization to cell-type–specific and network behavior in a functioning animal. Any compensatory effects also can be observed.

The mouse model that was published first has the SCN1A homologue deleted, whereas the second uses a nonsense mutation found independently in 3 patients with Dravet syndrome.29,30 Heterozygous mice, in which the genotype is analogous to that of patients with Dravet syndrome, had spontaneous seizures and ataxia beginning in the fourth postnatal week. Spontaneous death from a presumed seizure-related cause was frequent. Heterozygous mutant mice developed seizures and ataxia earlier, during the second postnatal week, and died during the third postnatal week.

Labelling studies in normal rat brains suggest that Na,1.1 makes up less than 15% of the total Na+.31 Na,1.1 is present in the axon hillocks and soma of neurons, including interneurons and pyramidal cells. These studies have not been repeated in mice.

Studies in mutant mice suggest that the contribution of Na,1.1 to the functioning of pyramidal cells is minimal. Instead, in the hippocampus and neocortex, Na,1.1 is critical for GABAergic interneurons. In the heterozygous mutants, there is a 50% loss in sodium current density in interneurons without any change in the kinetics of the channels. This suggests that not only is most sodium current in interneurons due to Na,1.1 but also that interneurons are susceptible to haploinsufficiency of Scn1a. At a neuronal level, interneurons initiated but did not maintain bursts of fast-spiking activity.30 In situ hybridization and immunolabelling also supported Scn1a being most prominently expressed in interneurons. Although an increase in the number of interneurons staining for Na,1.3 suggests that this protein is being upregulated in heterozygotes, the electrophysiologic findings demonstrate that this is inadequate to compensate for the loss of Scn1a.29

A similar specificity to GABAergic neurons is also seen in the cerebellum.32 Purkinje cells are the only output of the cerebellar cortex and they use GABA as a transmitter. Antibodies to Na,1.1 label Purkinje cells strongly. In heterozygote mice, a loss in Purkinje cell sodium current density similar to that in neurocortical interneurons was seen. The GABAergic interneurons in the molecular layer of the cerebellum may also rely on Na,1.1, but this proposition awaits confirmation.30

The mouse findings suggest that Scn1a haploinsufficiency causes a loss of cellular excitability in inhibitory cells. The failure of GABAergic interneurons then produces an increase in overall cortical excitability. In humans, Na,1.1 is present in the cerebral cortex in interneurons and pyramidal cells. Whether a similar Na,1.1 dependence of interneurons in humans exists awaits quantitative cellular studies.

It is also not yet clear how GEFS+- and FHM-related mutations cause disease. Most mutations in both diseases seem to increase rather than decrease membrane excitability in model systems. Whether this effect reverses under in vivo conditions or whether some mechanism other than the interneuronopathy seen with Scn1a haploinsufficiency is present awaits further study.

SCN1A MICE AND MODIFIER GENES

Although the phenotype of homozygous Scn1a mutant mice does not vary with the genetic background, the heterozygote phenotype is markedly dependent on mouse strain. In the deletion model,29 mice from a C57BL/6 background had catastrophic seizures and 80% mortality by 15 weeks of age. Heterozygote mice with the same Scn1a genotype from a 129/SvJ background had no spontaneous seizures. A cross between the 2 strains showed spontaneous seizures, with 40% mortality. Ogiwara et al30 showed similar variability due to genetic background with their nonsense mutation model. The alteration of severity with genetic background has correlates in human disease. Dravet syndrome varies markedly between patients, particularly in developmental outcome. Modifier genes are also thought to be crucial in Dravet mutations inherited from mildly affected parents.13,14

A double-transgenic mouse with Scn1a and Scn8a mutations has been used to look at the question of modifier genes.31 Scn8a codes for Na,1.6, a sodium channel in the peripheral and central nervous systems. Scn8a mutation or deletion in mice affects cerebellar and neuromuscular function in a recessive manner, but also increases seizure threshold to pharmacologically induced seizures. In mice heterozygous for Scn1a and Scn8a mutations, there was a reduction in spontaneous seizures and an increase in seizure threshold that partially compensated for the Scn1a mutation. The magnitude of this effect was less than that of the altered background strain mentioned previously herein, but Scn8a may be part of the group of genes that modify the severity and outcome of Dravet syndrome.

CONCLUSIONS

In the 7 years since mutations in SCN1A were first described, much has been learned about this gene, its related phenotypes, and the pathologic abnormalities of the diseases it causes. Particularly, the understanding of Dravet syndrome has been expanded by the clinical genetics of SCN1A. Recognition of the various presentations of SCN1A-related epileptic encephalopathy is important because it will enable earlier, more aggressive treatment that may improve long-term prognosis. From the perspective of basic science, the development of transgenic mice has produced a model that gives novel and important in-
sights into the pathogenesis of epilepsy. Interneuronopa-
thy offers an unexpected and coherent explanation of
Dravet syndrome in humans associated with haploinsuf-
ficiency and new information for understanding the func-
tion of missense mutations.

Dravet syndrome is a catastrophic disease, and re-
cent advances lead us significantly closer to understand-
ing and effectively treating this condition. Mouse mod-
els, by recapitulating the seizures and motor disturbance of
Dravet syndrome, offer the possibility of major advances in
therapeutics to improve seizure control and develop-
mental outcome.

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script: Mullen and Scheffer. Critical revision of the manu-
script for important intellectual content: Scheffer. Study sup-
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