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The Contribution of Voltage-Gated Sodium Channels to Inherited Epilepsies

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Abstract
Epilepsy is a common neurological disorder affecting approximately 3 million people in the United States. Epilepsies with unknown origin are attributed to genetic mutations with complex inheritance. Voltage-gated sodium channels are responsible for the initiation and propagation of action potentials and regulate neuronal excitability. Over 700 mutations have been identified in voltage-gated sodium channel genes *SCN1A* and *SCN2A* in human epilepsies, including Genetic (Generalized) Epilepsy with Febrile Seizures Plus (GEFS+) and Dravet Syndrome (or Severe Myoclonic Epilepsy of Infancy). Affected family members with the same mutation display variability in clinical severity of the disease. This suggests that additional genes modify the effect of the primary mutation, resulting in variable clinical presentation. Several mouse models have been generated to study the *in vivo* effects of genetic epilepsies. Many of the seizure phenotypes depend upon the genetic background of the mouse mutant strain, suggestive of genetic modifiers in epilepsy. Several neuronal ion channels have been identified as epilepsy modifier genes in mouse seizure models. Generation of mice with multiple neuronal ion channel mutations has resulted in more severe or ameliorated seizure phenotypes. In support of human epilepsy modifiers, mutations have also been identified in human orthologs of mouse epilepsy modifier genes. Identification of modifier genes that improve or exacerbate epilepsy may increase the understanding of the molecular events of epileptogenesis, advance molecular diagnostic capabilities and identify novel therapeutic targets for improved treatment of human patients.

Keywords: *Epilepsy; Genetics; Modifier Genes; Mouse Models; Voltage-Gated Sodium Channels*

Introduction

Epilepsy currently affects approximately 3 million Americans of all ages and 1% of the worldwide population[1]. Two-thirds of patients diagnosed with epilepsy have no known cause for their disease and in over 30% of patients, seizures cannot be controlled with currently available anti-epileptic drugs[2]. During the past 15 years, extensive research has identified genes that contribute to monogenic epilepsy. These mutations have been identified in genes encoding nicotinic acetylcholine receptors, GABA receptors, chloride, calcium, and voltage-gated potassium and sodium channels[3]. In contrast, less progress has been made identifying genes involved in common, genetically-complex epilepsies.

Voltage-Gated Sodium Channels

Voltage-gated sodium channels are responsible for the initiation and propagation of action potentials and are vital regulators of neuronal excitability. Voltage-gated sodium channel brain complexes were identified as a single α subunit associated with auxiliary β subunits[4]. The α structure contains four homologous domains (D1-D4), each consisting of six α–helical transmembrane segments (S1-S6)[5]. The S4 segments are positively charged and form the voltage sensor of the complex, which initiates channel activation[6-12] (Figure 1). Furthermore, there is evidence of S4/D4 having a unique function in inactivation[5,9,13]. The β subunits (β1-β4) are single transmembrane segments that modulate voltage dependence, kinetics and localization of the α subunits[14,15]. The α subunits primarily expressed in the brain are encoded by *SCN1A*, *SCN2A*, *SCN3A* and *SCN8A*[5,16-18]. *SCN1A* and *SCN3A* channels are located mainly in neuronal cell bodies. *SCN2A* channels are localized to dendrites, unmyelinated or pre-myelinated axons and *SCN8A* channels are found in dendrites and the nodes of Ranvier[19-23].

Voltage-Gated Sodium Channels and Epilepsy

Currently more than 700 mutations in *SCN1A* have been reported in patients with various types of epilepsy, making it the most common cause of monogenic epilepsy. Mutations in voltage-gated sodium channels are responsible for several types of human epilepsy, including Genetic Epilepsy with Febrile Seizures Plus (GEFS+) and Dravet Syndrome (DS), formerly known as Severe Myoclonic Epilepsy of Infancy[3]. GEFS+ is a benign, childhood-onset syndrome with autosomal dominant inheritance (OMIM 604233). This familial syndrome is characterized by febrile seizures that persist beyond six years of age and afebrile, generalized seizure types later in life[24,25]. In 1998, the GEFS+ mutation $SCN1B^{C121W}$ was identified in the β1 subunit gene[26]. The effect of this mutation results in impaired modulation of the sodium channel α subunit[27]. In 1999, linkage analysis of two large families identified a second GEFS+ locus localized to chromosome 2[28,29]. The nonrecombinant interval contains a sodium channel gene cluster that includes *SCN1A, SCN2A, SCN3A* and *SCN9A*. It was found that affected individuals from one family were heterozygous for $SCN1A^{R1648H}$ and affected members from another family were heterozygous for $SCN1A^{T875M}$ [30]. When $SCN1A^{T875M}$ and $SCN1A^{R1648H}$ mutations were heterologously expressed with β1 and β2 subunits, both GEFS+ mutations exhibited noninactivating inward sodium currents[31]. Additionally, single channel analysis of $SCN1A^{R1648H}$ activity revealed mutants had a higher probability of late channel openings[31]. The data suggest that these GEFS+ variants result in gain-of-function mutations caused by defects in sodium channel inactivation, thereby enhancing sodium current. Persistent sodium influx is hypothesized to extend neuronal depolarization, initiate hyper-excitability and increase seizure susceptibility[31].

DS is a disease most frequently associated with mutations of *SCN1A*[32]. Over 70% of reported *SCN1A* mutations have been identified in DS patients[32]. Approximately 90% of *SCN1A* mutations found in DS patients arose *de novo* and nearly half are nonsense, frameshift or splice site mutations that result in protein truncation[3,33,34]. This infant-onset syndrome is characterized by generalized clonic, generalized tonic-clonic or hemiclonic seizures. Although development is normal prior to disease onset, progression is often coupled to a severe decline of psychomotor and cognitive development[35,36]. DS patients develop other types of seizures, including absence and partial seizures and respond poorly to anti-epileptic drugs.

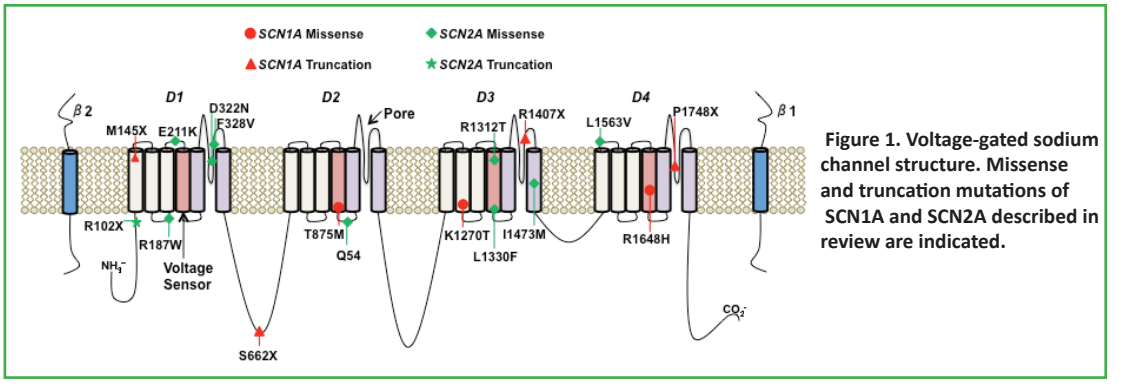

Figure 1. Voltage-gated sodium channel structure. Missense and truncation mutations of SCN1A and SCN2A described in review are indicated.

A smaller number of mutations have been reported in the other neuronal sodium channels *SCN2A, SCN3A* and *SCN9A. SCN2A* is a paralogous sodium channel gene closely linked to *SCN1A* on chromosome 2. Approximately 20 missense mutations in *SCN2A* have been detected in patients with GEFS+, Benign Familial Neonatal-Infantile Seizures (BFNIS) and DS[37]. The GEFS+ missense mutation *SCN2A*^{R187W} results in a delay of channel inactivation, hypothesized to cause persistent sodium current and repetitive firing during depolarization[38]. These abnormalities may be responsible for the hyperexcitability leading to seizures at the neuronal level[38]. BFNIS is characterized by the onset of afebrile generalized seizures typically between 2 days and 3.5 months of life, which spontaneously remit by age one[39]. *SCN2A*^{R1319Q}, *SCN2A*^{L1563V} and *SCN2A*^{L1330F} missense mutations were found in BFNIS patients[40,41]. Biophysical analysis revealed *SCN2A*^{R1319Q} and *SCN2A*^{L1330F} result in loss of channel function, with deficits in activation/inactivation and enhanced use-dependence, respectively[42]. *SCN2A*^{L1563V} impairs fast inactivation, resulting in a depolarizing shift in the voltage dependence[42]. Furthermore, all three mutations display significantly lower levels of protein expression at the cell surface[42]. These *SCN2A* mutants exhibit a wide range of functional abnormalities hypothesized to contribute to seizure generation. Missense mutations *SCN2A*^{D322N}, *SCN2A*^{F328V}, *SCN2A*^{R1312T}, *SCN2A*^{E211K} *and SCN2A*^{I1473M} and the nonsense mutation *SCN2A*^{R102X} were all identified in patients with DS[43-45]. *SCN2A*^{E211K} and *SCN2A*^{I1473M} mutations cause hyperpolarizing shifts in voltage dependence of activation which would be predicted to result in premature channel opening and hyperactivity[44]. The *SCN2A*^{R102X} mutation shifts the voltage dependence of inactivation in the hyperpolarizing direction, which is frequently associated with less channel availability, causing hypoexcitiablity[43]. Only one mutation of *SCN3A* has been identified in epilepsy. The missense mutation *SCN3A*^{K345Q} was found in an individual with partial epilepsy[46]. Functional analysis of *SCN3A*^{K345Q} revealed increased persistent current, decreased current threshold, spontaneous action potentials and paroxysmal depolarizing shift complexes[47]. These abnormalities are suggestive of epileptiform activities.

Variable Expressivity of Sodium Channel Mutations in Epilepsy

A common feature of inherited epilepsy due to sodium channel mutations is that family members who carry the same mutation often display a difference in the clinical severity of the disease. This is seen in both GEFS+ and DS. In a GEFS+ family carrying the *SCN1A*^{R1648H} mutation, four mutation carriers had epilepsy, one carrier had febrile seizures and seven had both[28,30]. Those with epilepsy had varied seizure types, including GTCS, myoclonic, partial, hemiclonic and absence seizures[28,30]. In another GEFS+ family with the *SCN1A*^{K1270T} mutation, 11 family members had only febrile seizures plus and five family members had evidence of temporal lobe epilepsy[48]. In rare cases, DS patients have inherited an *SCN1A* mutation from a mildly affected parent[49-51]. Gennaro and colleagues described a family in which two siblings with DS inherited the *SCN1A*^{P1748fsX1779} mutation from their mother, who had only a single febrile seizure in childhood[50]. Recently, Yu *et al*. identified two *SCN1A* truncation mutations that did not result in DS. Instead, *SCN1A*^{S662X} and *SCN1A*^{M145fsx148} produced GEFS+ and focal seizures, much milder forms of epilepsy not commonly associated with SCN1A truncations[52].

Variable expressivity suggests that other factors besides primary mutations influence the clinical manifestation of epilepsy. Contributing factors may include stochastic events during development, accumulation of somatic mutations throughout a lifetime or environmental insults such as trauma[53]. Variation in inheritance of genetic susceptibility alleles in different family members may also modify the clinical severity of epilepsy.

Epilepsy Models With Sodium Channel Mutations

Several mouse models with seizure-related phenotypes recapitulating GEFS+ and DS have been generated from mutations in voltage-gated sodium channel α subunits. A GEFS+ model was developed by knocking-in the *SCN1A*^{R1648H} mutation into the orthologous mouse gene[54]. To study DS, we have developed a targeted null allele of *Scn1a*, as has the Caterall laboratory[55]. Also, a knock-in of *Scn1a*^{R1407X} has been generated to examine the effects of truncated *Scn1a*[56].

SCN1A^{R1648H} was the first human *SCN1A* GEFS+ mutation studied *in vivo*. *Scn1a*$^{R1648H/R1648H}$ homozygous mice experienced premature lethality by postnatal day 26 (P26)[54]. Behavioral observations revealed both heterozygous and homozygous mutant animals exhibited spontaneous, generalized seizures that were confirmed by electrocorticography (ECoG) recordings[54]. Heterozygous mutants were more susceptible to seizure induction by the chemiconvulsant flurothyl and therefore had reduced times to seizure onset[54]. Flurothyl-induced seizure thresholds returned to wildtype levels after injection of the anticonvulsant valproic acid, commonly used to treat GEFS+ patients, validating the knock-in as a model for GEFS+[54]. Electrophysiological analysis demonstrated that cortical GABAergic bipolar interneurons from heterozygous and homozygous mice had reduced total sodium current amplitudes, increased use-dependence and slower recovery from inactivation[54]. Additionally, homozygous animals had a significant reduction in action potential firing in these interneurons[54]. It is hypothesized that reduced excitability of GABAergic interneurons is a key contributor to seizure generation in the *Scn1a*^{R1648H} GEFS+ model[54].

A DS mouse model was generated by disruption of the *Scn1a* gene. *Scn1a*$^{-/-}$ null mice exhibited spontaneous seizures and ataxia by P9, with premature lethality by P15[57]. *Scn1a*$^{+/-}$ heterozygous mice displayed frequent, spontaneous seizures that were confirmed by ECoG recordings[57]. *Scn1a*$^{+/-}$ heterozygotes experienced sporadic death between P21 and P27, with 40% lethality by the 15th week of life[57]. Electrophysiological analysis from hippocampal GABAergic interneurons revealed a significant reduction of sodium current levels in *Scn1a*$^{+/-}$ heterozygous and *Scn1a*$^{-/-}$ homozygous mice[57]. GABAergic interneurons also exhibited significant decreases in action potential firing, frequency and amplitude in both *Scn1a*$^{+/-}$ heterozygous

and *Scn1a*$^{-/-}$ homozygous mice[57]. These abnormalities are indicative of reduced GABA transmission, a major contributor to neuronal hyperexcitability and seizure generation.

An additional knock-in model of DS was generated with a premature stop codon recapitulating the human *SCN1A*^{R1407X} mutation identified in three unrelated patients[49,56,58,59]. Mice homozygous for the mutation exhibited tonic-clonic seizures confirmed by ECoG starting at P12 and experienced premature lethality by P21[56]. Heterozygous *Scn1a*^{R1407X} mice developed seizures verified by ECoG at P21 with a 40% mortality rate by three months of age[56].

Our laboratory has developed a mouse model with a missense mutation of *Scn2a*, designated *Scn2a*^{Q54}, that resembles an epilepsy phenotype of human patients. The transgenic *Scn2a*^{Q54} mouse has a gain-of-function mutation [GAL(879-881)QQQ], located in the S4-S5 intracellular linker in D2. *Scn2a*^{Q54} mice have a progressive epilepsy phenotype which begins with brief, partial motor seizures[60]. As they age, *Scn2a*^{Q54} mice exhibit more frequent partial seizures, along with secondarily generalized seizures and have a reduced lifespan[60]. Recordings of isolated excitatory hippocampal pyramidal neurons from *Scn2a*^{Q54} mice revealed increased persistent sodium current which is hypothesized to contribute to seizure generation by increasing neuronal hyperexcitability[60]. Functional studies of several human GEFS+ mutations in heterologous expression systems have also shown increased persistent current of similar magnitude[31,61,62]. Hippocampal slice recordings from *Scn2a*^{Q54} mice demonstrated network hyperexcitability during recording of spontaneous and evoked activity, supporting the hypothesis that increased persistent current leads to neuronal hyperexcitability[63].

Genetic Background Influences Epilepsy Models

A common feature of mouse seizure models, including sodium channel mutants, is that seizure frequency and survival vary significantly depending on the genetic background of the mouse, indicative of genetic modifiers in epilepsy. Consequently, these models provide a useful system for identifying modifier genes that may also contribute to variable expressivity in human epilepsy patients. Genes that influence a mutant phenotype can be identified systematically by crossing the mutation onto different background strains. Modifier loci have been mapped for several diseases in human and mouse, including cystic fibrosis, cancer, retinal, cochlear and motor neuron degeneration, aganglionosis, otocephaly, tremor and dystonia[64-71]. Modifier genes have been identified for several of these loci[66,72-77].

Early studies revealed that there were considerable differences in seizure susceptibility dependent on genetic background[78,79]. Ferraro and colleagues demonstrated that genetic factors in C57BL/6J (B6) and DBA/2J (DBA) influence seizure susceptibility, with the B6 strain being far more seizure resistant than the DBA strain to a variety of seizure induction methods[80-85]. Genetic mapping approaches identified *Kcnj10*, an inward rectifying potassium channel, as a candidate gene for seizure susceptibility in these two strains[86-88].

Scn1a$^{+/-}$ heterozygotes on a B6 background have an 80% lethality rate by 13 weeks of age and frequent, spontaneous seizure activity[55]. When *Scn1a*$^{+/-}$ heterozygotes were bred to and maintained on a 129/SvJ background, only 10% of heterozygotes died by 15 weeks and seizure activity was not observed[55]. Loss of *Scn1a* is more severe on the B6 background, suggesting the 129/SvJ background contributes modifier genes that improve the epilepsy phenotype. Similarly, the *Scn1a*^{R1407X} mutation was found to be far less penetrant on the 129/SvJ background[56].

Scn2a^{Q54} mice on a B6 background exhibit a low incidence of seizures, with less than 20% having seizures at three months of age and more than 75% survive beyond six months of age[89]. When B6.*Scn2a*^{Q54} mice are crossed to the SJL/J (SJL) background, the resulting (SJL x B6)F1.*Scn2a*^{Q54} offspring display a high incidence of seizures (>80%) with early onset and only 25% survival to six months of age[89]. This observation indicates the SJL strain contributes dominant modifiers which affect the severity of the epilepsy phenotype[89]. Genetic mapping was performed which identified two modifier loci responsible for the strain difference in *Scn2a*^{Q54} mice: *Moe1* (Modifier of Epilepsy 1) and *Moe2*[89]. The voltage-gated potassium channel *Kcnv2* (Kv8.2) was found to be a strong candidate for *Moe2*[90].

Genetic Modifiers of Epilepsy

The contribution of genetic modifiers in influencing clinical severity is becoming increasingly important for understanding the pathophysiology of inherited disease. Several genes have already been identified in mouse models, which alter seizure phenotype.

Scn8a has been identified as a modifier of DS. The *Scn8a*$^{med\text{-}jo}$ mouse model contains a missense mutation that results in neuromuscular abnormalities, but has increased thresholds to seizure induction[91-96]. When *Scn8a*$^{med\text{-}jo/+}$ heterozygotes were crossed with *Scn1a*$^{+/-}$ heterozygotes to generate double heterozygous mutants, the *Scn8a*$^{med\text{-}jo}$ allele was able to rescue reduced seizure thresholds of *Scn1a*$^{+/-}$ mice and improve their premature lethality[96]. These findings suggest reduced *Scn8a* function can improve the *Scn1a* seizure phenotype.

The calcium channel mutant *Cacna1a*$^{tg/tg}$ recapitulates absence epilepsy and was identified as a modifier of the temporal lobe epilepsy model *Kcna1*. *Kcna1* mutants lack the Kv1.1 α-subunit of the Shaker-type potassium (K^+) channels and therefore the loss of K^+ channel regulation of action potential firing. *Kcna1*$^{-/-}$ null mutants experienced premature lethality with a 26% survival rate to ten weeks of age and frequent, severe, tonic-clonic seizures[97]. When *Cacna1a*$^{tg/tg}$ is crossed to *Kcna1*$^{-/-}$ nulls to generate double homozygous mutants, 87% of animals survived to ten weeks of age[97]. Additionally, double homozygous mutants lacked absence seizures and had a 60% and 80% reduction in tonic-clonic frequency and length of seizure, respectively[97]. The modifier effect is hypothesized to be the reduced neurotransmission of *Cacna1a*$^{tg/tg}$ diminishing *Kcna1*$^{-/-}$ hyperexcitability.

The voltage-gated potassium and sodium channel mutants *Kcnq2*^{V182M} and *Scn1a*^{R1648H} mutants were identified as modifiers of the *Scn2a*^{Q54} seizure model[97,98]. *Kcnq2*$^{V182M/+}$ heterozygous animals have a reduced threshold to seizure induction but no spontaneous seizure activity[99]. When *Kcnq2*$^{V182M/+}$ heterozygotes were combined with *Scn2a*^{Q54}, double heterozygous mutants experienced early-onset, tonic-clonic seizures and juvenile lethality by three weeks of age, unlike their single mutant littermates[100]. When *Scn1a*$^{R1648H/+}$ heterozygotes were combined with *Scn2a*^{Q54}, double heterozygous mutants experienced 100% mortality by P24 and frequent, spontaneous tonic-clonic seizures[98]. These modifier effects demonstrate that neuronal excitability is influenced by the net activity of multiple ion channels[98].

In support of human genetic modifiers in epilepsy, mutations have been identified in *CACNA1A*, *KCNJ10*, *KCNQ2* and *KCNV2* in patients with absence, generalized, BFNIS and partial epilepsies, respectively[101-106].

Conclusion

Genetic epilepsies with complex inheritance likely account for approximately half of all epilepsies with unknown origin[107]. In complex inheritance, each individual gene may have only a small effect on clinical severity of epilepsy, but in combination with other risk genes, the additive effects can be devastating. Mutations in voltage-gated sodium channels are major contributors to genetic epilepsies. *SCN1A* mutations are found in ~70% of DS and ~10% of GEFS+ patients[108]. Among affected family members who possess the same mutation, clinical severity of the disease can be strikingly different. Increasing evidence suggests that other genes are modifying the primary mutation, resulting in a more or less severe phenotype.

Generation of mouse models recapitulating voltage-gated sodium and other neuronal ion channel mutations have allowed for more accurate models of DS, GEFS+, absence and temporal lobe epilepsies. These *in vivo* models are not only beneficial to assess pathophysiological consequences of ion channel mutations, but are also useful for studying the molecular mechanisms of mutations, thereby increasing our understanding of epilepsy.

An increasing amount of evidence has shown that seizure phenotypes from gene mutations are modified by the genetic strain background. Genetic approaches have identified several epilepsy modifier genes in mouse models, including *Cacna1a*, *Kcnj10*, *Kcnq2*, *Kcnv2*, and *Scn8a*. Patient mutations have also been identified in the human orthologs of these genes supporting a role for genetic modifiers in human epilepsy. Identification of modifier genes that improve or exacerbate epilepsy may increase the understanding of the molecular events involved in epileptogenesis, advance molecular diagnostic capabilities and identify novel therapeutic targets for improved treatment of human patients.

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