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SCN8A encephalopathy: Research progress and prospects

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Abstract

On April 21, 2015, the first *SCN8A* Encephalopathy Research Group convened in Washington, DC, to assess current research into clinical and pathogenic features of the disorder and prepare an agenda for future research collaborations. The group comprised clinical and basic scientists and representatives of patient advocacy groups. *SCN8A* encephalopathy is a rare disorder caused by de novo missense mutations of the sodium channel gene *SCN8A*, which encodes the neuronal sodium channel Na_v1.6. Since the initial description in 2012, approximately 140 affected individuals have been reported in publications or by *SCN8A* family groups. As a result, an understanding of the severe impact of *SCN8A* mutations is beginning to emerge. Defining a genetic epilepsy syndrome goes beyond identification of molecular etiology. Topics discussed at this meeting included (1) comparison between mutations of *SCN8A* and the *SCN1A* mutations in Dravet syndrome, (2) biophysical properties of the Na_v1.6 channel, (3) electrophysiologic effects of patient mutations on channel properties, (4) cell and animal models of *SCN8A* encephalopathy, (5) drug screening strategies, (6) the phenotypic spectrum of *SCN8A* encephalopathy, and (7) efforts to develop a bioregistry. A panel discussion of gaps in bioregistry, biobanking, and clinical outcomes data was followed by a planning session for improved integration of clinical and basic science research. Although *SCN8A* encephalopathy was identified only recently, there has been rapid progress in functional analysis and phenotypic classification. The focus is now shifting from identification of the underlying molecular cause to the development of strategies for drug screening and prioritized patient care.

Keywords

Encephalopathy; Bioregistry; Na_v1.6; Sodium channel; Mutation; Drug screening; *SCN8A*

Epilepsy is a common pediatric neurologic disorder, affecting up to 12 patients per 1,000.¹ Pharmacoresistant epilepsies make up 30% of cases and include epileptic encephalopathies (EEs). These severe disorders present in infancy or childhood and are characterized by

multiple seizure types and significant developmental slowing and regression.² The frequent epileptic activity in EE is thought to contribute to cognitive and behavioral impairment. *SCN8A* encephalopathy is a newly defined EE caused by de novo mutations of the gene *SCN8A* encoding the sodium channel Na_v1.6 (OMIM #614558). Most cases result from de novo mutations,³ with the exception of two cases of inheritance from a mosaic parent.^{4,5} The disorder typically presents with developmental epileptic encephalopathy within the first 2 years of life.

SCN8A is one of nine human genes encoding voltage-gated sodium channel α subunits. Mutations of the related genes *SCN1A* and *SCN2A* are responsible for the EEs Dravet syndrome (OMIM #606208) and *SCN2A* encephalopathy (OMIM #613721). *SCN1A*, *SCN2A*, and *SCN3A* are also implicated in a range of milder, self-limited neonatal and infantile epilepsy syndromes.^{6–11} Targeted and genome-wide next-generation sequencing has greatly increased the number of individuals identified with *SCN8A* encephalopathy, allowing researchers to prioritize functional studies and develop an understanding of the phenotypic spectrum.^{12–14}

Mutations of *SCN1A* in patients with inherited epilepsy and the sporadic Dravet syndrome were first identified in 2000 and 2001.^{11,15} Since then, a substantial body of knowledge regarding prognosis, comorbidities, optimal care, and quality of life has become available. In contrast, *SCN8A* encephalopathy was first identified in 2012, and an understanding of the severe impact of *SCN8A* mutations is just beginning to emerge.¹⁶ Awareness of this need, fueled by devoted, caring, and highly informed families, led to the first *SCN8A* research and family advocacy group meeting in Washington, DC, on April 21, 2015. The goal of the meeting was to review current knowledge and identify future needs for patient care groups and clinical investigators. Herein we discuss these efforts and future steps for the *SCN8A* community in advancing toward therapeutic trials and improved outcomes.

Clinical Aspects: Phenotype of *SCN8A* Encephalopathy

The frequency of *SCN8A* mutations in patients with EE was measured in four recent studies that in combination identified 13 cases in 1,157 EE patients.^{4,13,17,18} *SCN8A* mutations thus appear to account for approximately 1% of EE. More than 140 individuals with EE are known to have *SCN8A* mutations, including 50 published and 90 unpublished cases (*SCN8A* Family Group, personal communication, April 2015).^{12,13,16,18–22} The location within the Na_v1.6 channel protein of 31 published *SCN8A* mutations from 50 patients is shown in Figure 1. The number is rapidly growing with the inclusion of *SCN8A* in clinical epilepsy gene panels and the expanded use of whole exome sequencing for diagnostic evaluation of patients with epilepsy syndromes.^{3,13,29}

Within *SCN8A* encephalopathy, individuals have been diagnosed with syndromes including unclassified EE, early infantile EE, and Dravet-like presentation.^{12,13,16,18–22} The mean age of seizure onset for *SCN8A* encephalopathy is 4–5 months, with a range from the first day of life to 18 months, and in utero seizures may be part of the clinical spectrum.^{12,16,19,24–26} Tonic–clonic seizures are often seen at onset, and these are usually not triggered by fever (25 individuals reported).^{12,13,16,18–22} Most of the 50 patients in published series have multiple

seizures types including tonic (21 individuals), absence seizures (10 individuals), myoclonic (10 individuals), focal (6 individuals), clonic (6 individuals), and epileptic spasms (6 individuals).^{12,13,16,18–22} In addition, 11 of the 50 individuals were reported to have convulsive or nonconvulsive status epilepticus.^{12,13,16,18–22} Electroencephalography (EEG) features include diffuse moderate to severe background slowing with focal or multifocal epileptiform abnormalities.¹³ Magnetic resonance imaging (MRI) brain studies are typically normal with a few reports of progressive cerebral atrophy.¹³

The majority of affected individuals have pharmacoresistant seizures and a mixed response to antiepileptic drugs (AEDs).¹³ Several individuals have had a positive response to sodium channel blocking drugs such as valproic acid, phenytoin, carbamazepine, and oxcarbazepine.^{13,20,30} Families have reported both positive and negative responses to some of the more widely used AEDs.

Although development of an infant with *SCN8A* encephalopathy may be delayed from birth, in many cases development is normal prior to seizure onset. After seizure onset, among 50 published cases,^{12,13,16,18–22} development slowed in 29 individuals and regressed in 10 individuals. Intellectual disability was common, and ranged from mild (n = 2) to moderate (n = 15) or severe (n = 23). Motor features included hypotonia (n = 22), ataxia (n = 13), dystonia (n = 6), hyperreflexia (n = 4), and choreoathetosis (n = 4).^{12,13,16,18–22} Eleven individuals had no speech. In some cases, immobility leading to wheelchair dependence developed during disease progression (n = 10). Sudden unexpected death in epilepsy (SUDEP) was reported in five individuals. Most of the published patients are in the first two decades of life.

Comparison of *SCN8A* Encephalopathy with Dravet Syndrome (*SCN1A*) and *SCN2A* Encephalopathy

Three recognized sodium channel gene EEs are caused by mutations in *SCN8A*, *SCN1A* (Dravet syndrome), *SCN2A*, and *SCN8A*.^{11,16,31} The mean age at onset is similar in *SCN8A* encephalopathy and Dravet syndrome, but the variation is broader in *SCN8A* encephalopathy (neonatal period to 18 months of age) compared with Dravet syndrome (neonatal period to 12 months of age). Onset during the first week of life is frequently observed for *SCN2A* encephalopathy.³¹

Although febrile seizures are the hallmark at presentation in the majority of infants with *SCN1A* mutations, they are rare in *SCN8A* and *SCN2A* encephalopathies. Epileptic spasms are not a feature of Dravet syndrome but can occur in *SCN8A* and *SCN2A* encephalopathies. There is an important difference in response to treatment with sodium channel blockers. Patients with Dravet syndrome are well known to respond adversely to carbamazepine and phenytoin, for example, whereas these and other sodium channel blockers may be efficacious in *SCN8A* and *SCN2A* encephalopathies. EEG recordings in Dravet syndrome exhibit generalized spike wave activity as well as multifocal discharges.⁷ In contrast, *SCN8A* and *SCN2A* encephalopathies have predominantly focal and multifocal epileptiform discharges and voltage attenuation during epileptic spasms.³¹

All three sodium channel EEs are associated with a high mortality rate of approximately 10–15% by age 20, based on published reports. The rate of SUDEP in the sodium channel encephalopathies seems to be higher than in other disorders such as *PCDH19* encephalopathy.^{7,31}

As discussed below, most *SCN8A* mutations in EE are missense mutations that cause increased $\text{Na}_v1.6$ channel activity. The same is true for *SCN2A* mutations in EE. In contrast, most *SCN1A* mutations in Dravet syndrome result in reduced $\text{Na}_v1.1$ activity. This fundamental difference in mechanism is likely to explain why sodium channel blockers can be effective for some patients with *SCN8A* encephalopathy, who have an excess of *SCN8A* channel activity, but may exacerbate seizures in Dravet syndrome patients with a deficiency of *SCN1A* channel activity. This difference in drug response is one important reason to prioritize early genetic testing, since the results directly influence patient management.

Characteristics of Sodium Channel $\text{Na}_v1.6$ Encoded by *SCN8A*

SCN8A encodes the sodium channel α subunit $\text{Na}_v1.6$, the current-conducting component of a complex that also contains modulatory β subunits.³² As a member of the voltage-gated sodium (Na_v) channel family, $\text{Na}_v1.6$ has the typical structure with four homologous domains (DI–DIV), each containing six transmembrane segments (S1–S6) (Fig. 1). Voltage sensitivity is provided by positively charged arginine and histidine residues in the four S4 transmembrane segments. The channel “fast-inactivates” through a hingedlid mechanism (internal DIII–DIV linker) that occludes the intracellular mouth of the pore (composed of the S5–S6 segments of all four domains). A second, less well-defined “slow” inactivation mechanism may involve a collapse of the outer mouth of the pore.³³ The unique properties of $\text{Na}_v1.6$ were reviewed recently.²⁹ $\text{Na}_v1.6$ is predominantly expressed in neurons, and is one of the most abundant sodium channels in the central nervous system (CNS). $\text{Na}_v1.6$ is also expressed at a low level in heart.^{34–36} *SCN8A* transcripts are readily detected in prenatal brain. Adult levels of expression and splicing are reached by 1 month in the mouse,^{37,38} and between 1 and 9 years of age in humans.³⁹ Expression of $\text{Na}_v1.6$ is widespread throughout the central and peripheral nervous system in both excitatory and inhibitory neurons.^{29,37} An important aspect of $\text{Na}_v1.6$ biology is its concentration at two specialized membrane domains: the axon initial segment (the site of action potential initiation) and the node of Ranvier (the site of action potential regeneration during axonal saltatory conduction).^{40–46} These localizations of $\text{Na}_v1.6$, and its variable expression in different types of neurons, contribute to the unique features of *SCN8A* channelopathies.

Many biophysical properties of $\text{Na}_v1.6$ resemble the other neuronal Na_v channels, including voltage dependence and kinetics of inactivation and recovery.²⁹ However, $\text{Na}_v1.6$ uniquely generates higher levels of persistent and resurgent current, both of which contribute to repetitive neuronal firing.^{47,48} A working hypothesis for the mechanism of increased seizure susceptibility resulting from *SCN8A* gain-of-function mutations is that mutant $\text{Na}_v1.6$ mediates elevated transient, persistent, and/or resurgent sodium current. This hypothesis is supported by the functional analysis described in a later section, which has demonstrated that many disease-linked mutations directly increase channel activity. This hypothesis is consistent with studies in the mouse indicating that reduced *Scn8a* activity reduces seizure

susceptibility.⁴⁹ One approach to developing new treatments for *SCN8A* epilepsies is therefore to identify drugs that specifically block Na_v1.6. The extensive conservation between Na_v1.6 and the other Na_v channels has made this challenging.

Alternative Splicing and Rare Introns of *SCN8A*

The *SCN8A* gene contains two pairs of alternatively spliced exons that encode transmembrane segments S3 and S4 of domain I and domain III.³⁸ Both of these mutually exclusive exon pairs contain one neonatal (N) and one adult (A) exon. In domain I, the alternative exons differ by a single amino acid. In domain III, the neonatal exon contains an in-frame stop codon that results in protein truncation. Expression of the adult exon with the open-reading frame is restricted to neurons^{38,39} and a low level in heart,³⁵ whereas transcripts containing the in-frame stop codon are widely expressed at a low level in nonneuronal tissues. Another unusual feature of the *SCN8A* gene is the presence of two minor-class introns whose splice sites begin with an AT dinucleotide and end with AC, rather than the major-class GT and AG.⁵⁰ These nonconsensus splice sites influence the pattern of exon skipping that results from mutations in nearby splice sites.⁵⁰

Patient Mutations in *SCN8A* Encephalopathy

Patient mutations of *SCN8A* arise de novo in the affected individual and result in a single amino acid substitution rather than protein truncation. In contrast, the mutations of *SCN1A* in Dravet syndrome also arise de novo, but 60% of mutations cause protein truncation and loss of function. Without functional studies, the effects of amino acid substitutions are not obvious. Software algorithms such as PhyloP,⁵¹ SIFT,⁵² and PolyPhen-2⁵³ provide estimates of pathogenicity based on evolutionary conservation of the substituted amino acid and the chemical difference between the original amino acid and its replacement. Nonetheless, reliable predictions regarding the biophysical consequences of amino acid substitutions are not yet possible. Functional comparisons between wild-type and mutant Na_v channels can be made experimentally, using electrophysiologic patch-clamp experiments, but require extensive laboratory investigation. Ten missense mutations of *SCN8A* have thus far been functionally evaluated for their effect on Na_v1.6 channel activity,^{3,12,16,22,29,54} and eight (80%) resulted in elevated channel activity. Because sodium channels are involved in initiation and propagation of action potentials, elevated sodium channel activity in excitatory neurons can lead to central hyperactivity, the hallmark of seizures. Three functional changes leading to elevated channel activity in the mutated channels are illustrated in Figure 2: premature channel opening, impaired channel closing, and increased persistent current.^{3,12,16,22,29,54} These are classified as “gain-of-function” effects because they produce new channel properties not seen in the wild-type channel. (This is in distinction to “loss of function” mutations that reduce activity, often by protein truncation, as in Dravet syndrome.)

With the relatively small number of mutations analyzed to date, no clear correlation between phenotypic severity and genetic mutation has emerged. Patients with the identical genetic variant can differ in clinical severity, demonstrating an important role of genetic background, and possibly environment, in clinical outcome. For example, the mutation p.Arg1617Gln has been identified in five unrelated patients. This mutation replaces a positively charged

arginine residue with an uncharged glutamine residue in transmembrane segment 4 of domain IV. Functional analysis demonstrated impaired inactivation,⁵⁴ as predicted by the loss of a gating charge in the S4 segment of the domain IV voltage sensor, a region known to influence fast inactivation.^{3,55} The age of seizure onset among the five patients with this mutation varied from 3 to 12 months, the ability to sit without assistance was achieved between 8 and 24 months of age, and the EEG patterns and responses to medication were heterogeneous.³ This type of phenotypic heterogeneity is observed in other genetic epilepsies, for example among mutations of the potassium channel KCNT1.⁵⁶

The *SCN8A* gene contains several hot spots for recurrent mutations (indicated in Fig. 1). The 50 published cases include 19 recurrent mutations each identified in two to five unrelated individuals. Analysis of patients with recurrent mutations may permit identification of the contribution of genetic background and identification of modifier genes.

Mutations of *SCN8A* Can Cause Other Less Severe Disorders

One inherited *SCN8A* mutation with loss of channel function due to protein truncation resulted in moderate intellectual disability without seizures in four related heterozygous carriers.⁵⁷ The proband in this family had ataxic gait and cerebellar hypoplasia. Another mosaic, de novo intragenic deletion of *SCN8A* spanning exons 2–14 was identified in an individual with intellectual disability and absence seizures, but no convulsive seizures. The inherited *SCN8A* variant p.Glu1483Lys was described in three unrelated families with benign infantile seizures, paroxysmal dyskinesia, and normal cognition.⁵⁸ Thus, missense mutations of *SCN8A* can result in less severe disorders than EE.

Distinguishing between pathogenic and nonpathogenic missense variants is a major challenge in interpretation of genetic test results for *SCN8A*. Although most de novo patient mutations are likely to be pathogenic, it is not always the case. For example, the de novo missense mutation p.Asp58Asn in the cytoplasmic N terminus of *SCN8A* did not alter function and may be a nonpathogenic bystander.¹⁹ Several patients have de novo variants that are present in exome databases at low frequencies and may be nonpathogenic. Other missense mutations affect amino acid residues that are not well conserved during evolution, suggesting that they may be nondeleterious. Thus, identification of a de novo *SCN8A* variant in a patient should be followed up with expert interpretation.

iPSC-Derived Neuron Models of *SCN1A* and *SCN8A* Epilepsies

An efficient platform for development of precision therapy based on the electrophysiologic impact of individual mutations may come from induced pluripotent stem cells (iPSCs), reprogrammed from patient-derived skin or blood cells. The generation of neurons from iPSCs has been used in Dravet syndrome to characterize sodium current density using whole-cell voltage- and current-clamp recordings.^{59–61} The use of iPSCs provides a robust modeling tool, permitting the physiologic properties of multiple cell types with identical genotype to be examined. Study of different mutations may yield insight into the influence of a single mutation in different cell types.^{3,54,60} In iPSCs, the mutant channels are expressed in cells with the precise genetic background of the patient, which affords

functional analyses of unparalleled physiologic accuracy. CRISPR/Cas gene editing can be used to generate isogenic control lines with the mutation corrected for comparison. The technique is not without challenges, however, and independent studies have produced different outcomes.^{59–61} Nonetheless, iPSC disease models constitute, at present, the most native and flexible drug-testing platform. iPSCs can also be differentiated into cardiac myocytes, permitting analysis of pathogenic mechanisms that may contribute to SUDEP in *SCN8A* encephalopathy.

Strategies to Screen for Effective Therapies for *SCN8A* Encephalopathy

Existing *SCN8A* cell and mouse models provide an opportunity for early screening in vitro to be followed by in vivo testing based on appropriate evidence. Generation of *SCN8A* mutations in zebrafish may provide another model applicable to drug screening, as for *SCN1A* to model Dravet syndrome.^{62,63} The National Institutes of Health (NIH) Anticonvulsant Drug Development Program at the University of Utah provides a low-throughput but rigorous testing program to narrow down drug selection, accounting for efficacy as well as toxicity and safety issues.⁶⁴ All AEDs that have advanced to clinical trials have passed through this program since its inception in 1975. Surveying libraries of U.S. Food and Drug Administration (FDA)–approved compounds may provide an expedited opportunity for effective and approved therapies for *SCN8A* diseases.

Modeling *SCN8A* Mutations in the Mouse

Mouse models are useful for understanding pathogenic mechanisms as well as evaluation of new treatments emerging from cell-based screening programs. A mouse model carrying the first published patient mutation of *SCN8A* (p.Asn1768Asp) has been described.⁶⁵ These mice recapitulate the seizures, EEG abnormalities, and premature death that were observed in the original patient (Fig. 3).^{14,16} This mutation causes impaired channel inactivation, increased persistent current, and elevated channel activity.¹⁶ In addition to hyperexcitable neurons, the *Scn8a* mutant mice display abnormal firing of ventricular myocytes, suggesting that cardiac arrhythmia may contribute to SUDEP in *SCN8A* encephalopathy (CR Frasier and LL Isom, unpublished data). These mice and additional lines with other patient mutations will be important for preclinical testing of current and novel therapies. Correlating biophysical abnormalities of *SCN8A* mutants with in vivo responses may eventually provide personalized recommendations for treatment of newly diagnosed patients. Many fundamental questions can be addressed with mouse models, such as the impact of gain-of-function *SCN8A* mutations on various classes of neurons and on inhibitory versus general circuits.

Gaps in Bioregistry, Biobanking, and Clinical Outcome Information that Must Be Filled to Become Trial Ready

Building on the emerging molecular understanding of *SCN8A* encephalopathy, there is urgent need to develop clinical platforms for testing the efficacy of interventions. To be “trial ready” for assessing therapies for *SCN8A* encephalopathy, more data on the natural history of the disorder are needed, including a better understanding of the phenotypic spectrum. A

registry of mutations and the associated clinical outcomes will be essential. Comprehensive clinical data will be needed, including data regarding seizure phenotypes, developmental delay, developmental regression, movement disorders, other comorbidities, age at onset of later features, hospitalization rate, efficacy of antiepileptic and other medications, and survival. In combination with genomic studies, such a comprehensive database would also facilitate the systematic identification of modifier genes and pharmacogenetic interactions. Three important areas for development were discussed at the April 2015 meeting: bioregistry, biobanking, and documentation of clinical outcomes.

Bioregistry

Creation of a centralized registry would facilitate the early stages of research into innovative care for *SCN8A*-related disorders, and it will be important to identify long-term support for database maintenance and moderation. A community website hosting a patient-reported registry, modeled on the Patient-centered Outcomes Research Institute-funded *Rare Epilepsy Network* developed for other genetic encephalopathies,⁶⁶ is under development at the University of Arizona (www.SCN8A.net). This website provides information tailored to the interests of three groups: families, health care providers, and researchers. Features include the ability to determine whether an *SCN8A* variant has been previously reported, a directory of physicians who have treated patients with *SCN8A* mutations, and a private forum for families to ask questions and interact. The website includes information about scientific advances in *SCN8A* research, clinical tools developed for other early onset epileptic encephalopathies,⁶⁷ and links to groups such as CURE (<http://www.cureepilepsy.org>). A feature under development is a patient-reported registry that will allow participants to provide consent online and to fill out an extensive questionnaire designed specifically for *SCN8A*-related disorders. New information on clinical features that are shared among children with *SCN8A* mutations has already emerged. Eventually, the data will include a complete curated list of all known *SCN8A* variants, pathogenic or of unknown pathogenicity, with cross-reference to clinical information from individuals carrying those mutations. These data will benefit the physicians treating patients whose molecular test detects a potentially pathogenic *SCN8A* alteration.

Development of a patient registry will also be key to the systematic evaluation of responses of *SCN8A* encephalopathy patients to standard AEDs. To go beyond anecdotal reports, it will be necessary to combine detailed information for a cohort of patients, including clinical status prior to treatment, with precise data on dosage, timing of drug administration, and clinical impact. The frequent use of poly therapy, or combinations of AEDs, remains a confounding feature in sorting out the efficacy of specific AEDs. Lessons may be learned from a recent effort to assess AED effectiveness in a cohort of 58 patients with *PCDH19* mutations based on retrospective reports of caregivers.⁶⁸ With the expansion of early genetic testing, it may become possible in the future to carry out prospective studies of sequential monotherapy that could provide more definitive data.

The benefits of crowd-sourcing for this rare disorder are becoming clear, with the number of patient-reported mutations (n = 140) now exceeding those in the published literature (n = 50). However, a disadvantage of patient-reported registries is the lack of data from medical

records. It may become possible for patients/caregivers to request their records and upload them to a website or send them to the registry. In studies of very rare conditions, highly motivated participants may enroll in multiple studies or registries being conducted by different investigators. Results from these studies may appear to be confirmatory when in fact they are derived from overlapping patient populations.

Biobanking

Biobanking of patient samples with standardized sample collection is another high priority for advancing understanding and therapy for *SCN8A* encephalopathy. In combination with an online registry, collection of high-quality specimens with confirmed *SCN8A* mutations will facilitate the development of genotype/phenotype correlations. Modeling with patient-derived cells, by reprogramming of skin cells and peripheral blood monocytes, has already provided insight into the pathogenic roles of Na_v1.6. In the circumstance of SUDEP, mechanisms will be better investigated by banking tissue, fibroblast cultures, and DNA. As with all biobanking, quality control and making specimens available to the research community will be critical.

Clinical outcomes

Effective recording of clinical outcomes will require better definitions and methods of assessment. To advance the quality of patient self-reporting in clinical research and practice, the NIH has developed PROMIS, the *Patient-Reported Outcomes Measurement Information System*. This initiative is developing new ways to measure patient-reported outcomes (PROs) that impact quality-of-life such as pain, fatigue, physical functioning, emotional distress, and social role participation. Work is needed to develop additional PROs specific to epilepsy. In one such study, Berg and collaborators investigated the outcomes most highly valued by parents of children with epilepsy and found that highest priority was given to seizure freedom and improved cognition.^{69,70} Epilepsy patient support groups are also developing approaches to monitoring outcomes.

Conclusions

Previous experience with Dravet syndrome has demonstrated that understanding a genetic epilepsy syndrome requires more than identification of the molecular etiology. Careful clinical and electrophysiologic phenotyping will be required to reveal the consequences of specific *SCN8A* mutations and to personalize AED choice for patients. In parallel with continuing research on disease mechanisms, the development of robust natural history and outcome measures will be essential to evaluating targeted therapeutics. These data will ultimately reveal whether developmental outcomes can be affected by early intervention and informed choice of AED. With the availability of a mouse model of *SCN8A* encephalopathy and additional models in development, there should be a concerted effort to test the clinically available drugs to identify the agents most likely to be successful in clinical trials. Mouse models can also address fundamental questions such as the impact of a gain-of-function mutation of Na_v1.6 on inhibitory neuronal circuits.

Further efforts will be enhanced by the development of an interface between patients, clinicians, and researchers. Biobanking, and partnership with established epilepsy and *SCN8A* advocacy groups will be important steps. Although *SCN8A* encephalopathy was only recently discovered, important findings from functional studies and phenotypic classification has already shifted the focus from mutation identification to functional analysis and drug screening. These important steps have implications for all parties invested in *SCN8A* encephalopathy, as we work toward reducing the uncertainty that comes with this diagnosis, often obtained after a prolonged diagnostic odyssey.

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Biography



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Key Points

- *SCN8A* encephalopathy was first identified in 2012, and an understanding of the severe impact of *SCN8A* mutations is emerging
- *SCN8A* mutations account for approximately 1% of epileptic encephalopathies overall, >140 individuals have been identified to date
- Distinctive properties of the sodium channel Na_v1.6 include a higher level of persistent and resurgent currents and localization at the axon initial segment (AIS) and nodes of Ranvier
- Distinguishing between pathogenic and nonpathogenic variants is a challenge for interpretation of missense mutations of *SCN8A*
- Rapid progress in functional studies and phenotypic classification has focused current attention on the development of strategies for drug screening and assessment

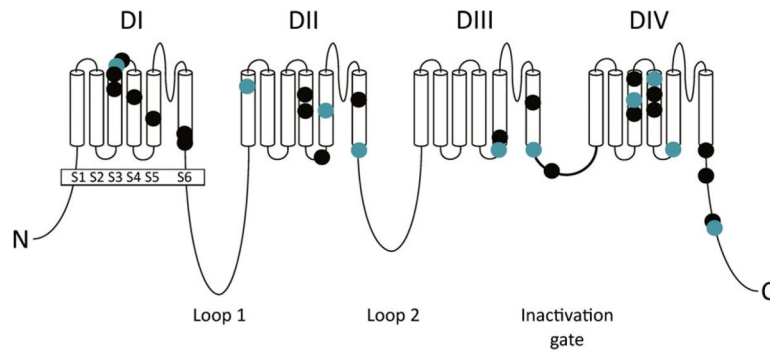


Figure 1.

Locations of missense mutations in *SCN8A* encephalopathy. The $\text{Na}_v1.6$ channel encoded by *SCN8A* is composed of four homologous domains (DI to DIV), each containing six transmembrane segments (S1–S6). The channel also contains intracellular N-terminal and C-terminal domains, two large intracellular loops, and a small intracellular loop between domain III and domain IV, which functions as the inactivation gate. Thirty-one published de novo mutations that were identified in 50 unrelated patients are shown. Pathogenic mutations are concentrated in transmembrane segments and in the N- and C-terminal domains. Black symbols, one patient; blue symbols, recurrent mutations found in multiple patients (Adapted from Wagnon and Meisler³). [Correction added after online publication on June 13, 2016: figure credit changed from Takahashi et al. to Wagnon and Meisler.]

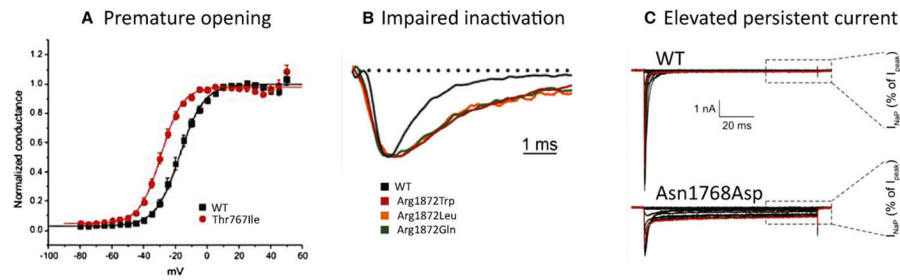


Figure 2.

Effects of gain-of-function mutations in *SCN8A* in patients with epileptic encephalopathy. **(A)** The Thr767Ile substitution in transmembrane segment S1 of domain II causes a hyperpolarizing shift in the voltage dependence of activation, resulting in premature channel opening.²² **(B)** Three mutations of Arg1872 in the cytoplasmic C-terminal domain remove a critical positive charge resulting in delayed channel inactivation.⁵⁴ **(C)** The substitution Asn1768Asp in transmembrane segment S6 of domain IV results in an increase in persistent sodium current that facilitates repetitive firing.¹⁶ [Correction added after online publication on June 13, 2016: reference numbers updated for parts (A), (B), and (C) in the caption.]

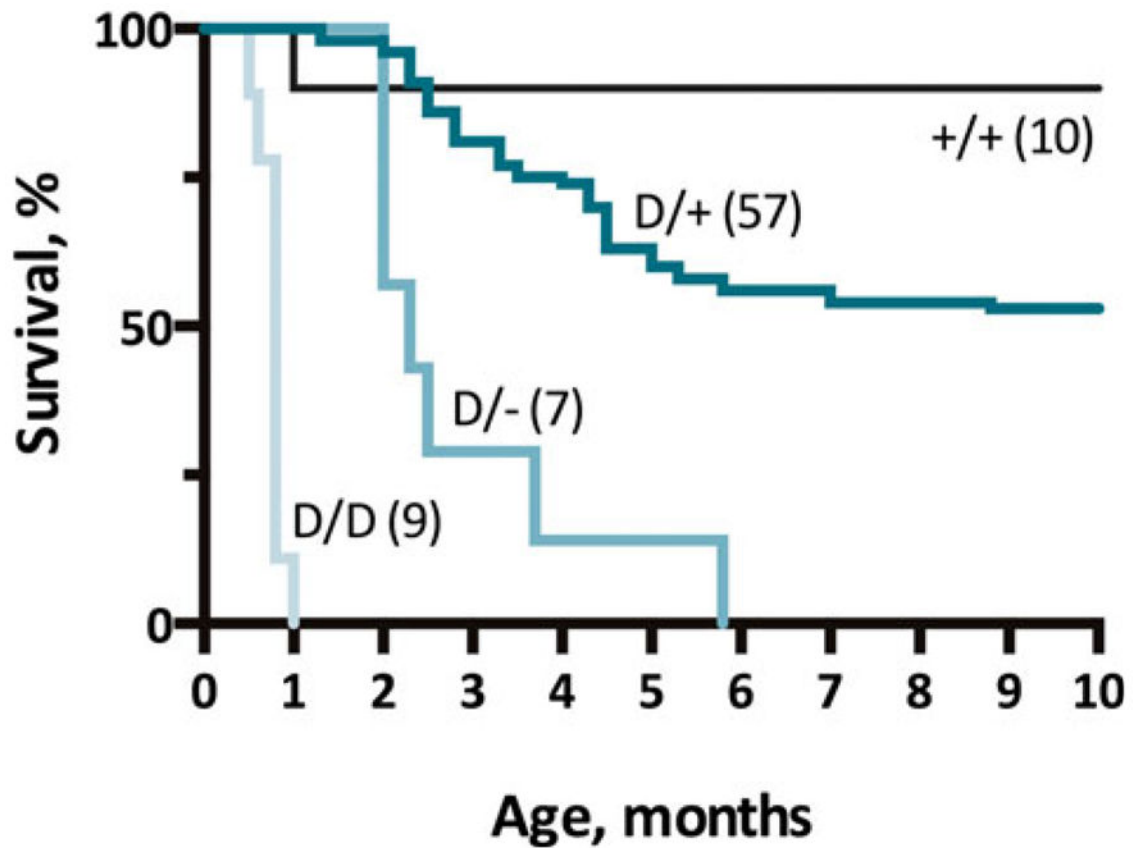


Figure 3.

A mouse model of *SCN8A* encephalopathy generated by knock-in of the patient mutation p.Asn1768Asp (N1768D). Approximately 45% of the heterozygous D/+ mice develop abnormal EEG findings and seizures leading to premature death before 6 months of age. Homozygous D/D mice and hemizygous D/- mice are more severely affected. The number of mice in each group is shown in parentheses (adapted from Wagnon et al.¹⁴). [Correction added after online publication on June 13, 2016: figure credit changed from Takahashi et al. to Wagnon et al.]