TOPICAL REVIEW

# Sodium channel gene family: epilepsy mutations, gene interactions and modifier effects

Miriam H. Meisler, Janelle E. O'Brien and Lisa M. Sharkey

*Department of Human Genetics, University of Michigan, Ann Arbor MI 48109-5618, USA*

**The human sodium channel family includes seven neuronal channels that are essential for the initiation and propagation of action potentials in the CNS and PNS. In view of their critical role in neuronal firing and their strong sequence conservation during evolution, it is not surprising that mutations in the sodium channel genes are responsible for a growing spectrum of channelopathies. Nearly 700 mutations of the *SCN1A* gene have been identified in patients with Dravet's syndrome (severe myoclonic epilepsy of infancy), making this the most commonly mutated gene in human epilepsy. A small number of mutations have been found in *SCN2A*, *SCN3A* and *SCN9A*, and studies in the mouse suggest that *SCN8A* may also contribute to seizure disorders. Interactions between genetic variants of *SCN2A* and *KCNQ2* in the mouse and variants of *SCN1A* and *SCN9A* in patients provide models of potential genetic modifier effects in the more common human polygenic epilepsies. New methods for generating induced pluripotent stem cells and neurons from patients will facilitate functional analysis of amino acid substitutions in channel proteins. Whole genome sequencing and exome sequencing in patients with epilepsy will soon make it possible to detect multiple variants and their interactions in the genomes of patients with seizure disorders.**

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**Corresponding author** M. H. Meisler: Department of Human Genetics, University of Michigan, Ann Arbor, MI 48109-5618, USA. Email: meislerm@umich.edu

**Abbreviations** BFNIS, benign familial neonatal-infantile seizures; GEFS+, generalized epilepsy with febrile seizures plus; SMEI, severe myoclonic epilepsy of infancy.

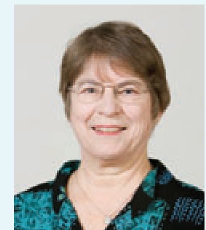
## Introduction

The human genome contains ten paralogous genes encoding the large transmembrane protein that constitutes the pore-forming $\alpha$-subunit of the voltage-gated sodium channel. Two clusters of tandemly duplcated genes are located on chromosomes 2q24 and 3p22, and two single genes are located on chromosomes 12q13 and 17q23 (Fig. 1). All of these genes except *SCN7A* encode proteins that exhibit sodium channel activity in exogenous expression systems. During the evolution of this gene family its members have diverged with respect to tissue-specific expression; the major expression site for each gene is shown in Fig. 2. The basic architecture of the four-domain protein with its 24 transmembrane segments (Fig. 2) is conserved in all family members, and the amino acid sequence identity varies from 50% to 85% between channels. In this review we address the roles of these channels and their mouse orthologues in epilepsy.

## *SCN1A*

Mutations in *SCN1A* encoding the sodium channel Nav1.1 are the most common genetic cause of inherited

**Miriam Meisler** is a geneticist at the University of Michigan who uses mouse mutants to characterize gene function and identify candidate genes for human disorders. In 1997 her lab developed the Q54 mouse expressing a mutant *Scn2a* sodium channel with elevated persistent current. The observation of seizures in the Q54 mouse, together with the linkage of human GEFS+ to chromosome 2q24 containing a sodium channel cluster, led the lab to identify the first mutations of *SCN1A* in 2000. Janelle O'Brien, a graduate student in Human Genetics, and Lisa Sharkey, a neuroscientist and postdoctoral fellow, are studying mutations of *SCN8A* in the Meisler lab.



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and sporadic epilepsy. *SCN1A* mutations were first identified in families with the mild inherited disorder generalized epilepsy with febrile seizures plus (GEFS+) (Escayg *et al.* 2000) and shortly thereafter in sporadic patients with the early onset, severe progressive disorder severe myoclonic epilepsy of infancy (SMEI), also known as Dravet's syndrome (Claes *et al.* 2001). More than 650 heterozygous mutations of *SCN1A* have been identified in patients with SMEI (∼85% of patients tested), and approximately 20 mutations in patients with GEFS+ (∼10% of patients tested). Half of these mutations result in protein truncation, clearly demonstrating haploinsufficiency of *SCN1A* (Meisler & Kearney, 2005; Kearney & Meisler, 2009). The remaining mutations are missense mutations which may cause either gain-of-function or loss-of-function, and only a few have been tested functionally. Interestingly, the GEFS+ mutation R1648H exhibits qualitative abnormalities in exogenous test systems but behaves like a null allele in knock-in mice (Martin *et al.* 2010). Two databases describing published patient mutations are available at http://www.scn1a.info (Lossin, 2009) and http://www.molgen.ua.ac.be/SCN1AMutations/Home (Claes *et al.* 2009).

The extreme heterogeneity of mutations in *SCN1A* is striking. Only a few sites of re-mutation have been observed (Kearney *et al.* 2006*a*); these include demethylation of certain CpG residues in arginine codons and duplication of short runs of simple sequence. The 'common disease/common variant' hypothesis clearly does not apply to *SCN1A* and epilepsy.

To address the mechanism of hyperexcitability resulting from loss of sodium channel activity in an *in vivo* system, four mouse models with null or missense mutations of *Scn1a* have been developed (Table 1). Both null alleles were generated by targeted mutagenesis in embryonic stem

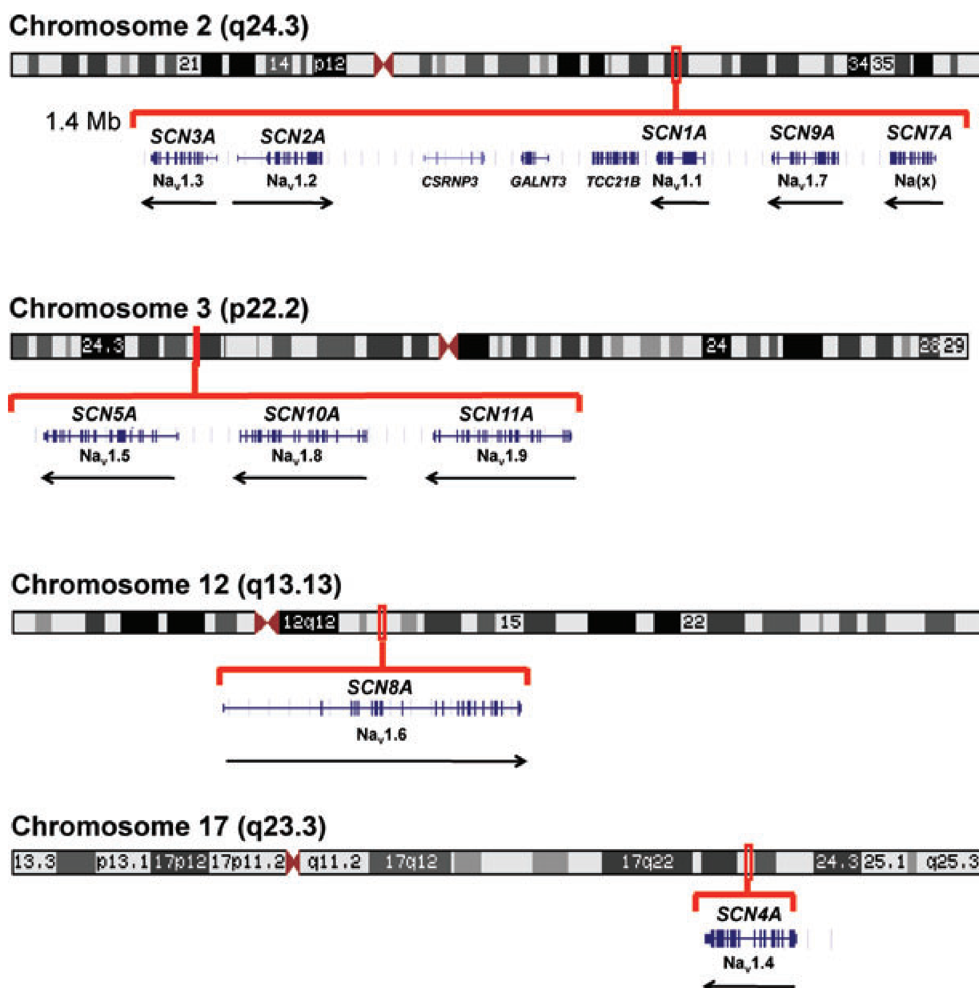


**Figure 1. Genomic arrangement of 10 paralogous human genes encoding α subunits of the voltage-gated sodium channels**

Protein nomenclature is indicated below the gene symbol. Arrows represent the direction of transcription. Data from the UCSC genome browser at www.genome.ucsc.edu

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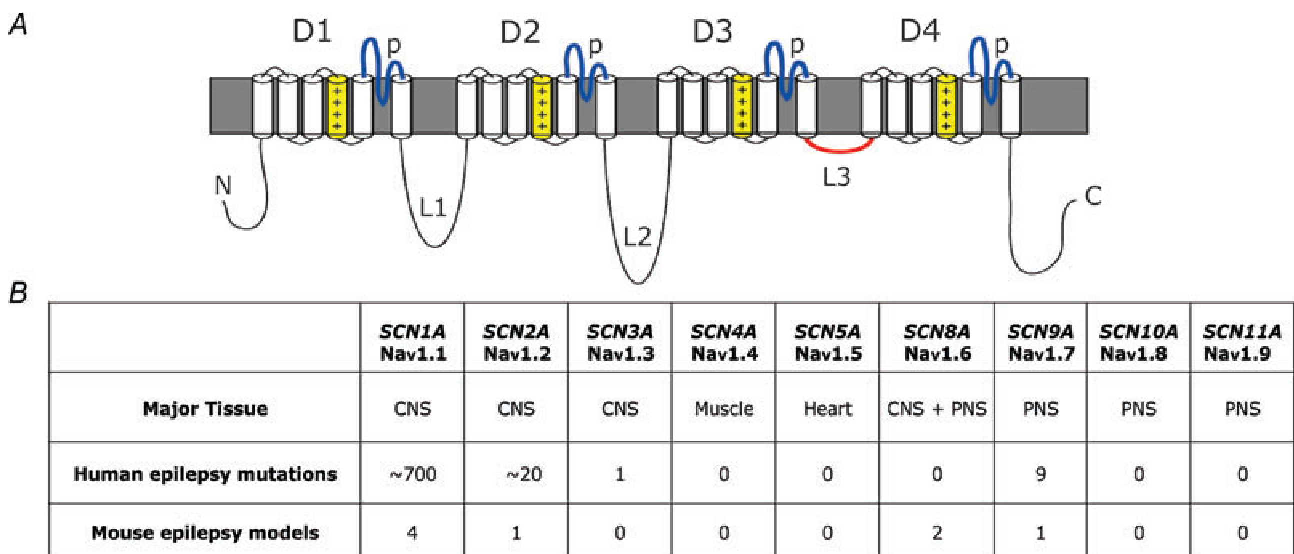
**Table 1. Mouse models of sodium channel mutations and epilepsy**

| Gene | Mutation | Seizure phenotype | Reference |
|---|---|---|---|
| *Scn1a* | Targeted knock-out | Spontaneous tonic and tonic-clonic | Yu *et al.* (2006) |
| *Scn1a* | Targeted knock-out | Spontaneous tonic and tonic-clonic | Ogiwara *et al.* (2007) |
| *Scn1a* | R1648H BAC transgene | Reduced threshold to kainic acid | Tang *et al.* (2009) |
| *Scn1a* | R1648H knock-in | Spontaneous generalized, febrile, flurothyl-induced | Martin *et al.* (2010) |
| *Scn2a* | GAL879-881QQQ transgene ('Q54') | Temporal lobe, spontaneous | Kearney *et al.* (2001, 2006*b*) |
| *Scn3a* | Targeted knock-out | Not reported | Nassar *et al.* (2006) |
| *Scn8a* | V929F/+, −/+ | Spike wave discharge, resistance to induced seizures | Papale *et al.* (2009)<br>Martin *et al.* (2007)<br>Blumenthal *et al.* (2009) |
| *Scn9a* | N641Y knock-in | Reduced threshold, increased corneal kindling | Singh *et al.* (2009) |

(ES) cells (Yu *et al.* 2006; Ogiwara *et al.* 2007). Homozygous null mice exhibit spontaneous seizures and die during the third week of postnatal life. Heterozygous null mice also exhibit spontaneous seizures, but approximately 50% survive to adulthood. Recorded sodium currents from −/− and +/− mice revealed substantial reduction of current density in inhibitory bipolar neurons and cerebellar Purkinje cells, but much smaller effects in excitatory neurons (Yu *et al.* 2006; Kalume *et al.* 2007). This difference between inhibitory and excitatory neurons was also observed in cortical neurons from mice carrying the GEFS+ mutation R1648H (Martin *et al.* 2010). The data from these mouse models indicate that Nav1.1 accounts for a larger proportion of total sodium channel activity in inhibitory neurons than in excitatory neurons and as a consequence the net effect of *Scn1a* mutations is reduced inhibitory signalling. This topic is discussed in detail in the review by Catterall *et al.* in this issue. Independent evidence for the critical role of inhibitory signals in epileptogenesis is provided by the discovery of heterozygosity for null alleles of the $GABA_A$ receptor in epilepsy patients (Kang & Macdonald, 2009).

## Haploinsufficiency of *SCN1A*

The unique haploinsufficiency of *Scn1a* compared with the other sodium channels appears to be a direct consequence of the development of severe seizures in heterozygotes. The dependence of inhibitory neurons on the levels of this specific sodium channel could be a consequence of its subcellular localization, for example its function at the axon initial segment. Deletions that disrupt two or more of the genes in the cluster on chromosome 2q24 have been observed in patients with SMEI (Table 2). The phenotypes of patients with multi-gene deletions are not more severe than patients with loss-of-function of *SCN1A*




| | SCN1A Nav1.1 | SCN2A Nav1.2 | SCN3A Nav1.3 | SCN4A Nav1.4 | SCN5A Nav1.5 | SCN8A Nav1.6 | SCN9A Nav1.7 | SCN10A Nav1.8 | SCN11A Nav1.9 |
|---|---|---|---|---|---|---|---|---|---|
| **Major Tissue** | CNS | CNS | CNS | Muscle | Heart | CNS + PNS | PNS | PNS | PNS |
| **Human epilepsy mutations** | ~700 | ~20 | 1 | 0 | 0 | 0 | 9 | 0 | 0 |
| **Mouse epilepsy models** | 4 | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |

**Figure 2. Tissue specificity and number of reported epilepsy mutations in the 9 functional voltage-gated sodium channel genes**
*A*, conserved domains of the sodium channel $\alpha$-subunit protein. D, homologous domains; p, pore loops; L, inter-domain loops; +, positively charged transmembrane segments contributing to voltage sensing. *B*, major sites of expression of the sodium channel genes and numbers of mutations identified in patients with epilepsy.

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**Table 2. Multi-gene deletions of the sodium channel cluster on chromosome 2q24 identified in patients with SMEI**

| Size of deletion | Genes deleted | No. of patients |
|---|---|---|
| 3 to 9 Mb | *SCN1A*, *SCN7A*, *SCN9A*, *SCN2A*, *SCN3A* | 4 |
| 0.6 to 6 Mb | *SCN1A*, *SCN7A*, *SCN9A* | 9 |
| 0.2 to 0.6 Mb | *SCN1A*, *SCN9A* | 2 |

For details see Pereira *et al.* (2004), Madia *et al.* (2006), Suls *et al.* (2006) and Marini *et al.* (2010).

alone, supporting the view that *SCN1A* is the only channel that is haploinsufficient. This view is also supported by the normal phenotypes of mice that are heterozygous for null alleles of *Scn2a* (Planells-Cases *et al.* 2000), *Scn3a* (Nassar *et al.* 2006) and *Scn9a* (Nassar *et al.* 2004).

## *SCN2A*

Approximately 20 missense mutations of *SCN2A* have been detected in patients with mild seizure disorders including benign familial neonatal-infantile seizures (BFNIS) and GEFS+. More recently, three missense mutations of *SCN2A* were identified in patients with SMEI (Ogiwara *et al.* 2009; Shi *et al.* 2009). The SMEI mutations E211K and I1473M result in hyperpolarizing shifts in voltage dependence of activation, consistent with premature channel opening and hyperactivity (Ogiwara *et al.* 2009). In contrast, the BFNIS mutation R1319Q results in a depolarizing shift in voltage dependence of activity, consistent with reduced activity under physiological conditions (Misra *et al.* 2008). The three BFNIS mutations all exhibited reduced current density, consistent with reduced channel activity (Misra *et al.* 2008). One nonsense mutation in *SCN2A* was identified in a patient with intractable epilepsy and mental decline (Kamiya *et al.* 2004). This mutation, R102X, truncates the channel protein within the cytoplasmic N-terminal domain. The authors reported a dominant negative effect of the N-terminal fragment on activity of the wild-type channel. Taken together, the functional tests of *SCN2A* mutations suggest that the severity of the biophysical effect is correlated with clinical severity. In the mouse, heterozygotes for the *Scn2a* knockout allele were not reported to exhibit seizures (Planells-Cases *et al.* 2000).

A model of temporal lobe epilepsy was generated in the 'Q54' mouse strain that carries a transgene with the gain-of-function missense mutation GAL879QQQ. This three amino acid substitution is located in an intracellular linker in domain 2 and results in elevated persistent current *in vivo* (Kearney *et al.* 2001). Mice carrying the Q54 transgene on a (B6XSJL)F1 strain background exhibit severe spontaneous seizures with onset at 1 month and lethality by 6 months. However, on a pure C57BL/6J background, onset is delayed and the phenotype is mild. Two modifier loci responsible for the difference in severity between strains C57BL/6J and SJL have been mapped, and the evidence points to the voltage-gated potassium channel gene *Kcnv2* as one modifier (Bergren *et al.* 2005; Bergren *et al.* 2009). The Q54 mutation also interacts with another potassium channel, *Kcnq2*. Double heterozygous mice inheriting mild alleles of *Scn2a* and *Kcnq2* exhibit severe myoclonic seizures (Kearney *et al.* 2006*b*). The 'modifier' effect of these potassium channel mutations may be a model for gene interactions underlying human polygenic epilepsies.

## *SCN3A*

A single patient with partial epilepsy and a mutation in *SCN3A* has been described (Holland *et al.* 2008). The proband was heterozygous for the missense mutation K354Q located in the pore loop of domain 1. Functional studies of this lysine to glutamine substitution demonstrated slowing of fast inactivation and increased persistent current. Although SCN3A expression appears to be widespread in human adult brain (Whitaker *et al.* 2000), in rodents the expression of Scn3a is highest in young animals and is low in adults (Felts *et al.* 1997). In a mouse with targeted inactivation of *Scn3a* there were no reported spontaneous seizures (Nassar *et al.* 2006), but the species difference in expression may limit the relevance of the mouse mutant.

## *SCN8A*

A single human family with a null muation of *SCN8A* has been described (Trudeau *et al.* 2006). The four heterozygous carriers of the null allele exhibited cognitive deficits but no history of seizures. EEG studies of the SCN8A heterozygotes were not available. However, three mouse studies implicate *Scn8a* in seizures. First, a missense mutation of *Scn8a* was found to ameliorate the seizure phenotype of *Scn1a* null heterozygotes (Martin *et al.* 2007). The proposed mechanism was that reduction of Nav1.6 in excitatory neurons reduces firing capacity and compensates for the loss of Nav1.1 in inhibitory neurons. In addition, *Scn8a* null heterozygotes were found to be resistant to kainate- or fluorethyl-induced seizures (Martin *et al.* 2007) and were also resistant to kindling by electrical stimulation (Blumenfeld *et al.* 2009).

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Finally, *Scn8a* heterozygous null mice exhibit altered spike wave discharges similar to the interictal patterns seen in seizure-prone mutants (Papale *et al.* 2009). The discharges were responsive to administration of the drug ethosuximide, leading to the suggestion that *SCN8A* might play a role in human absence epilepsy.

### *SCN9A*

The major site of expression of *SCN9A* is in sensory neurons of the PNS, and distinct mutations in this channel are responsible for three inherited pain syndromes (Dib-Hajj *et al.* 2009). It was therefore surprising when the missense mutation N641Y in *SCN9A* was identified in a family with febrile seizures linked to the chromosome 2q24 sodium gene cluster (Singh *et al.* 2009). No mutations in *SCN1A* were found in this family. Furthermore, a knock-in mouse carrying the N641Y mutation exhibited reduced thresholds to electrically stimulated seizures. Several patients with mutations in both *SCN1A* and *SCN9A* were also described, but the relative contributions of the two mutations to the patient phenotype is not yet clear.

### Sodium channel $\beta$ subunit mutations and epilepsy

There are four $\beta$ subunit genes in the human genome, *SCN1B* to *SCN4B*. The $\beta$ subunits are single transmembrane domain proteins that modulate the subcellular localization and properties of the pore-forming $\alpha$ subunits (Isom *et al.* 1992, 1995). The extracellular domain of the $\beta$ subunit also participates in cell–cell interactions (Brackenbury *et al.* 2008). The recent localization of $\beta$ subunits at the action initial segment suggests a mechanism for influence on neuronal excitability (Brackenbury *et al.* 2010). A heterozygous mutation in the extracellular domain of *SCN1B* encoding the $\beta$1 subunit was first identified in a large family with GEFS+ in 1998 (Wallace *et al.* 1998). Several additional mutations have been described in patients with mild epilepsies (Wallace *et al.* 2002; Audenaert *et al.* 2003; Burgess, 2005; Yamakawa, 2005; Scheffer *et al.* 2007). In 2009, the recessive mutation R125C, which prevents trafficking of the $\beta$1 subunit to the cell surface, was identified in a patient with SMEI (Patino *et al.* 2009). Homozygous *Scn1b* knockout mice also exhibit spontaneous seizures (Chen *et al.* 2007), confirming the role of $\beta$1 in epilepsy.

### Genetic interaction between sodium channel mutations and variants in other channels

It is evident that the firing pattern of a neuron is determined by the net 'channelome' expressed in that cell, both qualitative and quantitative. Several examples of interactions between channel variants have recently been described. Kearney *et al.* (2006*b*) combined the Q54 mutation in *Scn2a* (described above) with a subclinical mutation of the potassium channel *Kcnq2* and observed dramatic exacerbation of seizures. Heterozygosity for a null mutation of *Scn8a* can compensate for haploinsufficiency of *Scn1a* (Martin *et al.* 2007). Interactions between mutations of the calcium channel gene *Cacna1a* and the potassium channel gene *Kcna1* have also been described (Glasscock *et al.* 2007). In human epilepsy, a recent report describes modification of the severity of *SCN1A*-related Dravet's syndrome due to co-segregation of mutations in the closely linked *SCN9A* gene (Singh *et al.* 2009). In the future, whole genome sequencing of epilepsy patients will reveal the extent to which gene interaction contributes to common types of human epilepsy.

### Low level expression of neuronal channels in non-neuronal tissues

Sensitive methods like RT-PCR and immunostaining have detected a low level expression of sodium channels in unexpected tissues beyond their major sites of expression. For example, expression of brain sodium channels in heart (e.g. Maier *et al.* 2003) and the heart channel in brain (e.g. Wang *et al.* 2009). It is not clear whether these low level transcripts have specific functions. Many tissues express a low level of an alternative splice form of *SCN8A* containing the exon 18N with an in-frame stop codon that is unlikely to encode an active channel protein (Plummer *et al.* 1997). *In situ* hybridization detects both the full length- and truncation-encoding transcripts, but the functional implications of the two are quite different. One feasible approach to testing the biological function of low-level transcripts to knock out their expression using CRE recombinase in the mouse, but this has not yet been reported.

### Future prospects

In view of their critical role in neuronal excitability, it is not surprising that mutations in the sodium channels genes result in abnormal firing patterns in epilepsy. Although the majority of mutations have been found in the *SCN1A* gene, the data reviewed here suggest that variants in several other sodium channel genes may have a greater role in human disease than is currently recognized. The application of new methods of whole genome sequencing to patients with seizure disorders is likely to replace the screening of individual candidate genes in the future, increasing the likelihood of detecting multiple variants in individual patients. Genetic variants may also influence individual responses to environmental epileptogenic exposures (Heinzen *et al.* 2007).

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Another new tool with considerable promise for the study of channelopathies is the generation of neuronal cells from skin fibroblasts taken from patients (Takahashi & Yamanaka, 2006; Vierbuchen *et al.* 2010). Recent papers describe the generation of neurons from patients with spinal motor atrophy (Ebert *et al.* 2009), amyotrophic lateral sclerosis (ALS) (Dimos *et al.* 2008) and Parkinson's disease (Soldner *et al.* 2009). Applied to epilepsy, this technology will make it possible to assess the effects of channel mutations in the context of all the other variants in the patient's genome, and to record from neuronal cells that will contain tissue-specific accessory proteins and splice factors not available in other test systems. Current limitations include the low yield of some classes of neurons, and the difficulty of assessing circuit-level effects. However, preliminary studies on induced neurons from patients with *SCN1A* mutations have demonstrated that sodium currents from both excitatory and inhibitory neurons can be recorded (unpublished observations). This approach will make it possible to evaluate the inhibitory-neuron hypothesis for *SCN1A* mutations in human neurons and to evaluate drugs for correction of the specific channelopathy expressed in each individual patient.

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## Author contributions

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