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# Ion Channels in Genetic Epilepsy: From Genes and Mechanisms to Disease-Targeted Therapies

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**Abstract**—Epilepsy is a common and serious neurologic disease with a strong genetic component. Genetic studies have identified an increasing collection of disease-causing genes. The impact of these genetic discoveries is wide reaching—from precise

diagnosis and classification of syndromes to the discovery and validation of new drug targets and the development of disease-targeted therapeutic strategies. About 25% of genes identified in epilepsy encode ion channels. Much of our understanding of

**ABBREVIATIONS:** ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; CAE, childhood absence epilepsy; EEG, electroencephalography; GEFS<sup>+</sup>, genetic epilepsy with febrile seizures plus; GGE, genetic generalized epilepsy; HCN, hyperpolarization-activated cyclic nucleotide-gated; iPSC, induced pluripotent stem cell; JME, juvenile myoclonic epilepsy; nAChR, nicotinic acetylcholinergic receptor; NMDA, N-methyl-D-aspartate.

**disease mechanisms comes from work focused on this class of protein. In this study, we review the genetic, molecular, and physiologic evidence supporting the pathogenic role of a number of different voltage- and**

**ligand-activated ion channels in genetic epilepsy. We also review proposed disease mechanisms for each ion channel and highlight targeted therapeutic strategies.**

## I. Introduction

Epilepsy, with a lifetime prevalence of 3%, is a common and serious neurologic disease occurring due to either primary genetic determinants or as a consequence of a variety of metabolic and structural disorders of the brain. It is characterized by recurrent seizures resulting from hypersynchronous discharges. Despite optimal treatment with modern antiepileptic drugs, about one third of patients still continue to have seizures, and side effects from these drugs are common. Epilepsy was recognized to have a genetic component as early as 400 BC, when Hippocrates suggested that its origins may lie in heredity. The first gene for genetic epilepsy was identified in 1995 (Steinlein et al., 1995), with discoveries in subsequent decades slowly beginning to unravel the genetic basis of the epilepsies (Reid et al., 2009). More recently, a combination of improvements in gene-screening technologies, the creation of large international consortia, and use of more powerful bioinformatic tools has led to an explosion in the number of genes identified in epilepsy. This has allowed the mechanistic basis of human epilepsy to be probed in a way not previously possible.

### A. General Clinical Principles in Epilepsy

Over 50 epilepsy syndromes are described, and they are broadly divided into focal (formerly partial) and generalized epilepsies based on the concept that the former have seizures generated in a local unilateral network, whereas the generalized epilepsies have seizures generated within bilateral networks. Focal epilepsies more often have a macroscopic structural abnormality as the primary underlying cause. The classification of epilepsy and seizure types has recently been revised (Fisher et al., 2017; Scheffer et al., 2017). Diagnosis begins with seizure type(s), and then, where sufficient electroclinical information is available, an epilepsy type can be defined that may be focal, generalized, combined focal and generalized, or unknown. A further aspect of classification is the epilepsy syndrome based on a combination of epilepsy type, etiology (genetic, structural, infectious, metabolic, immune), and comorbidities (e.g., developmental delay, autism spectrum disorders, intellectual disability).

The broad group of generalized epilepsies is largely comprised of genetic generalized epilepsy (GGE), which is also known as idiopathic generalized epilepsy. These are a family of related syndromes, typically beginning in childhood or adolescence and associated with a characteristic electroencephalography (EEG) pattern of generalized spike-and-wave discharges.

Patients have combinations of absence, myoclonic, and tonic-clonic seizures, and the four classic GGE syndromes are childhood absence epilepsy (CAE), juvenile absence epilepsy, juvenile myoclonic epilepsy (JME), and generalized tonic-clonic seizures alone (Scheffer et al., 2017). Rarer genetic epilepsy syndromes include many epileptic encephalopathy syndromes, with refractory seizures and overall developmental delay (McTague et al., 2016). In this review, we highlight specific epilepsy syndromes associated with mutations in a given gene. Table 1 summarizes the clinical aspects of the epilepsy genes discussed, including their Online Mendelian Inheritance in Man number.

### B. Genetic Architecture of Epilepsy

A clearer picture is emerging of epilepsies as a collection of distinct genetically defined disorders. Many of the early gene discoveries were made in familial epilepsies. Data from large families allowed for genetic linkage, with the subsequently identified pathogenic variant running through affected members like a golden thread. More recent studies suggest that many severe epilepsies beginning in infancy and childhood, especially the developmental and epileptic encephalopathies, are due to de novo mutations (absent in both parents) (Allen et al., 2013).

Somatic mosaicism is a concept that is becoming increasingly relevant in neurologic disease (Poduri et al., 2013). In this case, an individual has at least two cell populations with different genotypes. Improved genetic screening methods have allowed for better detection of mosaicism. Somatic mutations can arise at any time during brain development to cause epilepsy. The pathogenic outcome depends on the proportion and cell types affected. It is important to note that unaffected parents, who are germline mosaics for a pathogenic variant, can pass the mutation onto their affected children. The percentage mosaicism in the parental lymphocyte DNA may reflect their extent of affectedness. This has been shown in studies of Dravet children with inherited *SCN1A* mutations from mosaic parents. Parents who were <45% mosaic were unaffected, whereas those with >45% mosaicism were affected, and the severity of their epilepsy correlated with their percentage mosaicism (Depienne et al., 2010).

In contrast to rare epilepsies, an understanding of the genetic architecture of more common epilepsies has lagged. GGE has a complex inheritance pattern likely caused by a contribution of multiple susceptibility alleles, or de novo mutations in some cases. There is debate as to whether the genetic contribution is largely

TABLE 1  
Ion channel genes mutated in epilepsy, functional impact, and available mouse models

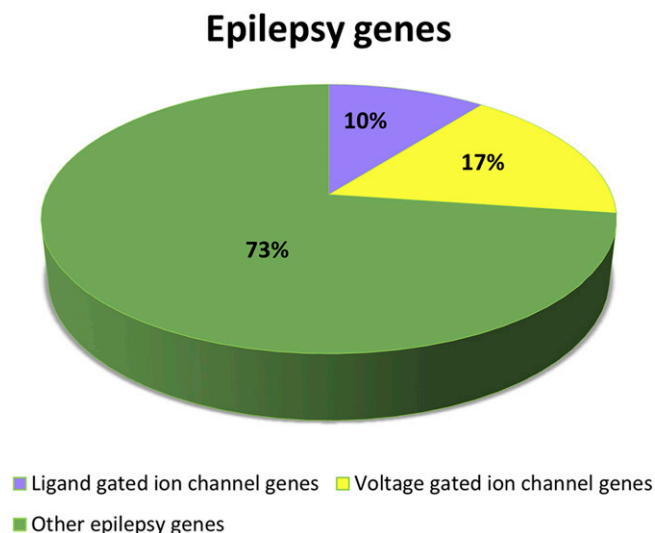
Gene	Protein	Phenotype	OMIM Nr	Functional Impact	Human Mutation-Based Mouse Models
Voltage-Gated					
<i>SCN1A</i>	Nav 1.1	Dravet syndrome; GEFS <sup>+</sup>	182389	LOF	R1407X (Yu et al., 2006); R1648H (Martin et al., 2010) C121W (Wimmer et al., 2010)
<i>SCN1B</i>	Navβ1	GEFS <sup>+</sup> , temporal lobe epilepsy, an early infantile epileptic encephalopathy	600235	LOF	
<i>SCN2A</i>	Nav1.2	BFNIE, early-onset epileptic encephalopathies, neurodevelopmental disorders	182390	GOF LOF	A263V (Schattling et al., 2016)
<i>SCN8A</i>	Na <sub>v</sub> 1.6	BFIE, epileptic encephalopathy	600702	GOF	N1768D (Lopez- Santiago et al., 2017)
<i>KCNA1</i>	K <sub>v</sub> 1.1	Partial epilepsy and episodic ataxia	176260	LOF	V408A (Herson et al., 2003)
<i>KCNA2</i>	K <sub>v</sub> 1.2	Epileptic encephalopathy	176262	GOF LOF	
<i>KCNB1</i>	K <sub>v</sub> 2.1	Epileptic encephalopathy	600397	LOF	
<i>KCNC1</i>	K <sub>v</sub> 3.1	Progressive myoclonus epilepsy	176258	LOF	
<i>KCNMA1</i>	K <sub>Ca</sub> 1.1	Epilepsy and paroxysmal dyskinesia	600150	LOF	
<i>KCNQ2</i>	K <sub>v</sub> 7.2	BFNE, epileptic encephalopathy	602235	GOF LOF	A306T (Singh et al., 2008)
<i>KCNQ3</i>	K <sub>v</sub> 7.3	BFNE	602232	GOF LOF	G311V (Singh et al., 2008)
<i>KCNT1</i>	K <sub>Na</sub> 1.1	ADNFLE, EIMFS	608167	GOF	
<i>KCTD7</i>	KCTD7	Progressive myoclonus epilepsy	611725	LOF	
<i>HCN1</i>	HCN1	<i>IGE</i>	602780	GOF LOF	
<i>CACNA1A</i>	Ca <sub>v</sub> 2.1	Epilepsy, episodic ataxia, epileptic encephalopathy	601011	LOF	
<i>CACNA1H</i>	Ca <sub>v</sub> 3.2	GGE	607904	GOF	
Ligand-Gated					
<i>GRIN1</i>	GluN1	Epileptic encephalopathy	138249	LOF	
<i>GRIN2A</i>	GluN2A	Epileptic encephalopathy	138253	GOF LOF	
<i>GRIN2B</i>	GluN2B	Epileptic encephalopathy	138252	GOF LOF	
<i>GRIN2D</i>	GluN2D	Epileptic encephalopathy	602717	GOF	
<i>GABRA1</i>	GABRA1	GGE, epileptic encephalopathy	137160	LOF	A322D (Arain et al., 2015)
<i>GABRB3</i>	GABRB3	CAE, epileptic encephalopathy	137192	LOF	
<i>GABRG2</i>	GABRG2	FS/GEFS <sup>+</sup> , epileptic encephalopathy	137164	LOF	R43Q (Tan et al., 2007); Q390X (Kang et al., 2015)
<i>CHRNA2</i>	CHRNA2	ADNFLE	118502		
<i>CHRNA4</i>	CHRNA4	ADNFLE	118504	GOF	S252F (Klaassen et al., 2006); +L264 (Klaassen et al., 2006)
<i>CHRN2</i>	CHRN2	ADNFLE	605375	GOF	

BFIE, benign familial infantile epilepsy; BFNIE, benign familial neonatal-infantile epilepsy; EIMFS, epilepsy of infancy with migrating focal seizures; FS, febrile seizures; GOF, gain-of-function; LOF, loss-of-function; OMIM, Online Mendelian Inheritance in Man.

from numerous common variants of small effect, discoverable by Genome Wide Association Studies (International League Against Epilepsy Consortium on Complex Epilepsies, 2014) or from rare variants of larger effect detectable by massively parallel sequencing. Recent evidence argues that a proportion of GGE is contributed to by ultra-rare variants in known epilepsy genes (Epi4K Consortium and Epilepsy Phenome/Genome Project, 2017). To date, rare structural genomic variants, including microdeletions at 15q13.3, 15q11.2, and 16p13.11, are the most common identified genetic risk factors for GGE, considerably increasing genetic risk (Dibbens et al., 2009; Helbig et al., 2009, 2013; de Kovel et al., 2010). There is also increasing evidence for the genetic basis of focal epilepsies, traditionally believed to be due to acquired insults. This was first appreciated in clinical studies of small and large families (Scheffer et al., 1998; Dibbens et al., 2013), but more recently, clear signals from exome-sequencing studies indicate a genetic component to focal epilepsy that falls outside the familial setting (Epi4K Consortium

and Epilepsy Phenome/Genome Project, 2017). Therefore, although it is difficult to establish an exact proportion, it is becoming increasingly clear that genetic factors play a significant pathogenic role in a majority of the epilepsies (Thomas and Berkovic, 2014).

Early gene discovery implicated mostly ion channels and raised the concept that the genetic epilepsies were likely to be a family of channelopathies (Wallace et al., 1998; Reid et al., 2009). Although this concept has evolved, with many biologic pathways now implicated in disease, ion channels still account for a significant proportion of known genetic epilepsies (Fig. 1). As such, there is a rich literature that has begun to unravel the molecular, cellular, and neuronal network mechanisms underlying genetic epilepsy caused by mutations in ion channels. This is laying the foundation for the development of disease-targeted therapy in the genetic epilepsies. In this review, we focus on ion channels as an exemplar of how genetic discoveries have driven basic science, and how the circle back to the clinic is beginning to close (Fig. 2).



**Fig. 1.** Visualization showing the contribution of ion channels to genetic epilepsy.

### *C. A Path for Translational Research in Genetic Epilepsy Caused by Mutations in Ion Channels*

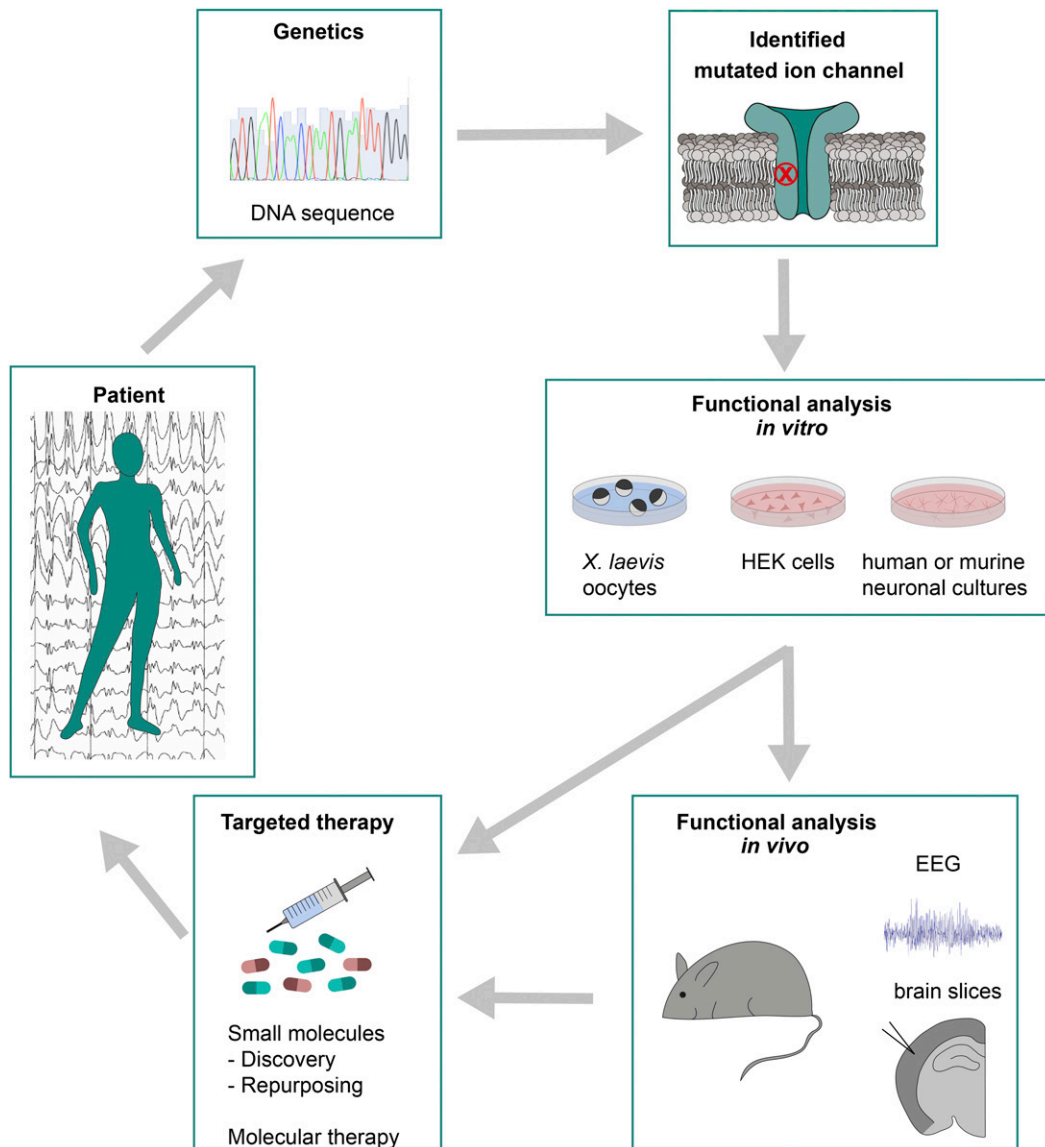
A mutation in a protein can have its impact on both temporal and spatial scales, and understanding the cellular consequence of these changes is central to our understanding, and eventual treatment, of epilepsy. A translational pathway is beginning to develop based on the use of several experimental platforms (Fig. 2). The mainstay of current discovery uses heterologous expression systems, including *Xenopus laevis* oocytes or human embryonic kidney cell models. These platforms have the significant advantage of providing an opportunity to investigate protein function in isolation. Electrophysiological methods provide the gold standard for studying ion channels, giving good signal-to-noise and temporal resolution. Much of what we know about the molecular basis of disease has been developed on these platforms. If mutations in a single gene give rise to a common functional consequence, this provides a strong target for therapy. However, as will become apparent, this is not always the case. It is important to note that these platforms cannot report on the cellular components that drive neuronal hyperexcitability. Ion channels in particular operate in very specialized and interactive temporal and spatial domains. For example,  $\text{Na}^+$  channels work with  $\text{K}^+$  channels in a dynamic manner to generate action potentials. Another important reason that these simple functional assays may not be predictive is that they are opaque to cell compartment-specific trafficking deficits and emerging pathologies. Much mechanistic insight has come from animal models of epilepsy based on genetic manipulation that can, at least partially, overcome these issues.

Genetic rodent models provide a major experimental avenue for dissecting out cellular and neuronal network mechanisms of disease. They also provide invaluable

preclinical tools that can be used to test both targeted precision medicine and general therapeutic approaches. Initially, it is worth stipulating what we require our animal models to deliver for them to serve as valid tools for investigating human epilepsy. A good model of disease would be expected 1) to be based on a known human genetic lesion, 2) to recapitulate the seizure phenotypes represented in the epilepsy patients, including their pharmacosensitivity, and 3) to model comorbidities. For variants that cause definitive loss-of-function, traditional knockout mice can be effective models of disease. However, even in this case, the position that a truncation occurs in a gene can be a critical component of the underlying pathogenic mechanism. For example, truncated protein products expressing functional domains may act in a dominant-negative manner, impacting other proteins to cause disease. As such, the new gold standard in genetic research is to engineer knock-in mice based on human mutations. These syndrome-specific models more often recapitulate the epilepsy phenotypes noted in humans, making them good preclinical models that are ideal for investigating disease mechanisms (e.g., Kearney et al., 2001; Yu et al., 2006; Kalume et al., 2007; Ogiwara et al., 2007; Tan et al., 2007; Oakley et al., 2009; Martin et al., 2010; Wimmer et al., 2010; Kang et al., 2015; Wagnon et al., 2015b).

It is important to note that mice lack the neuronal complexity seen in the primate brain, and that knock-in mouse models do not always recapitulate the human disease. It follows that although these approaches represent the most useful methods we have for identifying the mechanistic causes of genetic epilepsy, we need to continue to develop new methods and models (Maljevic et al., 2017). Induced pluripotent stem cell (iPSC) technology provides an avenue in which neurons can be derived directly from patient tissue. Several recent reports have demonstrated the utility of this approach in neurologic disorders, including epilepsy (Parent and Anderson, 2015; Barral and Kurian, 2016; Sun et al., 2016), suggesting that iPSC-based methods are likely to become an important part of the disease-mechanism discovery toolkit.

In the remaining part of this review, we will outline the genetic, molecular, cellular, and behavioral evidence that is used in identifying mechanisms of disease. A cartoon representing the major epilepsy proteins and where they reside on both excitatory and inhibitory neurons is presented in Fig. 3. Although the molecular mechanisms are discussed in terms of gain- and loss-of-function, we accept that in many cases this represents an oversimplification. More complex distinctions will evolve as models of disease for each gene develop. However, in pragmatic terms, this distinction provides a useful way to represent general principles of disease mechanisms and has already helped in defining disease classes caused by different variants within single genes (Wolff et al., 2017).



**Fig. 2.** Schematic illustrating a path to the development of targeted therapeutic strategies in genetic epilepsy. Genetic screening is identifying large numbers of causative mutations. For ion channels, functional analysis usually involves electrophysiological recordings. Knock-in mice based on human mutations provide good preclinical models on which disease mechanisms can be determined and on which treatments can be tested. This can lead to the development of various targeted therapies that can be based on small molecules or newer molecular techniques.

## II. Voltage-Gated Ion Channels in Epilepsy

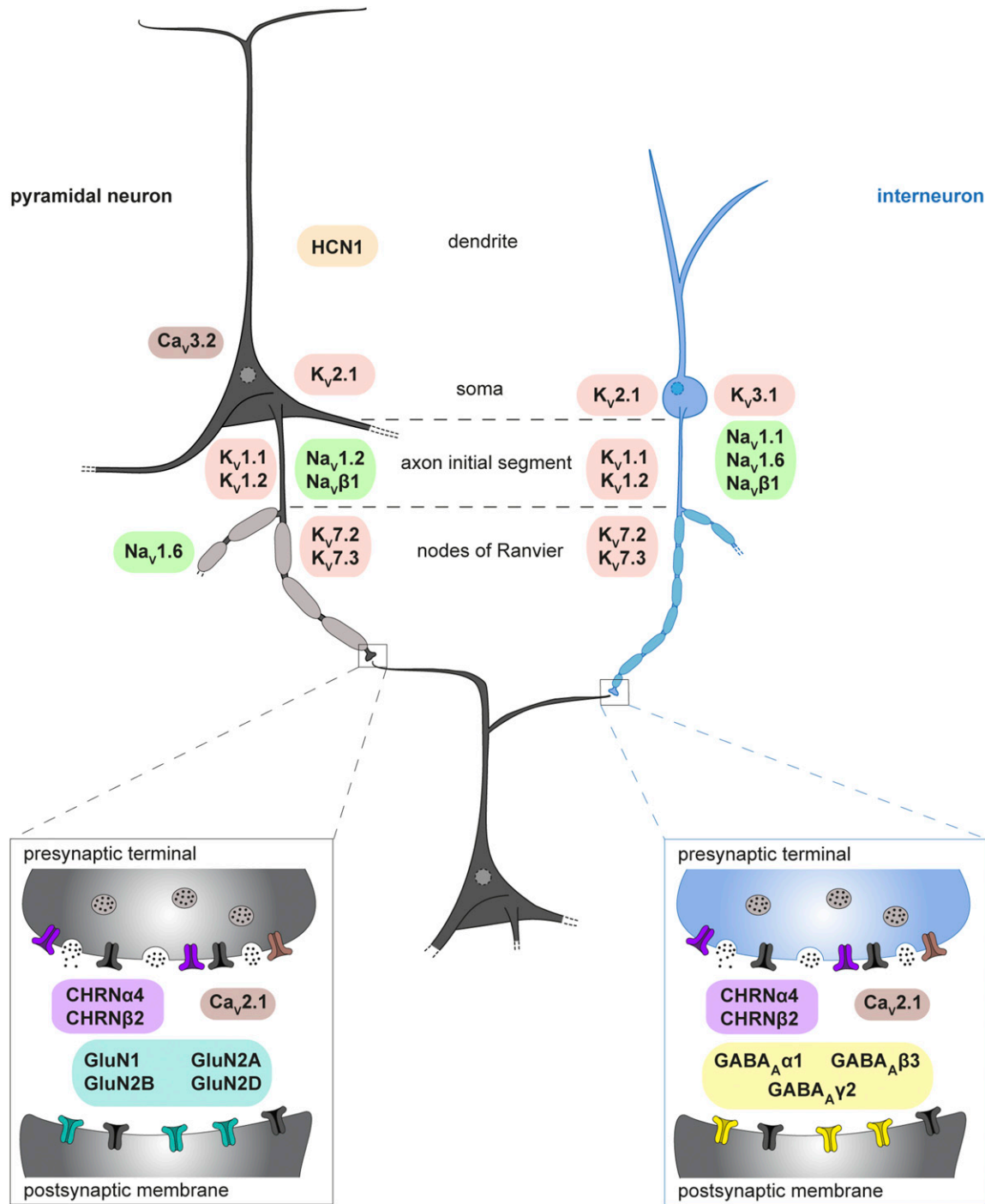
### A. Voltage-Gated $\text{Na}^+$ Channels

The primary role of voltage-gated  $\text{Na}^+$  channels is in the initiation and propagation of action potentials, making them critical determinants of neuronal excitability (Alexander et al., 2015a; [www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=82](http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=82)). Nine genes encode the pore-forming  $\alpha$ -subunits, with four genes encoding the ancillary  $\beta$ -subunits. The  $\alpha$ -subunits have a tetrameric structure comprising four homologous domains (I–IV), each with six transmembrane segments (S1–S6), encoded by a single gene. They are usually associated with one or more  $\beta$ -subunits, transmembrane proteins with a single extracellular loop that influence  $\alpha$ -subunit localization and function (Catterall et al., 2005).

To date, mutations have been identified in three major pore-forming  $\alpha$ -subunits found in the brain, and in one of the  $\beta$ -subunits.

1. **SCN1A.** *SCN1A* encodes the  $\text{Na}_v1.1$  subunit expressed predominantly in inhibitory GABAergic neurons and is enriched at the axon initial segment, implicating a role in the initiation and propagation of action potentials in these cells (Yu et al., 2006; Ogiwara et al., 2007; Duflocq et al., 2008).

a. *Clinical syndrome and molecular findings.* Since first discovered in 2000, several hundred *SCN1A* mutations have been described in epilepsy, making it the most common known epilepsy gene (Oliva et al., 2012). Missense mutations are associated with genetic (previously generalized) epilepsy with febrile seizures



**Fig. 3.** Cartoon illustrating the known expression patterns of ion channels implicated in genetic epilepsy. Gene groups are represented by different colors.

plus (GEFS<sup>+</sup>). This is a familial syndrome in which affected individuals have a variety of epilepsy phenotypes, including febrile seizures, febrile seizures plus, and febrile seizures associated with absence, myoclonic, and even focal seizures. Seizures typically continue into later childhood or adolescence, where they usually resolve (Scheffer and Berkovic, 1997; Singh et al., 1999).

At the more severe end of the GEFS<sup>+</sup> phenotypic spectrum, patients harboring *SCN1A* mutations suffer

from Dravet syndrome (Claes et al., 2001; Harkin et al., 2007; Scheffer et al., 2009; Escayg and Goldin, 2010). This devastating disease begins with prolonged seizures with fever at about age 6 months, followed by multiple seizure types, developmental regression, and gait abnormalities (Scheffer, 2012; McTague et al., 2016). Dravet syndrome usually occurs as a sporadic disorder with de novo mutations. Approximately half the mutations are missense mutations, and half predict



protein truncation with deletions of whole exons, multiple exons, or, more rarely, the whole gene (Claes et al., 2001; Ohmori et al., 2002, 2006; Fujiwara et al., 2003; Nabbout et al., 2003; Kearney et al., 2006; Madia et al., 2006; Mulley et al., 2006; Suls et al., 2006; Marini et al., 2011). Although several biophysical changes that suggest increased channel function have been reported for GEFS<sup>+</sup> *SCN1A* missense mutations (Spampanato et al., 2001, 2004a,b; Cossette et al., 2003; Kahlig et al., 2006), the prevailing view is that loss-of-function is the likely basis of disease in most cases. Indeed, this is self-evident in cases with haploinsufficiency due to truncation variants.

*b. Mechanisms and potential targeted therapies.* The Na<sub>v</sub>1.1 knockout mouse models the loss-of-function mutations suggested by molecular studies (Yu et al., 2006). In some genetic backgrounds, heterozygous mice develop spontaneous seizures and sporadic death, reflecting the severity of the disease in humans. Recordings from this mouse model indicated that, although Na<sup>+</sup> currents were essentially unchanged in hippocampal excitatory pyramidal neurons, the current was substantially reduced in inhibitory GABAergic interneurons. This reduction is responsible for the collapse of action potentials at higher firing frequencies and occurs only in inhibitory neurons (Yu et al., 2006). Similarly, a pronounced action potential attenuation during continuous firing was seen in fast-spiking parvalbumin-positive inhibitory interneurons of heterozygous Na<sub>v</sub>1.1 (R1407X) knock-in mice carrying a truncating mutation (Ogiwara et al., 2007). The Na<sub>v</sub>1.1 (R1648H) mouse model based on a GEFS<sup>+</sup> mutation also had impaired GABAergic interneuron function (Martin et al., 2010; Hedrich et al., 2014). Furthermore, using a conditional mouse model, it was possible to show that the selective deletion of Na<sub>v</sub>1.1 in GABAergic inhibitory neurons was sufficient to cause a Dravet-like phenotype (Cheah et al., 2012). Even though early studies using human iPSC cells from Dravet patients produced mixed results (Higurashi et al., 2013; Jiao et al., 2013; Liu et al., 2013a), more recent work based on differentiating iPSCs into telencephalic excitatory neurons or medial ganglionic eminence-like inhibitory neurons demonstrates an inhibitory neuron deficit (Liu et al., 2016; Sun et al., 2016). Taken together, these data provide convincing evidence that an inability of GABAergic interneurons to fire robustly results in hyperexcitability, leading to seizures in Dravet syndrome.

The Na<sub>v</sub>1.1 knockout-based Dravet mouse models recapitulate many of the pharmacosensitivity profiles seen in patients. A loss of GABAergic inhibitory neuron function may provide a basis for the seizure aggravation properties of Na<sup>+</sup> channel-blocking agents, such as lamotrigine, carbamazepine, and phenytoin, often observed in Dravet syndrome (Guerrini et al., 1998). In this study, the block by these drugs of already compromised

Na<sup>+</sup> channel function in GABAergic interneurons would be expected to further enhance network excitability. Consistent with this, Na<sup>+</sup> channel blockers were not effective or exacerbated seizures in a Na<sub>v</sub>1.1 knockout model of Dravet (Hawkins et al., 2017). The Na<sub>v</sub>1.1 knockout-based Dravet mouse models also respond well to stiripentol and clobazam, which are commonly used as first drugs in this disease (Chiron and Dulac, 2011; Cao et al., 2012; Oakley et al., 2013; Hawkins et al., 2017). This provides confidence in the preclinical value of such mouse models.

Understanding the molecular, cellular, and network consequences of harboring *SCN1A* mutations allows predictive design of targeted therapies. The most obvious strategy would be to selectively enhance Na<sub>v</sub>1.1 function. Peptides with these properties exist (Osteen et al., 2016). Small molecules (AA43279) with the desired properties have also been reported (Frederiksen et al., 2017). Another approach that restores Na<sub>v</sub>1.1 activity is to take advantage of the recently discovered natural regulatory mechanism based on inhibitory long noncoding RNA. Oligonucleotides designed to block this site enhance Na<sub>v</sub>1.1 expression and, at least partially, rescued the seizure phenotype in a mouse model of Dravet (Hsiao et al., 2016). Other strategies could include enhancing GABAergic inhibitory neuron function through secondary mechanisms. For example, the selective activation of K<sub>v</sub>3.1 channels that underlie fast-spiking in certain GABAergic inhibitory neurons may help sustain activity and consequently reduce seizure susceptibility.

A number of strategies that are not disease-targeted based have been tried in mouse models of Dravet. For example, GS967, a drug that preferentially blocks persistent Na<sup>+</sup> current, is very effective in reducing seizures and death in a Na<sub>v</sub>1.1 knockout mouse model (Anderson et al., 2017). These mice could also provide a robust model on which to determine the mechanism of action of newer drugs used in the disease. For example, the amphetamine analog, fenfluramine, has been used with some success in a few Dravet patients, but the mechanistic basis of efficacy remains unknown (Schoonjans et al., 2017). These preclinical rodent models can also be used to inform already completed clinical studies. For instance, cannabidiol has recently been shown to be effective in Dravet syndrome, but its mechanism is unknown; interpretation is confounded by the fact that patients were already on several other antiepileptic drugs (Devinsky et al., 2017). Validated preclinical models provide a mechanism for testing drugs in isolation and/or in combination with other drugs (Hawkins et al., 2017), something that is difficult in humans. In summary, patients with *SCN1A*-based disease are well placed to significantly benefit from disease-targeted therapeutic strategies.

**2. SCN1B.** *SCN1B* encodes the  $\beta$ 1-ancillary subunit of Na<sup>+</sup> channels. The  $\beta$ -subunits are multifunctional,



modulating channel gating, regulating the level of channel expression, and potentially acting as cell adhesion molecules (Isom, 2002). These proteins are found in high abundance in several brain regions and are enriched at axon initial segments and nodes of Ranvier of both excitatory and inhibitory neurons (Wimmer et al., 2015).

*a. Clinical syndrome and molecular findings.* Heterozygous mutations in *SCN1B* that are located mostly in the immunoglobulin-like extracellular domain of the protein have been described in families with GEFS<sup>+</sup> (Wallace et al., 1998; Audenaert et al., 2003; Scheffer et al., 2007). Patients harboring *SCN1B* mutations seem to be at greater risk of developing temporal lobe epilepsy (Scheffer et al., 2007). Also, there are now several reports of *homozygous SCN1B* mutations causing an early infantile epileptic encephalopathy with features that strongly resemble Dravet syndrome (Patino et al., 2009; Ramadan et al., 2017).

Functional analysis has uniformly ascribed a loss-of-function to mutations in *SCN1B* associated with epilepsy (reviewed in Reid et al., 2009; O'Malley and Isom, 2015). However, given that the  $\beta 1$ -subunit is not pore-forming, the consequent impact on neuronal function is more difficult to interpret. Coexpression with other pore-forming  $\alpha$ -subunits suggests that the loss of modulatory action of the  $\beta 1$ -subunit can increase excitability through various biophysical mechanisms, including slowing of inactivation, increased availability of channels at hyperpolarized potentials, and reduction in channel rundown during high-frequency activation (Wallace et al., 1998; Meadows et al., 2002; Thomas et al., 2007; Xu et al., 2007). Protein dysfunction is not limited to altered channel kinetics, with a cell adhesion assay indicting a disruption in the ability of mutated  $\beta$ -subunits to mediate protein–protein interactions (Kruger et al., 2016).

*b. Mechanisms and potential targeted therapies.* The *SCN1B* (C121W) knock-in mouse model is based on a GEFS<sup>+</sup> mutation and recapitulates the febrile seizure phenotype seen in patients (Wimmer et al., 2010; Kruger et al., 2016). A temperature-sensitive increase in axon initial segment excitability was observed, consistent with the exclusion of the mutant protein from this neuronal compartment (Wimmer et al., 2010). It is important to note that a more pronounced febrile seizure phenotype is observed in *SCN1B* (C121W) mice when compared with *SCN1B* knockout mice. This suggests that the *SCN1B* (C121W) epilepsy mutation has an impact over and above simple haploinsufficiency (loss of one allele) that may be related to the  $\beta 1$  protein's adhesion role (Kruger et al., 2016). The multiple biologic roles of  $\beta 1$  make it difficult to devise a therapeutic strategy that would best target heterozygous disease.

Homozygous *SCN1B* variants are associated with severe epilepsy phenotypes (Patino et al., 2009; Ramadan et al., 2017). This is seen in both the homozygous

*SCN1B* knockout (Chen et al., 2004) and the *SCN1B* (C121W) mouse models (Reid et al., 2014), with both having a severe phenotype similar to Dravet syndrome. The homozygous *SCN1B* (C121W) mouse shows a significant reduction in dendritic branching consistent with a defect in  $\beta 1$ -mediated cell–cell adhesion (Chen et al., 2004; Davis et al., 2004; Reid et al., 2014). The contraction of the dendritic arbor increases the electrical compactness of the hippocampal neurons, which results in an increase in the voltage depolarization caused by excitatory synaptic input, increasing both the likelihood of action potential firing and consequently network excitability (Reid et al., 2014). Although it is not feasible to correct the morphologic deficit in the *SCN1B* (C121W) mouse, the addition of the K<sup>+</sup> channel activator, retigabine, is able to reverse the impact on electrical compactness, providing a potential targeted therapy. In keeping with this, retigabine is very effective at reducing febrile seizure susceptibility in the homozygous *SCN1B* (C121W) mouse model of Dravet (Reid et al., 2014).

The severe seizure and comorbid phenotypes observed in both Na<sub>v</sub>1.1 and homozygous *SCN1B* (C121W) knock-in mouse models recapitulate several features of Dravet syndrome, suggesting that both are good models of the disease (Yu et al., 2006; Reid et al., 2014). Comparisons between these models of Dravet highlight an important concept in genetic epilepsy. Genetic heterogeneity is a phenomenon in which a single disease phenotype may be caused by mutations in different genes. As discussed above, mutations in *SCN1A* are the most common genetic cause of Dravet syndrome in which an inhibitory neuron deficit is the well-established disease mechanism. In contrast, no inhibitory neuron deficit is seen in the homozygous *SCN1B* (C121W) mouse model, indicating that two very different cellular mechanisms can underlie the same epilepsy syndrome. This has clear implications for targeted therapy, with different strategies possibly required for the same syndrome depending on the causative gene.

**3. *SCN2A*.** *SCN2A* encodes the Na<sub>v</sub>1.2 subunit that is expressed predominantly in excitatory neurons, particularly in the proximal axon initial segment, where it is proposed to play an important role in promoting back propagation to the soma and dendrites (Westenbroek et al., 1989; Hu et al., 2009).

*a. Clinical syndrome and molecular findings.* For a long time, *SCN2A* mutations were thought to only associate with benign familial neonatal–infantile seizures, a mild, self-limited epilepsy syndrome of the first year of life (Heron et al., 2002; Berkovic et al., 2004; Herlenius et al., 2007). More recently, *SCN2A* has emerged as one of the most prominent epilepsy genes associated with a wide spectrum of seizure and neurodevelopmental phenotypes. These include early-onset epileptic encephalopathies with reported epilepsy syndromes,

including Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), Lennox-Gastaut syndrome, Dravet-like syndrome, as well as unclassified epileptic encephalopathies (Howell et al., 2015; Wolff et al., 2017). Interestingly, *SCN2A* has also emerged as one of the most prominent genes associated with neurodevelopmental disorders, including autism, intellectual disability, and schizophrenia, with most patients carrying truncation mutations not having recognized seizures (Jiang et al., 2013; Iossifov et al., 2014; Sanders et al., 2015; Carroll et al., 2016; Wang et al., 2016; Ben-Shalom et al., 2017). The genotype-phenotype relationship in epilepsy is more complex with both loss-of-function and gain-of-function changes observed. A recent retrospective study that reverse-phenotyped epilepsy patients with *SCN2A* mutations began to dissect this conundrum. A phenotypic classification based on seizure onset, cognitive outcome, and movement disorders revealed that patients carrying gain-of-function mutations show an earlier onset of the disease, more severe seizure phenotype, and better responsiveness to Na<sup>+</sup> channel blockers than the carriers of loss-of-function mutations (Ben-Shalom et al., 2017; Wolff et al., 2017). It is possible that the biophysical measures indicating both loss-of-function and gain-of-function for similar phenotypes are not targeting the critical cellular mechanism of Na<sub>v</sub>1.2 in these disorders. Clarification of this has significant implications for diagnosis, treatment strategies, and mechanistic understanding in diseases associated with *SCN2A* mutations.

*b. Mechanisms and potential targeted therapies.*

The classification of *SCN2A*-related epilepsy into either a gain-of-function or a loss-of-function grouping already has significant implications for targeted therapy. As suggested above, one simple prediction of this finding is that antiepileptic drugs that act as Na<sup>+</sup> channel blockers should have a differential impact on the two populations. Consistent with this, Wolff et al. (2017) show that phenytoin is reasonably effective in ameliorating disease caused by gain-of-function mutations, but less effective, or possibly even exacerbates seizures in patients with loss-of-function mutations (Wolff et al., 2017). These findings strongly argue that biophysical characterization should be part of a complete evaluation of subjects with *SCN2A* mutations. With time, a comprehensive database will develop, meaning that many mutations will be ascribed a functional class. This will significantly aid diagnosis and help devise the best treatment strategy for a given patient.

The finding that both loss and gain of Na<sub>v</sub>1.2 function can cause disease adds complexity to the development of targeted therapy (Ben-Shalom et al., 2017; Wolff et al., 2017). For gain-of-function *SCN2A* mutations, it is reasonable to assume that molecular strategies that reduce protein expression or protein function may be effective. However, in the context of loss-of-function

*SCN2A* mutations, these would be expected to increase seizure susceptibility, as well as exacerbating neurodevelopmental symptoms. A converse argument for strategies based on loss-of-function mutations can be made. This suggests that any approach that directly targets the specific *SCN2A* deficit is likely to have narrow therapeutic windows and will rely heavily on accurate functional diagnosis.

Mouse models, in which emerging pathologies can be discovered, may provide alternative targets based on disease mechanism. The Na<sub>v</sub>1.2 (Q54) transgenic mouse expresses a gain-of-function channel mutation that results in a progressive epilepsy phenotype beginning with spontaneous focal motor seizures that evolve to include bilateral convulsive seizures with age (Kearney et al., 2001). Recordings from hippocampal pyramidal neurons exhibit an enhanced persistent Na<sup>+</sup> current (Kearney et al., 2001). The Na<sub>v</sub>1.2 (A263V) knock-in mouse line, which is homozygous for a mild disease gain-of-function mutation, presents with frequent seizures and increased mortality (Schattling et al., 2016). At the cellular level, current clamp recordings in slices reveal increased excitability in hippocampal pyramidal neurons (Schattling et al., 2016). These mouse lines provide preclinical models of gain-of-function disease. Comparing the genetically different models may also reveal points of mechanistic convergence that could be targeted. For example, if the increase in persistent Na<sup>+</sup> current was evident in both, this would provide a clear target for which strategies already exist (see *SCN8A*).

The Na<sub>v</sub>1.2 knockout mouse model is of interest in light of evidence implicating loss-of-function *SCN2A* mutations in both epilepsy and other neurodevelopmental disease. Initial observations report that heterozygous Na<sub>v</sub>1.2 knockout mice appear normal (Planells-Cases et al., 2000). This suggests that overt seizures are not part of the heterozygous phenotype, although a full behavioral analysis that includes probing neurodevelopmental deficits is clearly needed. Homozygous Na<sub>v</sub>1.2 knockout mice die within 1–2 days of birth. It will be important to develop new knock-in mouse models of loss-of-function disease based on human mutations, which may have impacts over and above simple haploinsufficiency.

**4. *SCN8A*.** *SCN8A* encodes the Na<sub>v</sub>1.6 subunit that is found throughout the adult mammalian brain. Na<sub>v</sub>1.6 is expressed in the distal compartment of the axon initial segment and thought to be important for action potential initiation (Hu et al., 2009). It is also expressed at nodes of Ranvier and is therefore critical to saltatory conduction along myelinated axons (Caldwell et al., 2000; Van Wart et al., 2007; Gasser et al., 2012).

*a. Clinical syndrome and molecular findings.* Heterozygous mutations in *SCN8A* are associated with an epileptic encephalopathy characterized by developmental delay, seizure onset within the first 18 months of life, and intractable epilepsy. These patients have

multiple seizure types, including infantile spasms, generalized tonic-clonic seizures, absences, and focal seizures (Veeramah et al., 2012; Allen et al., 2013; Carvill et al., 2013a; Vaher et al., 2014; Blanchard et al., 2015; Larsen et al., 2015; Takahashi et al., 2015; Wagnon et al., 2015a; Boerma et al., 2016). Mirroring the situation with *SCN1A* and *SCN2A*, where there are both mild and severe phenotypes, very recently there were two reports of familial benign infantile seizures, without cognitive impairment, and some with paroxysmal dyskinesias with missense variants in *SCN8A* (Anand et al., 2016; Gardella et al., 2016).

The majority of mutations in *SCN8A* associated with epileptic encephalopathy are missense mutations. Functional analysis has predominantly identified changes predicting gain-of-function that are likely to increase neuronal excitability. These include incomplete channel inactivation, depolarizing shift in the voltage dependence of steady-state fast inactivation, and hyperpolarizing shifts in the voltage dependence of activation (Veeramah et al., 2012; de Kovel et al., 2014; Estacion et al., 2014; Blanchard et al., 2015; Wagnon et al., 2015a; Barker et al., 2016). One common finding for *SCN8A* variants tested is an increase in persistent  $\text{Na}^+$  current (Estacion et al., 2014), a biophysical property that has been implicated in several epileptic states (Stafstrom, 2007).

*b. Mechanisms and potential targeted therapies.* The heterozygous  $\text{Na}_v1.6$  (N1768D/+) knock-in mouse model recapitulates the seizures, ataxia, and sudden death seen in patients with the mutation, providing a robust preclinical model (Wagnon et al., 2015b; Lopez-Santiago et al., 2017; Sprissler et al., 2017). Consistent with functional analysis in heterologous assays, recordings from excitatory and inhibitory neurons reveal an increase in persistent  $\text{Na}^+$  current. *CA1* excitatory neurons also have unusual depolarizing events that are proposed to be due to a change in the function of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger caused by excessive internal  $\text{Na}^+$  concentrations (Lopez-Santiago et al., 2017).

Although the human genetic evidence is not strong, there is good evidence from animal models that loss of  $\text{Na}_v1.6$  function can also result in nonconvulsive seizures (Papale et al., 2009). Elegant recent work has demonstrated reduced function of inhibitory neurons in the thalamus as the likely basis of increased susceptibility to spike-and-wave discharge seizures (Makinson et al., 2017). Specifically, a reduction in the ability of thalamic reticular nucleus GABAergic neurons to sustain tonic firing results in the disruption of intrathalamic reticular nucleus inhibition, leading to an increase in oscillatory behavior in the thalamus. Interestingly, a pyramidal neuron-specific loss of  $\text{Na}_v1.6$  function is protective against convulsive seizures (Makinson et al., 2017). Reduced  $\text{Na}_v1.6$  function was

also able to ameliorate seizure severity in a *Scn1a* mouse model of Dravet syndrome, suggesting that it could act as a modifier of disease (Martin et al., 2007). This study highlights the importance of understanding the cell-specific impact of epilepsy mutations, allowing insight into not only pathogenic mechanisms, but also the potential adverse impact of any therapeutic intervention.

Mechanistic insights provide a number of potential targeted therapeutic options. In particular, targeting the increased persistent  $\text{Na}^+$  current makes sense. Significantly, GS967 (PRAX-330), a specific blocker of persistent  $\text{Na}^+$  current, extends survival of the  $\text{Na}_v1.6$  (N1768D/+) mouse (Anderson et al., 2014). A further possibility is the use of the persistent  $\text{Na}^+$  current blocker, riluzole, an approved drug that is used to treat amyotrophic lateral sclerosis. Riluzole is effective in blocking the early depolarization events seen in *CA1* pyramidal neurons (Lopez-Santiago et al., 2017), but as yet there is no published evidence of its efficacy in the  $\text{Na}_v1.6$  (N1768D/+) mouse. Patel et al. (2016) have also demonstrated that increased persistent current of  $\text{Na}_v1.6$  mutant channels can be preferentially reversed with cannabidiol. Another strategy could be to block the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger that is implicated in the disease mechanism (Lopez-Santiago et al., 2017). Approved drugs, including amiodarone (Watanabe and Kimura, 2000), bepridil (Watanabe and Kimura, 2001), aprindine (Watanabe et al., 2002), and cibenzone (Yamakawa et al., 2012), have been found to have inhibitory actions on the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger, potentially providing repurposing opportunities. Finally, given the gain-of-function observed with the majority of *SCN8A* epilepsy mutations, developing molecular knockdown strategies may be beneficial. It is worth noting that these knockdown strategies could potentially result in an increase in susceptibility to non-convulsive spike-and-wave seizures (Makinson et al., 2017).

## B. Voltage-Gated $\text{K}^+$ Channels

$\text{K}^+$  channels are the most diverse group of ion channels, playing important roles in a myriad of cellular processes (Alexander et al., 2015a; <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=81>). They can be classified into three structural families depending on the number of transmembrane domains in each subunit and the gating mechanisms. Voltage-gated  $\text{K}^+$  channels, which are encoded by about 40 genes, comprise four subunits, each with six transmembrane domains. Four (S1–S4) form the voltage sensor, whereas two (S5 and S6) form the pore region. These channels are critical for the regulation of neuronal excitability, including defining the resting membrane potential, modulation of action potential firing, and the modulation of neurotransmitter release (reviewed in Jan and Jan, 2012; Maljevic and Lerche, 2013).

**1. KCNA1.** *KCNA1* encodes the  $K_v1.1$  subunit of the voltage-gated  $K^+$  channel that is widely expressed throughout the central nervous system, with particularly high levels of expression in the hippocampus (Wang et al., 1994; Jan and Jan, 2012). The  $K_v1.1$  subunit is predominantly localized in the axon initial segment, axon preterminal, and the juxtaparanodal domain adjacent to the nodes of Ranvier, where it helps to repolarize and shape action potentials (Shieh et al., 2000; Goldberg et al., 2008; Trimmer, 2015).

*a. Clinical syndrome and molecular findings.* The majority of human *KCNA1* mutations are associated with episodic ataxia type 1 (Browne et al., 1994, 1995; Zuberi et al., 1999; Eunson et al., 2000; Rajakulendran et al., 2007). Patients with episodic ataxia type 1 are ten times more likely to have seizures than the general population, strongly implicating mutations in this gene as a cause of epilepsy (Rajakulendran et al., 2007). Another common feature of *KCNA1* disease is myokymia, characterized by involuntary twitching of facial and limb muscles (Browne et al., 1994, 1995). Furthermore, this gene has been suggested as one of the contributing genes to sudden unexpected death in epilepsy in a 3-year-old proband with pharmacoresistant epileptic encephalopathy (Klassen et al., 2014). The majority of functional studies of *KCNA1* mutations revealed loss-of-function through a variety of mechanisms, including changes to the voltage threshold and gating properties of  $K_v1.1$ -containing  $K^+$  channels, reduction in peak  $K^+$  current amplitude, and channel trafficking defects (Rajakulendran et al., 2007; D'Adamo et al., 2015).

*b. Mechanisms and potential targeted therapies.*  $K_v1.1$  knockout mice display similar phenotypes to human patients, including frequent spontaneous seizures and in some cases sudden unexpected death, suggesting that it is a good preclinical model of disease (Smart et al., 1998; Lopantsev et al., 2003; Wenzel et al., 2007; Glasscock et al., 2010). The heterozygous  $K_v1.1$  (V408A) knock-in mouse model based on a human mutation linked to episodic ataxia type 1 has stress-fear responses and induced motor dysfunctions that recapitulate some disease phenotypes, but no spontaneous seizures (Herson et al., 2003).

The cellular basis of morbidity is not clear but may involve changes in neurotransmitter release. It is well established that blocking  $K_v1$  channels broadens the action potential, thus increasing the flux of  $Ca^{2+}$  into the presynaptic terminal and as a consequence increasing triggered neurotransmitter release (Shu et al., 2006; Foust et al., 2011). Consistent with this, the overexpression of a human  $K_v1.1$  epilepsy mutation in cultured rat hippocampal neurons enhances neurotransmitter release probability (Heeroma et al., 2009).  $K_v1.1$  is localized in the axon initial segment of fast-spiking neocortical GABAergic interneurons and has a critical role in regulating the excitability of these cells (Goldberg et al., 2008). Functional studies have reported

an increase in GABAergic inhibitory synaptic transmission in both the  $K_v1.1$  knockout and  $K_v1.1$  (V408A) knock-in mouse models (van Brederode et al., 2001; Herson et al., 2003). At a neuronal network level, multielectrode array analysis of hippocampal slices from  $K_v1.1$  knockout mice indicates an increase in spontaneous spike-wave and high-frequency ripples that are associated with hyperexcitability (Simeone et al., 2013). This is proposed to be due to increased synaptic release within the CA3 region, decreasing precision of CA3 principal cell spike timing, which in turn leads to the altered hippocampal network oscillatory behavior (Simeone et al., 2013).

There are no reported effective targeted therapies based on our understanding of cellular mechanisms. However, the preclinical knockout mouse model has provided some insights. Interestingly, homozygous  $K_v1.1$  knockout mice have disrupted sleep, and seizures peak during times of light (Wright et al., 2016). Almorexant, a dual orexin receptor antagonist used in sleeping disorders, improves sleep and reduces seizure severity, suggesting that it may be useful for patients with mutations in *KCNA1* (Roundtree et al., 2016). Treatment of homozygous  $K_v1.1$  knockout mice with a ketogenic diet also reduces seizure frequency (Fenoglio-Simeone et al., 2009) and has been shown to successfully extend life span (Simeone et al., 2016). Finally, homozygous  $K_v1.1$  knockout mice with partial genetic ablation of  $Na_v1.2$  exhibit reduced duration of spontaneous seizures, and a significant improvement of survival rates argues that blockers of this  $Na^+$  channel may have some treatment value (Mishra et al., 2017).

**2. KCNA2.** *KCNA2* encodes the  $K_v1.2$  shaker-type voltage-gated  $K^+$  channel subunit, which is highly expressed in the central nervous system, predominately in the axon (Monaghan et al., 2001; Melé et al., 2015). The  $K_v1.2$  channel belongs to the delayed rectifier class of  $K^+$  channels, which enable the repolarization of the neuronal membrane following an action potential (Maljevic and Lerche, 2013).

*a. Clinical syndrome and molecular findings.* De novo mutations in *KCNA2* have been identified in cases of early infantile epileptic encephalopathy (Pena and Coimbra, 2015; Syrbe et al., 2015; Allen et al., 2016; Hundallah et al., 2016). Seizure onset is between 5 and 17 months, with a phenotypic spectrum including febrile and afebrile, hemiclonic, myoclonic, myoclonic-atonic, absence, focal dyscognitive, focal, and generalized seizures; mild to moderate intellectual disability; delayed speech development; and severe ataxia (Pena and Coimbra, 2015; Syrbe et al., 2015). The *KCNA2* spectrum also encompasses milder familial epilepsy (Corbett et al., 2016). De novo *KCNA2* mutations in patients with neurodegenerative hereditary spastic paraplegia and ataxia have also been reported (Helbig et al., 2016; Manole et al., 2017). In heterologous

expression systems, de novo mutations in *KCNA2* can cause both loss- and gain-of-function, all with a dominant effect (Syrbe et al., 2015).

*b. Mechanisms and potential targeted therapies.* The idea that loss-of-function can cause disease is consistent with findings from animal models. Homozygous  $K_v1.2$  knockout mice display severe seizures and die early (Brew et al., 2007). Heterozygous  $K_v1.2$  knockout mice do not display spontaneous seizures but are more sensitive to a proconvulsant challenge compared with wild-type littermates (Brew et al., 2007). The *Pingu* mutant mouse that carries a loss-of-function mutation in  $K_v1.2$ , induced through N-ethyl-N-nitrosourea mutagenesis, provides another potential model of disease (Xie et al., 2010). This mouse carries a mutation in the S6 segment, which is in close proximity to the loss-of-function mutation found in patients with epileptic encephalopathy, including ataxia (Syrbe et al., 2015). Both heterozygous and homozygous mutant mice display significant gait abnormalities (Xie et al., 2010). No mouse models with a gain-of-function *KCNA2* variant have been reported to date.

The cellular basis of hyperexcitability due to either loss- or gain-of-function *KCNA2* mutations is not clear. This is in part because  $K_v1.2$  is found in both excitatory and inhibitory neurons (Wang et al., 1994; Lorincz and Nusser, 2008). It is also due to the fact that  $K_v1.2$  channels potentially play dual roles in defining cellular excitability. By rapidly repolarizing neurons, they can help sustain rapid firing rates. In addition, they play a critical role in defining membrane potential. Cellular studies in mouse models highlight this complexity by showing contrasting changes in firing patterns. Recordings from inhibitory cerebellar basket cells of the *Pingu* mutant mouse show an increased firing rate (Xie et al., 2010). In contrast, firing is reduced in  $K_v1.2$  knockout glycinergic neurons (Brew et al., 2007).

Despite the limited understanding of the cellular basis of disease, therapeutic strategies based on molecular findings are possible. The 4-aminopyridine is an approved  $K^+$  blocker already being trialed in patients carrying gain-of-function mutations (H. Lerche, personal communication). The use of molecular knockdown strategies may also prove to be useful in this patient cohort. There are currently no obvious mechanism-based therapeutic strategies for loss-of-function disease. However, Xie et al. (2010) have tested a nontargeted approach and report that the carbonic anhydrase inhibitor, acetazolamide, is capable of rescuing the motor incoordination in *Pingu* mice. This led to a successful clinical outcome in a single patient with ataxia and myoclonic epilepsy caused by a *KCNA2* mutation, which highlights the potential utility of the preclinical mouse model (Pena and Coimbra, 2015).

3. *KCNB1*. *KCNB1* encodes the  $K_v2.1$  pore-forming and voltage-sensing  $\alpha$ -subunit of the delayed-rectifier

$K^+$  channel (Labro and Snyders, 2012; Maljevic and Lerche, 2013). In the mammalian brain, the  $K_v2.1$  subunit is expressed in both excitatory and inhibitory neurons, and is localized to the soma, proximal dendrites, and axon initial segments (Du et al., 1998; Trimmer, 2015), where it plays a critical role in regulating excitability (Mohapatra et al., 2007; Speca et al., 2014). An interesting characteristic of this channel is that its activity can be modulated by phosphorylation (Mohapatra et al., 2007; Speca et al., 2014). Increased neuronal activity leads to dephosphorylation, which results in facilitated channel opening and consequently suppressed neuronal excitability. Reduced neuronal activity leads to hyperphosphorylation of  $K_v2.1$  that has the opposite effect (Speca et al., 2014). The widespread expression of  $K_v2.1$  suggests that this channel may have a major role in homeostatic suppression of both excitatory and inhibitory neuronal excitability (Mohapatra et al., 2007; Speca et al., 2014).

*a. Clinical syndrome and molecular findings.* Several de novo mutations in *KCNB1* have been identified in cases of infantile epileptic encephalopathy (Torkamani et al., 2014; Saitsu et al., 2015; Thiffault et al., 2015; Allen et al., 2016). The phenotypic spectrum includes cognitive and motor dysfunction, severe infantile generalized seizures with high-amplitude spike-and-wave discharges, and prominent stimulus and photosensitive epilepsy (Saitsu et al., 2015; Allen et al., 2016). A range of functional impacts has been reported for epilepsy-associated *KCNB1* mutations. For example, mutations located within the pore domain of  $K_v2.1$  were associated with a loss of  $K^+$  selectivity. This could lead to an increased inward conductance of cations, resulting in neuronal depolarization (Torkamani et al., 2014; Thiffault et al., 2015). Other biophysical findings include changes in gating, with mutant channels showing less voltage dependence and an ability to be constitutively open (Torkamani et al., 2014). Expression of a de novo missense mutation in heterologous cells revealed significant changes in protein expression and localization (Thiffault et al., 2015).

*b. Mechanisms and potential targeted therapies.* There are currently no good rodent models for *KCNB1* disease. A homozygous  $K_v2.1$  knockout mouse model exhibits no spontaneous seizures, but does exhibit a reduced threshold for induced seizures, in addition to reduced spatial learning and hyperactivity (Speca et al., 2014). This mimics loss-of-function aspects of disease and argues that it can cause some level of hyperexcitability. However, given the biophysical changes seen, including altered ion selectivity and changes in voltage sensitivity, it is not entirely surprising that simple loss-of-function does not recapitulate more severe disease. Saitsu et al. (2015) have investigated the impact of two different human epilepsy mutations on neuronal excitability in an overexpression culture model. They report that expression of both mutant channels slows action

potential firing in excitatory pyramidal neurons by reducing repolarization. How this translates to increased network excitability in epilepsy remains unclear. Knock-in mutant mice based on human *KCNB1* mutations are more likely to serve as better preclinical models. Given the lack of functional insight, it is difficult to propose potential targeted therapy in *KCNB1* disease.

4. *KCNC1*. *KCNC1* encodes the  $K_{V3.1}$  channel, which has biophysical properties optimized for high-frequency action potential firing (Rudy and McBain, 2001). The channel is preferentially expressed in specific subsets of fast-spiking neurons, including fast-spiking inhibitory GABAergic interneurons (Rudy and McBain, 2001).  $K_{V3.1}$  channels are also expressed in granule cerebellar neurons (Matsukawa et al., 2003).

*a. Clinical syndrome and molecular findings.* A recurrent de novo mutation in *KCNC1* has been identified as a major cause of progressive myoclonus epilepsy (Muona et al., 2015; Oliver et al., 2017). This is a distinctive epilepsy syndrome characterized by myoclonus, generalized tonic-clonic seizures, and progressive neurologic deterioration. An interesting clinical trait is the transient clinical improvement that occurs with fever in some patients (Oliver et al., 2017). In vitro analysis has revealed two key biophysical changes resulting from the recurrent *KCNC1* mutation: a dominant-negative impact that significantly reduces currents, and a concomitant hyperpolarizing shift in the activation voltage (Muona et al., 2015; Oliver et al., 2017). A nonsense mutation in *KCNC1* has also been described in one family with intellectual disability, but no epilepsy (Poirier et al., 2017).

*b. Mechanisms and potential targeted therapies.* The cellular mechanism underlying *KCNC1*-mediated disease is not understood. One possibility is that the reduced current levels lead to an inability of fast-spiking GABAergic interneurons to sustain firing, with a consequent increase in network excitability caused by disinhibition (Muona et al., 2015; Oliver et al., 2017). However, the hyperpolarizing shift in activation would act to increase channel function, tempering this reduced current. Interestingly, in vitro analysis demonstrates that the hyperpolarizing shift is enhanced at febrile temperatures, and this may explain the clinical improvement seen with fever (Oliver et al., 2017). The homozygous  $K_{V3.1}$  knockout mouse displays only a mild phenotype that includes impaired coordinated motor skills, but no spontaneous seizures, suggesting that this mouse is not a good preclinical model of the disease (Ho et al., 1997). RE1, a  $K_{V3.1}$  channel opener, provides a potential therapeutic option. Importantly, RE1 partially restores impaired firing in fast-spiking neurons from a mouse model of 15q13.3 microdeletion syndrome (Thelin et al., 2017). However, the utility of this and other  $K_{V3.1}$  channel agonists is yet to be tested in *KCNC1* disease models.

5. *KCNMA1*. *KCNMA1* encodes the  $\alpha$ -subunit of the large conductance  $Ca^{2+}$ -sensitive  $K^{+}$  channel [also known as BK (for Big  $K^{+}$ ), Maxi-K,  $K_{Ca1.1}$ , or Slo1] that is widely expressed in the central nervous system. *KCNMA1* channels produce a robust hyperpolarizing potential in response to elevation in intracellular  $Ca^{2+}$  and/or membrane depolarization, which influences the shape, frequency, and propagation of action potentials and modulates neurotransmitter release (Contet et al., 2016).

*a. Clinical syndrome and molecular findings.* A mutation in *KCNMA1* was first reported in a large family with autosomal dominant generalized epilepsy and paroxysmal nonkinesigenic dyskinesia (Du et al., 2005). Two de novo mutations and an autosomal recessive homozygous frameshift duplication have also been described (Zhang et al., 2015b). Functional analysis provided in the first study showed that the mutant BK channel had a greater macroscopic current, likely due to an increase in  $Ca^{2+}$  sensitivity. In contrast, the homozygous frameshift duplication is likely to result in loss-of-function.

*b. Mechanisms and potential targeted therapies.* The activation of BK channels can both increase and decrease firing activity in neurons depending on context. Du et al. (2005) propose that enhancement of BK channels leads to increased excitability by allowing rapid repolarizing action potentials, resulting in increased firing rates. A reduction in BK activity has been implicated in causing neuronal depolarization at rest that consequently increases excitability by taking the neuron closer to the firing potential (Verma-Ahuja et al., 1995). Therefore, predicting how a given mutation impacts excitability is difficult. The *KCNMA1* knockout mouse exhibits intention tremor and abnormal gait consistent with cerebellar ataxia but is seizure-free and is therefore not a good model of epilepsy (Sausbier et al., 2004). There are a range of small organic molecules and peptides that can both activate and block BK channels (Bentzen et al., 2014; Yu et al., 2016). These provide a rich source of pharmacological tools that could be used to probe efficacy once a good model of disease is developed.

6. *KCNQ2 and KCNQ3*. Heteromeric and homomeric channels encoded by *KCNQ2* ( $K_{V7.2}$ ) and *KCNQ3* ( $K_{V7.3}$ ) can form homo- and heterotetramers that are responsible for the M-current, a slow noninactivating  $K^{+}$  current that regulates membrane potential at the subthreshold voltage range and constrains repetitive neuronal firing (Brown and Adams, 1980; Schroeder et al., 1998; Delmas and Brown, 2005).

*a. Clinical syndrome and molecular findings.* Mutations in both *KCNQ2* and *KCNQ3* cause an autosomal-dominant self-limited epilepsy known as benign familial neonatal epilepsy (Biervert et al., 1998; Charlier et al., 1998; Schroeder et al., 1998; Singh et al., 1998; Lerche et al., 1999; Maljevic and Lerche, 2014).

More recently, screening of patients with neonatal onset epileptic encephalopathy revealed many cases of de novo mutations in *KCNQ2* (Weckhuysen et al., 2012, 2013; Maljevic and Lerche, 2014), with fewer mutations reported in *KCNQ3* (Miceli et al., 2015a,b). Approximately half of *KCNQ2* mutations are predicted to truncate the protein, with the other half being missense mutations (Maljevic and Lerche, 2014). Functional analysis revealed a loss-of-function caused by a different molecular mechanism (Maljevic and Lerche, 2014). It should be noted that disease-related gain-of-function mutations have been more rarely reported for both *KCNQ2* and *KCNQ3* (Miceli et al., 2015b; Millichap et al., 2016). A genotype–phenotype correlation has been suggested, with mutations in severe epileptic encephalopathies more likely to have a dominant-negative impact (Orhan et al., 2014).

*b. Mechanisms and potential targeted therapies.*  $K_V7.2$  and  $K_V7.3$  colocalize at the axon initial segment and/or nodes of Ranvier (Devaux et al., 2004; Schwarz et al., 2006), where they play an integral role in defining excitability, including reducing spiking frequency during trains of activity (spike-frequency adaption) (Schwarz et al., 2006). A reduction in the M-current will reduce adaptation and is the likely basis of neuronal hyperexcitability in loss-of-function *KCNQ2* and *KCNQ3* disease. Support for this idea comes from a conditional transgenic mouse that has spontaneous seizures and carries a dominant-negative pore mutation (Peters et al., 2005). *CA1* pyramidal neurons have a smaller medium after-hyperpolarization current, and as a consequence a reduced ability to adapt action potential firing (Peters et al., 2005). *CA1* pyramidal neurons from a spontaneous  $K_V7.2$  mutant mouse also have a reduced ability to adapt action potential firing (Otto et al., 2006). The mechanism of disease for gain-of-function mutations is less clear. Both  $K_V7.2$  and  $K_V7.3$  proteins are found in parvalbumin-positive hippocampal interneurons (Lawrence et al., 2006; Nieto-Gonzalez and Jensen, 2013; Grigorov et al., 2014) with a reduction in spike adaption in these cells possibly increasing network excitability. The  $K_V7.2$  (A306T) and  $K_V7.3$  (G311V) knock-in mouse models are both based on loss-of-function mutations found in benign familial neonatal convulsions (Singh et al., 2008; Otto et al., 2009). In both cases, homozygous mice have spontaneous seizures, whereas heterozygous mice have increased seizure susceptibility, suggesting that they may act as reasonable models of mild disease (Singh et al., 2008; Otto et al., 2009). No mouse models with epileptic encephalopathy have been reported to date.

One striking feature of benign familial neonatal seizures is that, within a few weeks or months of birth, symptoms spontaneously remit in the vast majority of patients. The developmental pattern of  $K_V7.2$  and  $K_V7.3$  protein expression seems unlikely to explain remission, as the expression of both subunits increases during

maturation (Weber et al., 2006; Maljevic and Lerche, 2014). A plausible hypothesis is that remission coincides with a switch of the inhibitory neurotransmitter GABA, from a predominantly excitatory transmitter in early development to a more traditional inhibitory role in later development (Rivera et al., 1999).

From a therapeutic perspective, retigabine, a selective opener of the M-current (Rundfeldt and Netzer, 2000; Gunthorpe et al., 2012), is an obvious drug choice for loss-of-function *KCNQ2*- and *KCNQ3*-mediated disease. More broadly, retigabine has been used in the treatment of epileptic encephalopathy patients, with studies revealing significant improvement in some patients (Weckhuysen et al., 2013; Millichap et al., 2016). Unfortunately, the side effects seen in some patients have led to the removal from the market of this drug (Tompson et al., 2016). Ongoing efforts to develop similar but safer M-current activator are required, and these would be predicted to be particularly efficacious in epilepsy caused by most mutations in *KCNQ2* and *KCNQ3*.

7. *KCNT1.* *KCNT1* encodes  $K_{Na}1.1$ , a  $Na^+$ -activated  $K^+$  channel subunit, that has been called Slack (sequence like a  $Ca^{2+}$ -activated  $K^+$  channel, also known as  $K_{Ca}4.1$  or Slo2.2).  $K_{Na}1.1$  is expressed widely, including in the brain, heart, and kidney.  $K_{Na}1.1$  is thought to be expressed in the frontal cortex (Bhattacharjee et al., 2002), but more studies are required to better map its expression pattern.  $K_{Na}1.1$  channels may modulate the firing properties and general excitability of many neuronal types, although their precise function is yet to be fully resolved.

*a. Clinical syndrome and molecular findings.* Mutations in *KCNT1* have been identified in familial and sporadic cases with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). It is also the cause of about 40% of cases with a quite different syndrome, epilepsy of infancy with migrating focal seizures (Wilmshurst et al., 2000; Barcia et al., 2012; Heron et al., 2012; Lim et al., 2016). Other epileptic encephalopathies, such as Ohtahara syndrome, have also been linked to this gene (Møller et al., 2015). All mutations in *KCNT1* described to date are missense mutations (Lim et al., 2016). Notably, they all result in significantly increased  $K^+$  current, which argues strongly that this is the basis of disease. The extent of the gain-of-function may correlate with seizure phenotype severity (Milligan et al., 2014). However, the fact that two mutations have been described causing both nocturnal frontal lobe epilepsy and epilepsy of infancy with migrating focal seizures suggests a more complex genotype–phenotype correlation (Lim et al., 2016). *KCNT1*-mediated epilepsy has become an example of how quickly targeted therapy might enter the clinic through the repurposing of already approved drugs (see below).

*b. Mechanisms and potential targeted therapies.* The exact mechanisms underlying disease caused by mutation in *KCNT1* are still unclear. Rapid elevations



of intracellular  $\text{Na}^+$  concentrations in neurons are sensed by  $\text{Na}^+$ -activated  $\text{K}^+$  channels influencing firing patterns. For example, rapid repolarization by  $\text{K}^+$  channels can sustain rapid action potential firing, with an increase in function potentially enabling excitatory neurons to fire at aberrantly high rates (Bhattacharjee and Kaczmarek, 2005). Alternatively, during sustained activity, slow activation of such channels can lead to the cessation of firing that could cause inhibitory dysfunction similar to that observed in *SCN1A* disease (Bhattacharjee and Kaczmarek, 2005). Given that the expression pattern of  $\text{K}_{\text{Na}}1.1$  is largely unknown, it is difficult to make a prediction as to the likely mechanism. To date, no mouse model based on gain-of-function *KCNT1* mutations has been reported.

Despite the lack of progress on the underlying cellular basis of disease, the robust gain-of-function seen in all *KCNT1* disease provides a clear target. It has been known for some time that the approved antiarrhythmic drug, quinidine, is able to block rodent  $\text{K}_{\text{Na}}1.1$  channels (Santi et al., 2006; Yang et al., 2006). Milligan et al. (2014) showed that quinidine was able to also block human  $\text{K}_{\text{Na}}1.1$  channels, including those expressing epilepsy mutations. This has motivated clinical studies in which quinidine was repurposed and trialed in patients carrying *KCNT1* mutations. Several case reports suggested efficacy, particularly in very young patients (Bearden et al., 2014; Mikati et al., 2015; Fukuoka et al., 2017), whereas others have shown limited or no efficacy (Mikati et al., 2015; Chong et al., 2016; Fukuoka et al., 2017). Quinidine is not a safe drug, with severe life-threatening cardiac liability, and a small clinical trial in adults in ADNFLE failed to show efficacy, and doses were limited by cardiac toxicity (Mullen et al., 2017). The antiarrhythmic drug, clofilium, which also blocks  $\text{K}_{\text{Na}}1.1$  channels, potentially provides another repurposing opportunity, although it too has significant cardiac side effects (Castle, 1991). These drugs do form good lead compounds for the development of more specific and better tolerated drugs targeted against  $\text{K}_{\text{Na}}1.1$ . The consistent gain-of-function seen for all disease mutations in *KCNT1* argues that molecular strategies in which the channel is knocked down are likely to be effective. Importantly, the homozygous *KCNT1* knockout mouse has only minor phenotypes, suggesting that there may be a large therapeutic window for such strategies (Bausch et al., 2015).

8. *KCTD7*. *KCTD7* encodes a protein that has homology to the T1 domain in voltage-gated  $\text{K}^+$  channels, a domain critical for tetramerization. The precise nature and role of this protein are unclear. Given the small size of *KCTD7*, it was thought to be unlikely to be a transmembrane protein and consequently function as a  $\text{K}^+$  channel. However, recent evidence argues that the *KCTD7* protein can support a  $\text{K}^+$  conductance (Moen et al., 2016). *KCTD7* was also reported to have a modulatory role on the SAT2 neuronal glutamine

transporter (Moen et al., 2016). Modulation of cellular proliferation, differentiation, apoptosis, and metabolism has also been suggested for this class of protein (Liu et al., 2013b).

*a. Clinical syndrome and molecular findings.* Three members of a family with progressive myoclonic epilepsy were reported to harbor a homozygous mutation in *KCTD7* (Van Bogaert et al., 2007). Progressive myoclonic epilepsy is a disorder characterized by myoclonic and tonic-clonic seizures, ataxia, and cognitive regression (see *KCNC1*). Numerous other cases of progressive myoclonic epilepsy caused by mutations in *KCTD7* have since been reported (Blumkin et al., 2012; Kousi et al., 2012; Krabichler et al., 2012; Staropoli et al., 2012; Farhan et al., 2014).

*b. Mechanisms and potential targeted therapies.* As *KCTD7* channels have no clearly defined role, it is difficult to come up with a unifying mechanistic basis of disease. The *KCTD7* channel is widely expressed throughout the brain, with immunohistochemical analysis identifying expression in cortical neurons, in granular and pyramidal cell layers of the hippocampus, and in cerebellar Purkinje cells (Kousi et al., 2012). *KCTD7* mutations have been recently reported to reduce the ability of *KCTD7* channels to sustain a  $\text{K}^+$  conductance either through a trafficking or biophysical deficit (Moen et al., 2016). This suggests the reduction in function is likely to result in a more depolarized membrane potential of excitatory neurons, leading to hyperexcitability.  $\text{K}^+$  channel openers, such as retigabine, may be expected to be beneficial based on this mechanism. However, the impact of mutations on the SAT2 neuronal glutamine transporter or other cellular roles as a basis of excitability cannot be ruled out. No good animal models of *KCTD7*-mediated disease have been reported to date.

### *C. Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel 1*

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are encoded by four genes (*HCN1–4*) (Alexander et al., 2015a; <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=71>). HCN channels mediate hyperpolarization-activated currents in the brain, where they contribute to resting membrane potential and to the shaping of synaptic inputs (He et al., 2014). They have also been implicated in the generation of rhythmic and synchronized neuronal activity. Both human and animal studies have reported transcriptional changes in HCN expression that associate with hyperexcitability in epilepsy (Reid et al., 2012; DiFrancesco and DiFrancesco, 2015).

*1. Clinical Syndrome and Molecular Findings.* Considering the strong evidence implicating transcriptional changes in HCN channels and excitability in animal models, there is surprisingly little evidence of genetic changes associated with epilepsy. Nava et al.

(2014) reported de novo *HCN1* missense mutations in patients suffering from early infantile epileptic encephalopathy. These patients had symptoms that resembled Dravet syndrome with intellectual impairment and autism. Functional analysis revealed that the majority of *HCN1* mutations caused a gain-of-function through changes in various biophysical properties, including depolarized shifts in half activation and changes in activation and deactivation kinetics (Nava et al., 2014). Loss of *HCN1* channel function was also reported (Nava et al., 2014). Variations in *HCN2* that cause gain-of-function have been reported to confer susceptibility in febrile seizure syndromes (Dibbens et al., 2010; Nakamura et al., 2013), with a further report of a loss-of-function homozygous *HCN2* mutation in a patient with sporadic GGE (DiFrancesco et al., 2011).

2. *Mechanisms and Potential Targeted Therapies.* The reported gain- and loss-of-function caused by mutations is consistent with the dual action HCN channels can play in defining neuronal excitability (Dubé et al., 2007; Dyhrfeld-Johnsen et al., 2009). In neurons, HCN channels are active at rest and contribute a depolarizing current to the resting membrane potential. The majority of reported *HCN1* mutations caused a gain-of-function. An increase in HCN channel function will therefore result in a more depolarized resting membrane potential, taking the neuron closer to the firing potential (Chen et al., 2001; Brewster et al., 2002; Dyhrfeld-Johnsen et al., 2008). An increase in neuronal hyperexcitability can also be explained for loss-of-function *HCN1* mutations. HCN1 channels are expressed robustly on dendrites, where they influence synaptic integration. A reduction in HCN1 channel function increases the temporal summation of synaptic input and facilitates dendritic burst firing (Strauss et al., 2004; Kole et al., 2007). These properties are proposed to contribute to network excitability in the *WAG/Rij* model of absence epilepsy (Strauss et al., 2004; Kole et al., 2007). This dual role of HCN channels in the central nervous system makes it difficult to develop targeted approaches for genetic epilepsy caused by *HCN1* mutations. Nevertheless, in gain-of-function disease, blockers of HCN1 may be useful. Ivabradine is a use-dependent broad-spectrum blocker of HCN channels approved for use in angina pectoris (Abed et al., 2016; Giavarini and de Silva, 2016). Ivabradine has a good safety profile potentially providing a repurposing opportunity, although it is not clear whether it can cross the blood brain barrier (Savelieva and Camm, 2006). Moreover, the hypnotics propofol and ketamine, as well as the anesthetic isoflurane, are reported to inhibit HCN1 channels (Cacheaux et al., 2005; Chen et al., 2005, 2009,a,b; Lyashchenko et al., 2007). Although far from ideal, these drugs may provide some therapeutic options in patients harboring gain-of-function *HCN1* mutations. The antiepileptic drugs, lamotrigine and gabapentin, have both been reported to enhance HCN

currents (Poolos et al., 2002; Surges et al., 2003; Strauss et al., 2004), with patients harboring loss-of-function mutations potentially benefiting more from these drugs.

#### D. Voltage-Gated Calcium Channels

Voltage-gated  $\text{Ca}^{2+}$  channels support a number of critical processes in neurons, from the control of pre-synaptic transmitter release to the electrogenic properties of dendrites (Alexander et al., 2015a; <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=80>). Electrophysiological studies indicate that there are six  $\text{Ca}^{2+}$  channel types, as follows: L-, N-, P-, Q-, R-, and T-type (Catterall, 2000). They can be divided into high voltage-activated or low voltage-activated classes based on the membrane potential range over which the channel is activated. The key determinant of the character of  $\text{Ca}^{2+}$  channel subtypes is their  $\alpha 1$  pore-forming subunit. The molecular diversity of voltage-gated  $\text{Ca}^{2+}$  channels is enhanced by auxiliary subunits, including the  $\alpha 1$ -,  $\beta$ -,  $\alpha 2\delta$ -, and  $\gamma$ -subunits that modulate trafficking and current properties (Campiglio and Flucher, 2015). Rodent models that are null for auxiliary subunits, including  $\alpha 2\delta$  (*ducky*) and  $\beta 4$  (*lethargic*) mice, display ataxia and spontaneous seizures (Felix, 2002). However, to date there is little evidence linking voltage-gated  $\text{Ca}^{2+}$  channel auxiliary subunits to genetic epilepsy in humans, and they will not be discussed further.

Much attention has been given to the low-threshold T-type  $\text{Ca}^{2+}$  channels due to their role in supporting burst-firing. These channels are found within the thalamocortical loop that is responsible for the aberrant activity that underlies spike-and-wave discharges (Huguenard and McCormick, 1992; Destexhe et al., 1996; Crunelli and Leresche, 2002). Early efforts found that variants in *CACNA1H*, which encodes the  $\text{Ca}_v3.2$  subunit, appear enriched in GGE (Chen et al., 2003; Khosravani et al., 2004; Vitko et al., 2005; Heron et al., 2007). The discovery of a *CACNA1H* variant in *genetic absence epilepsy rats from Strasbourg*, a rodent model of genetic generalized epilepsy, further supported the importance of this gene (Powell et al., 2009). Interestingly, the impact of this mutation on channel function was splice-form specific, highlighting an important concept in functional analysis (Powell et al., 2009). Recent large-scale studies of common and rare variants in GGE have not revealed a major impact of *CACNA1H* variants (Heinzen et al., 2012; Steffens et al., 2012; Epi4K Consortium and Epilepsy Phenome/Genome Project, 2017). Moreover, many of the initially reported variants have emerged in available databases at high frequencies, suggesting that they are benign polymorphisms (Lek et al., 2016; Becker et al., 2017). However, Glauser et al. (2017) have reported that genetic variation in *CACNA1H* and *CACNA1* can play a role in the differential drug response profile in CAE. At present, the most compelling evidence implicates mutations in *CACNA1A* as a cause of epilepsy in humans.

1. **CACNA1A.** *CACNA1A* encodes the  $\alpha 1$ -subunit of the  $\text{Ca}_v2.1$  (P/Q-type) calcium channel that is critical for transmitter release within the central nervous system (Simms and Zamponi, 2014). The first link of *CACNA1A* to epilepsy was the discovery of a mutation in this gene in the tottering mouse (Fletcher et al., 1996). Subsequently, mutations in *CACNA1A* have been reported to associate with several neurologic conditions, including episodic ataxia (Jodice et al., 1997), spinocerebellar ataxia (Jodice et al., 1997), and familial hemiplegic migraine (Ducros et al., 1999).

*a. Clinical syndrome and molecular findings.* Early evidence supported the idea that loss-of-function *CACNA1A* mutations were associated with GGE (Jouveneau et al., 2001; Imbrici et al., 2004). Microdeletions that encompass *CACNA1A* and a single truncating mutation have been associated with severe epileptic encephalopathies that include infantile spasms and West syndrome (Auvin et al., 2009; Damaj et al., 2015; Hino-Fukuyo et al., 2015). More recently, de novo missense mutations have been convincingly shown to cause severe epileptic encephalopathies with seizure types that typically include focal, tonic, and tonic-clonic seizures; severe intellectual disability; and motor impairment (Epi4K Consortium, 2016; Reinson et al., 2016). Although the biophysical impacts of all mutations are yet to be reported, the presence of deletions and truncating mutations argues that a loss-of-channel function is the primary underlying molecular deficit.

*b. Mechanisms and potential targeted therapies.* Homozygous *Cacna1a* knockout mice have progressive neurologic deficits that result in ataxia and dystonia, with mice dying within 4 weeks of birth (Jun et al., 1999; Fletcher et al., 2001). Similar phenotypes are seen in a range of spontaneous *Cacna1a* gene mutant mice with dystonia, ataxia, premature death, and epilepsy all observed in *leaner*, *tottering*, *rolling*, and *rocker* mice (Pietrobon, 2005). These potentially provide good pre-clinical mouse models of *CACNA1A* disease. Most reports investigating cellular mechanism in these mouse models implicate a reduction in excitatory synapse transmitter release, consistent with the integral role of these channels in this process. For example, reduced evoked postsynaptic currents have been measured at the Calyx of Held in the homozygous *Cacna1a* knockout mouse (Caddick et al., 1999). Similarly, a deficit has been reported at the cerebellar parallel fiber–Purkinje cell synapses and excitatory synapses within the ventrobasal nuclei in the *leaner* mouse model (Caddick et al., 1999). Recently, analysis of a conditional *Cacna1a* knockout mouse, in which deletion is limited to layer VI, reports that reduced excitatory neurotransmission at cortico-thalamic synapses is sufficient to generate generalized seizures (Bomben et al., 2016). How this change resulted in increased network excitability is not known. This lack of a robust cellular mechanism makes it difficult to

develop disease-targeted strategies. However, mouse models may be predictive of pharmacosensitivity. For example, high-power low-frequency oscillations, which are thought to be a marker of cortical excitability in the *tottering* mouse, were markedly decreased by acetazolamide and 4-aminopyridine, drugs that are treatment options for episodic ataxia 2 (Cramer et al., 2015). Of note is the finding that spontaneous seizures in the *Cacna1a* knockout mouse can be abolished by knocking out *Cacna1g* (Song et al., 2004). This suggests that T-type  $\text{Ca}^{2+}$  channel blockers, including ethosuximide, may be good therapeutic options (Zamponi, 2016).

### III. Ligand-Gated Ion Channels in Epilepsy

#### A. N-Methyl-D-Aspartate Receptors

Glutamate activates three main groups of ionotropic glutamate receptors named after their selective agonists: N-methyl-D-aspartate-type (NMDA), amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-type, and kainate (Smart and Paoletti, 2012; Alexander et al., 2015b; <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=75>). There are seven NMDA receptor subunits: GluN1, GluN2A–GluN2D, GluN3A, and GluN3B, each encoded by their respective gene, *GRIN1*, *GRIN2A–D*, and *GRIN3A–B* (Traynelis et al., 2010). NMDA receptors assemble as a tetramer requiring two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits (Traynelis et al., 2010; Paoletti et al., 2013). GluN3 can incorporate into NMDA receptors, although its functional role is unclear (Traynelis et al., 2010). NMDA receptor subunits have a structure composed of four modular domains: the extracellular amino-terminal domain also known as the N-terminal domain; the extracellular ligand-binding domain; the transmembrane domain with four hydrophobic regions M1–4, of which M1, M3, and M4 are membrane-spanning helices and M2 forms a re-entrant loop; and the intracellular carboxyl-terminal domain (Sobolevsky et al., 2009; Meyerson et al., 2014).

NMDA receptors are nonselective cation channels permeable to  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$  ions. For typical NMDA receptors,  $\sim 15\%$  of the total inward current is carried by the  $\text{Ca}^{2+}$  ion, which acts as a critical second messenger (Burnashev et al., 1995; Schneggenburger, 1996). Due to their extracellular  $\text{Mg}^{2+}$  block, NMDA receptors require membrane depolarization to allow ion flow (Mayer and Westbrook, 1987). This strong voltage dependence means that NMDA receptors have the ability to act as coincidence detectors of pre- and postsynaptic activity, a feature that may be crucial to associative synaptic plasticity (Lüscher and Malenka, 2012) and dendritic electrogenesis (Palmer et al., 2012). The different GluN2 subunits define the pharmacological and kinetic properties of NMDA receptors (Traynelis et al., 2010). For example, NMDA receptors containing

GluN2A are highly sensitive to  $Zn^{2+}$  block (Paoletti, 2011). In disease studies, mutations in epilepsy patients have been identified in *GRIN1*, *GRIN2A*, *GRIN2B*, and *GRIN2D*.

1. *GRIN1*. *GRIN1* encodes the GluN1 NMDA receptor subunit (also known as NMDAR1 and NR1), which is ubiquitously expressed throughout the central nervous system, in both the adult and developing brain (Traynelis et al., 2010; Paoletti, 2011).

a. *Clinical syndrome and molecular findings*. Both heterozygous and homozygous *GRIN1* mutations have been implicated in a spectrum of disease, including epileptic encephalopathies and intellectual disability. De novo heterozygous mutations seem to associate with profound developmental delay, with a lack of speech as a dominant feature. Associated phenotypes include seizures, hyperkinetic movements, involuntary movement, muscular hypotonia, oculogyric crises, and cortical blindness (Allen et al., 2013; Ohba et al., 2015; Lemke et al., 2016). Heterozygous *GRIN1* mutations have also been identified in autosomal-dominant mental retardation (Hamdan et al., 2011; Redin et al., 2014; Zhu et al., 2015; Zehavi et al., 2017). Functional analysis of pathogenic heterozygous de novo *GRIN1* mutations suggests they cause a loss-of-function (Lemke et al., 2016). Different mutations in *GRIN1* have been shown to exhibit dominant-negative interactions of varying degrees, but with no clear genotype–phenotype correlation (Lemke et al., 2016). Patients with homozygous *GRIN1* truncation mutations experience continuous seizure activity and early death (Lemke et al., 2016).

b. *Mechanisms and potential targeted therapies*. Numerous studies use mouse lines that allow the deletion of *Grin1* in a subset of neurons potentially modeling loss-of-function disease. Specific forebrain *Grin1* knockout results in impaired synaptic plasticity and memory storage (Nakazawa et al., 2002; Cui et al., 2004; Hasan et al., 2013). Seizures are not observed in any of these rodent models. This said, the impaired synaptic plasticity and memory deficits recapitulate the intellectual disability and motor disorders caused by mutations in *GRIN1*. The homozygous *Grin1* knockout mice die as neonates, but have no seizures, suggesting that they also only partially recapitulate the severe clinical phenotype seen in humans harboring homozygous *GRIN1* truncation mutations (Forrest et al., 1994). Therefore, although genetic mouse models exist, they have not faithfully recapitulated key features of *GRIN1* disease.

Molecular studies report that most mutations in *GRIN1* result in a loss-of-function. It is not immediately clear how this would lead to increased excitability, and it is possible that emerging pathologies are to blame. Correcting the loss-of-function deficit may benefit patients harboring loss-of-function mutations. However, activators of NMDA receptors are likely to increase

neuronal activity, arguing that such drugs would have a narrow therapeutic window. The lack of good preclinical models and, as a consequence, a lack of understanding of the mechanisms behind the *GRIN1* disease are currently hampering progress in developing targeted therapies.

2. *GRIN2A*. *GRIN2A* encodes the GluN2A NMDA receptor subunit. This subunit binds glutamate and is widely expressed throughout the brain (Akazawa et al., 1994).

a. *Clinical syndrome and molecular findings*. *GRIN2A* mutations have been associated with epilepsy and speech disorders (also known as epilepsy–aphasia spectrum disorders) that present as a broad clinical spectrum. At the less severe end of the spectrum, seizure phenotypes include typical or atypical rolandic epilepsy (also known as childhood epilepsy with centrotemporal spikes) (Lemke et al., 2013; Lesca et al., 2013). More severe phenotypes include epileptic encephalopathies such as Landau-Kleffner syndrome and epilepsy with continuous spikes and waves during slow-wave sleep (Endele et al., 2010; Carvill et al., 2013b; Lemke et al., 2013; Lesca et al., 2013; Turner et al., 2015; Gao et al., 2017). Speech impairment is seen in all individuals with *GRIN2A*-related disorders and includes acquired aphasia, auditory agnosia, dysarthria, speech dyspraxia, impaired intelligibility and language delay, and regression (Turner et al., 2015; Myers and Scheffer, 2016). Intellectual disability occurs in up to 70% of individuals (Lemke et al., 2013; Lesca et al., 2013).

*GRIN2A* mutations include missense, truncating, splice, and copy number variants and can result in both gain- and loss-of-function. To date, no clear genotype–phenotype correlation has emerged (Strehlow et al., 2015). Causes of gain-of-function include reduction of  $Zn^{2+}$ -mediated inhibition (Lemke et al., 2013; Serraz et al., 2016), increased glutamate binding (Pierson et al., 2014), altered duration of channel open and closed states (Lesca et al., 2013), and reduced  $Mg^{2+}$  block (Endele et al., 2010). Causes of loss-of-function for missense mutations include reduced agonist potency, decreased total protein levels, and reduced cell surface expression (Addis et al., 2017). Mutations predicted to cause truncation and deletion mutations further support the idea that loss-of-function can result in disease (Reutlinger et al., 2010; Carvill et al., 2013b; Lesca et al., 2013).

b. *Mechanisms and potential targeted therapies*. How both loss-of-function and gain-of-function mutations in *GRIN2A* cause disease is not clear. Gain-of-function mutations in NMDA receptor activation will increase hyperexcitability in brain networks. Blockers of NMDA receptors are therefore a potential effective targeted therapy. Pierson et al. (2014) have shown that the approved use-dependent NMDA receptor antagonist, memantine, can reduce currents back to normal levels for a gain-of-function mutation. Promisingly,

memantine has been shown to reduce seizure activity in a patient with this mutation, although cognitive function showed no improvement. The mechanism underlying pathology in loss-of-function mutations is less intuitive and likely to be part of an emerging pathology. In this case, a targeted therapy would enhance GluN2A-containing receptor function. Recently, a positive allosteric modulator of GluN2A-containing receptors (compound 275) has been reported to rescue loss-of-function missense mutations providing a preclinical pharmacologic tool, although this is yet to be tested in rodent models (Yu et al., 2015; Addis et al., 2017). With strategies for dealing with both gain- and loss-of-function available, epilepsy due to mutations in *GRIN2A* should benefit from targeted therapy led by genetic diagnostics and functional screening.

3. *GRIN2B*. *GRIN2B* encodes the NMDA receptor subunit GluN2B. GluN2B is expressed prenatally, and its expression decreases with age (Akazawa et al., 1994), paralleled by an increase in GluN2A expression (Monyer et al., 1994). This suggests a role for GluN2B in brain development and circuit formation (Hall et al., 2007).

*a. Clinical syndrome and molecular findings.* Mutations in *GRIN2B* have been associated with early infantile epileptic encephalopathies, including West syndrome with severe developmental delay, Lennox-Gastaut syndrome, and early-onset seizures with intellectual disability (Allen et al., 2013; Lemke et al., 2014; Zhang et al., 2015a; Smigiel et al., 2016). The mutated gene has also been associated with milder seizure syndromes, including early-onset focal epilepsy (Lemke et al., 2014). Intellectual disability associated with *GRIN2B* mutations can occur independently of epilepsy (Endele et al., 2010; Hamdan et al., 2014).

Initial functional assessment showed a decrease of  $Mg^{2+}$  block and higher  $Ca^{2+}$  permeability that correlated with the clinical phenotype severity (Lemke et al., 2014). These effects were seen for mutations located in the extracellular glutamate-binding domain region, as well as those variants affecting the re-entrant pore-forming loop implicated in  $Mg^{2+}$  block. Early-onset epileptic encephalopathy has also been associated with a de novo *GRIN2B* splice-site mutation, providing evidence for *GRIN2B* loss-of-function as a cause of epileptic encephalopathies. Thus, both gain and loss of NMDA receptor function can cause similar disease phenotypes (Smigiel et al., 2016).

*b. Mechanisms and potential targeted therapies.* It is yet to be understood how both gain- and loss-of-GluN2B function leads to a similar disease phenotype. The use-dependent NMDA receptor blocker, memantine, would be predicted to be useful in gain-of-function disease. However, despite some efficacy in vitro, memantine had limited impact in patients with gain-of-function *GRIN2B* mutations (Platzer et al., 2017). For loss-of-function *GRIN2B* mutations, a strategy based on

selective antagonism may be beneficial, but has not been tested. Again, a lack of good preclinical models is hampering progress with heterozygous GluN2B knockout mice not displaying a seizure phenotype. Homozygous *Grin2b* knockout mice die shortly after birth, but this is thought to be due to a defect in the suckling response (Kutsuwada et al., 1996).

4. *GRIN2D*. *GRIN2D* encodes the GluN2D NMDA receptor subunit. GluN2D expression is widespread during early development in the brain and decreases during adulthood (Akazawa et al., 1994; Monyer et al., 1994; von Engelhardt et al., 2015; Perszyk et al., 2016). In the adult hippocampus, striatum, and cortex, GluN2D is expressed in interneurons (Monyer et al., 1994; Standaert et al., 1996; Perszyk et al., 2016).

*a. Clinical syndrome and molecular findings.* A recurrent de novo mutation in *GRIN2D* has been identified in patients with early infantile epileptic encephalopathy, with phenotypes that include severe developmental delay, intellectual disability, and movement disorders (Li et al., 2016). The missense mutation found in *GRIN2D* occurs in the M3 transmembrane domain and results in a gain-of-function through slower deactivation, increased channel open probability, and increased glutamate and glycine potency (Li et al., 2016).

*b. Mechanisms and potential targeted therapies.* Transfection of cortical neurons with mutant GluN2D subunits leads to cell death. This is consistent with NMDA receptor overactivation and is blocked by the NMDA receptor blocker, memantine (Li et al., 2016). A clinical study using oral memantine decreased seizures in patients in which conventional antiepileptic drugs were unsuccessful (Li et al., 2016). One patient, who developed status epilepticus, improved with treatment of ketamine and magnesium, both NMDA receptor blockers (Li et al., 2016).

GluN2D knockout mice partially recapitulate some of the clinical features of human disease, with a reduction in spontaneous locomotor activity similar to that seen in patients (Ikeda et al., 1995). However, no seizures have been reported in heterozygous or homozygous GluN2D knockout mice (Ikeda et al., 1995). There is a clear need for a knock-in mouse model to provide further insights into the disease mechanism. Given the importance of this subunit in early development, the engineering of conditional mouse models will be important in dissecting out developmental versus acute impact of the mutation in defining seizure susceptibility (Perszyk et al., 2016).

## B. GABA<sub>A</sub> Receptors

The neurotransmitter GABA drives the majority of inhibitory signaling in the mature brain. It can activate two classes of receptors: the ligand-gated ionotropic GABA<sub>A</sub> receptors and the G protein-coupled metabotropic GABA<sub>B</sub> receptors (Alexander et al., 2015b;

<http://www.guidetopharmacology.org/GRAC/Family-DisplayForward?familyId=72>). The GABA<sub>A</sub> receptors are members of the Cys-loop receptor family and are heteropentameric proteins that assemble from various combinations of proteins encoded by the  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\theta$ , and  $\rho$  subunit gene families. These subunit combinations introduce considerable receptor heterogeneity and vary in their functional properties, response to pharmacological agents, and brain expression patterns. The common subunit combinations exist as two  $\alpha$ -, two  $\beta$ -, and one  $\gamma$ - or  $\delta$ -subunit (Macdonald and Olsen, 1994; Fritschy and Panzanelli, 2014).

GABA<sub>A</sub>-mediated inhibition acts predominately through GABA release from synaptic vesicles onto postsynaptically located GABA<sub>A</sub> receptors. In the mature central nervous system, this leads to a brief inward flow of Cl<sup>-</sup> and an inhibitory postsynaptic potential. This transient receptor activation, with high GABA concentrations acting at the synapse, is termed phasic inhibition. There is a less spatially and temporally restricted GABA<sub>A</sub>-mediated inhibition, in which low concentrations of GABA can act remotely from the synapse, termed tonic inhibition (Farrant and Nusser, 2005). Mutations in several genes encoding GABA<sub>A</sub> receptor subunits have been implicated in epilepsy. These include *GABRA1*, *GABRB3*, and *GABRG2*, which will be discussed in more detail below. Variants in *GABRB2*, *GABRD*, and *GABRA3* have also been reported (Dibbens et al., 2004; Lenzen et al., 2005; Srivastava et al., 2014; Ishii et al., 2017; Niturad et al., 2017).

1. *GABRA1*. *GABRA1* encodes the GABA<sub>A</sub> receptor  $\alpha 1$ -subunit, which is among the most abundantly expressed GABA<sub>A</sub> receptor subunits in the brain (Pirker et al., 2000). The  $\alpha 1$ -subunit containing GABA<sub>A</sub> receptors form the majority of postsynaptic GABA<sub>A</sub> receptors. These receptors mediate phasic inhibition (Hörtnagl et al., 2013).

*a. Clinical syndrome and molecular findings.* *GABRA1* mutations have been reported to associate with GGE (Cossette et al., 2002; Maljevic et al., 2006; Lachance-Touchette et al., 2011; Johannesen et al., 2016). Epilepsy syndromes include JME, CAE, and febrile seizures (Cossette et al., 2002; Maljevic et al., 2006; Lachance-Touchette et al., 2011; Johannesen et al., 2016). More recent evidence implicates *GABRA1* mutations in early infantile epileptic encephalopathies, including phenotypes of Dravet, Ohtahara, or West syndromes (Carvill et al., 2014; Johannesen et al., 2016; Kodera et al., 2016). Both GGE and the severe encephalopathies share common clinical features, including myoclonic seizures, tonic-clonic seizures, and photosensitivity (Cossette et al., 2002; Lachance-Touchette et al., 2011; Johannesen et al., 2016). Functional analysis has unanimously shown loss-of-function, including reduced surface expression of the assembled GABA<sub>A</sub> receptor (Lachance-Touchette et al., 2011). This can be caused by increased endoplasmic degradation of

the misfolded protein, as noted for the *GABRA1* (A322D) variant (Gallagher et al., 2004, 2005). A reduction in the sensitivity to GABA has also been reported (Krampfl et al., 2005; Carvill et al., 2014). Interestingly, there is a correlation between *GABRA1* mutations causing severe epilepsy and a significant loss of the GABA sensitivity of the receptor (Johannesen et al., 2016).

*b. Mechanisms and potential targeted therapies.* Heterozygous *Gabra1* knockout mice have spontaneous electrographic spike-wave discharges and behavioral absence-like seizures (Arain et al., 2012), recapitulating some of the milder GGE phenotypes. The *GABRA1* (A322D) knock-in mouse model based on a JME mutation (Cossette et al., 2002) also develops a spike-and-wave electrographic phenotype (Arain et al., 2015). A direct comparison with the *Gabra1* knockout indicated that both equally expressed the spike-and-wave discharge phenotype, suggesting that simple haploinsufficiency was the basis of disease (Arain et al., 2015). Both mutant mice develop myoclonic seizures later in life, which may model JME (Arain et al., 2015). These mice lines therefore are good preclinical models of GGE, providing an opportunity to devise and test new therapeutic strategies. New models that recapitulate more severe disease are still required.

Given that *GABRA1* mutations impair GABAergic inhibition, it is not surprising that they increase neuronal excitability and consequently result in seizure phenotypes. Drugs that specifically increase GABA<sub>A</sub> function are therefore likely to be highly effective in patients carrying *GABRA1* mutations. Consistent with this, vigabatrin and sodium valproate, both of which have been shown to maintain high GABA concentrations in the synaptic cleft (Connolly, 1993; Johannesen, 2000), successfully control seizures of patients with *GABRA1* mutations (Kodera et al., 2016). Unfortunately, barbiturates and benzodiazepines that specifically target phasic GABA<sub>A</sub> inhibition have significant side effects (Kwan et al., 2001).

2. *GABRB3*. *GABRB3* encodes the GABA<sub>A</sub> receptor  $\beta 3$ -subunit. The  $\beta 3$ -subunit is expressed at high levels in the embryonic brain, but its expression decreases to lower levels in the adult, except in the hippocampus. Additionally,  $\beta 3$ -subunit expression overlaps significantly with  $\alpha 2$ -subunit expression (Hörtnagl et al., 2013; Fritschy and Panzanelli, 2014).

*a. Clinical syndrome and molecular findings.* The Epi4K Consortium and Epilepsy Phenome/Genome Project were the first to provide strong evidence of *GABRB3* mutations in early infantile epileptic encephalopathy (Allen et al., 2013). Several more recent studies have confirmed this original finding (Allen et al., 2013; Hamdan et al., 2014; Zhang et al., 2015a; Papandreou et al., 2016; Møller et al., 2017). The affected patients display a broad spectrum of seizure types, which includes absence, tonic, myoclonic, and

generalized tonic-clonic seizures. Some of them also show delayed development, and mild to severe intellectual disabilities (Allen et al., 2013; Papandreou et al., 2016; Møller et al., 2017). Epilepsy syndromes reported include Lennox-Gastaut, infantile spasms, West, and Dravet syndromes (Allen et al., 2013; Møller et al., 2017). Milder syndromes caused by mutations in *GABRB3* include GEFS<sup>+</sup>, early-onset absence epilepsy, epilepsy with myoclonic-atonic seizures, and multifocal epilepsy (Møller et al., 2017). Mutations in *GABRB3*, typically whole-gene deletions, have also been associated with Angelman syndrome (Tanaka et al., 2012).

Functional analysis uniformly suggests loss-of-function of *GABRB3* variants through a variety of biophysical and trafficking deficits (Janve et al., 2016; Møller et al., 2017). As seen for *GABRA1* mutations, some *GABRB3* mutations causing more severe epilepsy show a significant loss of GABA sensitivity, suggesting a potential genotype–phenotype correlation (Møller et al., 2017). Similarly, mutations associated with Lennox-Gastaut syndrome have reduced GABA-evoked current amplitudes, whereas infantile seizure variants show changes in current kinetics (Janve et al., 2016).

*b. Mechanisms and potential targeted therapies.* Given the role of *GABRB3* in neuronal migration, synaptogenesis, and overall brain development, mutations in *GABRB3* are likely to be linked to abnormal development of neuronal networks (Noebels et al., 2012; Tanaka et al., 2012). Therefore, targeting therapies in early development may be required to rescue seizure and neurodevelopmental symptoms in these patients. Homozygous *Gabrb3* knockout mice show increased mortality and seizures and impaired social behavior, cognition, and motor coordination, whereas heterozygous mice have increased epileptiform EEG activity and seizure susceptibility (Homanics et al., 1997; DeLorey et al., 1998, 2008). These features recapitulate some of the phenotypes seen in *GABRB3* disease, including Angelman syndrome.

3. *GABRG2*. *GABRG2* encodes the  $\gamma 2$ -subunit found in the most common GABA<sub>A</sub> receptor in the brain, the  $\alpha 1\beta 2\gamma 2$  complex.

*a. Clinical syndrome and molecular findings.* Mutations in *GABRG2* have been associated with GEFS<sup>+</sup>, Dravet syndrome, CAE, familial febrile seizures, and epileptic encephalopathy (Baulac et al., 2001; Wallace et al., 2001; Harkin et al., 2002; Kananura et al., 2002; Audenaert et al., 2006; Shen et al., 2016; Hernandez et al., 2017). In vitro studies suggest a range of mutation-mediated functional deficits, including changes in benzodiazepine sensitivity, receptor kinetics, assembly, trafficking, and cell surface expression (Baulac et al., 2001; Bianchi et al., 2002; Bowser et al., 2002; Sancar and Czajkowski, 2004; Hales et al., 2005; Krampfl et al., 2005; Kang et al., 2006; Eugène et al., 2007; Kang and Macdonald, 2016; Hernandez et al.,

2017). In general, these functional analyses suggest that epilepsy-causing mutations result in a reduction in GABA<sub>A</sub> receptor-mediated inhibition, albeit through varying mechanisms. A consequent reduction in both phasic and/or tonic inhibition is proposed to underlie increases in neuronal hyperexcitability, resulting in seizures.

*b. Mechanisms and potential targeted therapies.* The *GABRG2* (R43Q) knock-in mouse model was one of the first syndrome-specific models developed for genetic epilepsy, and faithfully recapitulates both the absence epilepsy and febrile seizures seen in the family (Tan et al., 2007). The *GABRG2* (R43Q) mutation mouse model also recapitulates some of the genetic complexity seen in patients. Namely, the *GABRG2* (R43Q) mice only display an absence phenotype in a spike-and-wave prone mouse strain (DBA), whereas the febrile seizure phenotype is robust in all mouse strains tested. This observation matches the penetrance seen in humans, which is low for absence seizures, whereas febrile seizures segregate as a highly penetrant autosomal dominant trait (Wallace et al., 2001). This implies that genetic principles that occur in human populations can be recapitulated in mouse models, providing the tools to interrogate complex heritability. The *GABRG2* (R43Q) mouse model also has an expected pharmacosensitivity profile responding to first-line anti-absence drugs, ethosuximide and sodium valproate (Tan et al., 2007; Kim et al., 2015). The *GABRG2* (Q390X) knock-in mouse model recapitulates the more severe seizure phenotype seen in patients with truncation mutations (Warner et al., 2016). These models provide an excellent opportunity to identify cellular mechanisms, and act as good preclinical models of disease.

A comparison between *GABRG2* knock-in and knockout mice reveals that the molecular mechanisms for different seizure phenotypes may result from distinct molecular deficits. A spike-and-wave discharge phenotype in both the *GABRG2* (R43Q) and heterozygous *Gabrg2* knockout mice suggested that haploinsufficiency was sufficient to cause absence seizures (Reid et al., 2013; Warner et al., 2016). In contrast, only the *GABRG2* (R43Q) model displayed a thermogenic seizure phenotype, suggesting a mechanism over and above haploinsufficiency was responsible for febrile seizures. In the *GABRG2* (Q390X) mouse, which models a more severe epilepsy phenotype, a reduction in the expression of the GABA<sub>A</sub>  $\gamma 2$ -subunit is greater than that seen in the *Gabrg2* knockout, suggesting a dominant-negative effect of the mutant on the wild-type subunits (Warner et al., 2016). Whether disease caused by these distinct molecular mechanisms will require different targeted therapeutic strategies is yet to be determined.

The conditional *GABRG2* (R43Q) mouse model provides an opportunity to explore the impact of the mutation in early development (Chiu et al., 2008). Mice



harboring the GABRG2 (R43Q) mutation from birth were reported to be more susceptible to seizures (Chiu et al., 2008). This argues that mutation-mediated dysfunction can trigger a cascade of events (e.g., morphologic and/or transcriptional changes) that define long-term network stability. Therefore, targeted treatment early in development may be necessary to fully rescue patients harboring epilepsy-causing mutations.

In summary, mouse models of GABRG2-associated epilepsy have provided key insights into disease mechanisms. They suggest that phenotype severity may depend on the extent of dominant-negative impact of mutations and that different therapeutic strategies may be required for different seizure phenotypes. These models also highlight the potential need to treat early in development. Clearly, activators of the GABA<sub>A</sub> receptors, such as benzodiazepines, are likely to benefit these patients, with the early use of this class potentially overcoming the developmental consequences of harboring GABRG2 mutations (Haas et al., 2013).

### C. Nicotinic Acetylcholine Receptors (CHRNA4, CHRNB2, and CHRNA2)

Vertebrate nicotinic acetylcholinergic receptors (nAChRs) are pentameric ligand-gated ion channels assembled from homologous subunits. *CHRNA4* and *CHRNB2* encode the  $\alpha$ 4- and  $\beta$ 2-subunits, respectively, which combine to form the most abundant nAChR in the brain (Gotti et al., 1997; Hogg et al., 2003; Alexander et al., 2015b; <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=76>). *CHRNA2* encodes the  $\alpha$ 2-subunit that is found predominantly in GABAergic interneurons (Son and Winzer-Serhan, 2006). Synaptic responses mediated by nAChRs appear to mediate only a small fraction of cholinergic transmission (Dani, 2001). Consistent with this, nAChRs are predominantly located on presynaptic, perisynaptic, and extrasynaptic sites (Hurst et al., 2013). A major role of central nAChRs is to modulate the release of other neurotransmitters, including glutamate, GABA, dopamine, and noradrenaline (Hurst et al., 2013).

**1. Clinical Syndrome and Molecular Findings.** As the first epilepsy gene, *CHRNA4* holds an important place in the history of research into the genetic basis of epilepsy (Steinlein et al., 1995). It was discovered in an Australian family that presented with ADNFLE, an idiopathic epileptic syndrome with focal seizures arising from the frontal regions that occur predominantly during stage 2 of sleep (Scheffer et al., 1994). Several other mutations in *CHRNA4*, *CHRNA2*, and *CHRNB2* have been found in families with ADNFLE (Steinlein et al., 1995, 1997; Hirose et al., 1999; De Fusco et al., 2000; Phillips et al., 2001; Bertrand et al., 2005; Aridon et al., 2006; Conti et al., 2015; Trivisano et al., 2015). A range of biophysical consequences of the various identified mutations has been reported (Sutor and Zolles, 2001; Becchetti et al., 2015). However, a common effect

of mutations in the  $\alpha$ 4-,  $\beta$ 2-, and  $\alpha$ 2-subunits is an increase in the sensitivity of the receptor to acetylcholine, suggesting a convergent physiologic pathway may underpin disease (Bertrand et al., 2002, 2005; Aridon et al., 2006; Hoda et al., 2008).

**2. Mechanisms and Potential Targeted Therapies.** *CHRNA4* (S252F) and *CHRNA4* (+L264) knock-in mouse models based on human mutations provide support for a gain-of-function of the nAChR in ADNFLE (Klaassen et al., 2006). Mutant mice display abnormal EEG patterns consistent with seizure activity (Klaassen et al., 2006), as well as a dystonic phenotype that may form part of the spectrum observed in ADNFLE (Teper et al., 2007). One striking cellular phenotype is a more than 20-fold increase in nicotine-evoked synaptic release exclusively at inhibitory synapses (Klaassen et al., 2006). This implicates increased inhibitory activity as the basis of hyperexcitability, an idea supported by the fact that seizures are blocked by subconvulsive doses of a GABA<sub>A</sub> receptor antagonist. Although seemingly paradoxical, it has been proposed by others that circuit level increases in neocortical GABA<sub>A</sub> receptor-mediated current can be epileptogenic (Mann and Mody, 2008).

A transgenic mouse model based on a gain-of-function mutation in *CHRNB2* displays a spontaneous epileptic phenotype with very frequent interictal spikes and seizures (Manfredi et al., 2009). Mutant  $\beta$ 2-subunit expression is driven under a conditionally controlled promoter allowing the silencing of transgene expression. Using this model, it was shown that silencing during early development was sufficient to prevent the occurrence of seizures in adulthood (Manfredi et al., 2009). This is similar to findings in the conditional GABRG2 (R43Q) mouse model (see above), and highlights that mutation-mediated long-lasting alterations of neuronal networks in the developing brain may lead to epilepsy. Cellular analysis in this mouse model is limited to the relatively crude synaptosome preparation, but does reveal increased sensitivity of acetylcholinergic-mediated release of dopamine (O'Neill et al., 2013). A transgenic rat with a gain-of-function mutation also displays infrequent spontaneous epileptic seizures that are described as being similar to paroxysmal arousals observed in human ADNFLE, providing another potential preclinical model (Shiba et al., 2015).

Despite being identified over 20 years ago, no targeted therapies for mutations in acetylcholinergic receptor have eventuated. The mainstay of therapy in patients with nAChR mutations is carbamazepine with approximately 70% showing remission on low doses. Molecular and cellular studies argue that drugs that block nAChR should be effective in disease caused by mutation in *CHRNA4*, *CHRNB2*, and *CHRNA2*. Several studies have shown the potential of nAChR antagonists as anti-seizure drugs (Ghasemi and Hadipour-Niktarash, 2015).

Mechanistic studies in rodent models suggest that increased release of GABA may underlie hypersynchrony at the neuronal network scale (Klaassen et al., 2006). Therefore, low-dose GABA<sub>A</sub> receptor antagonists may benefit patients harboring *CHRNA4* mutations. However, this is unlikely to become a treatment strategy given the obvious narrow therapeutic window of such drugs. Finally, the developmental impact of the gain-of-function *CHRN2* mutation suggests that it may be necessary to treat patients early to fully overcome the epileptogenic process.

#### IV. Conclusion

The last two decades have begun to unravel the complexity of the genetic architecture of human epilepsy. It is now clear that hundreds of genes can play a pathogenic role in the disease. Table 1 summarizes the ion channels discussed and the proposed molecular and cellular deficits. Much of the hidden genetics in epilepsy that has not been apparent from traditional clinical studies can be explained by de novo mutations and mosaicism (Thomas and Berkovic, 2014). However, most common epilepsy syndromes still lack comprehensive genetic models. Electrophysiological testing on heterologously expressed ion channels remains the mainstay of functional validation. These are opaque to a number of important biologic readouts, and newer, more sophisticated in vitro models need to be developed, with assays based on human iPSC-derived neurons showing some promise. For loss-of-function mutations, standard knockout rodent models have proven to be useful. However, in most cases, the development of syndrome-specific mouse models based on human mutation (Table 1) has become the new expected standard. It is remarkable how frequently these knock-in mouse models recapitulate the disease phenotypes seen in patients and allow cellular and neuronal network function to be probed. They also act as good preclinical tools. Using a combination of these tools, we have been developing a much clearer idea of disease mechanisms in genetic epilepsy and consequently devising therapeutic strategies based on these mechanisms. Some success has been achieved in the repurposing of drugs that target the disease processes. Epilepsy is also well placed to take advantage of newer molecular and antibody technologies that can selectively target the affected genes. This includes antisense technology to reduce function where mutations cause a gain-of-function. Also, ingenious application of new molecular technologies can be used to increase function in loss-of-function disease. For example, the use of CRISPR-on could activate genes to increase activity to restore function (Cheng et al., 2013). Genetic epilepsy is primed to benefit from the genetic revolution, with the promise of further powerful and targeted therapeutic strategies to come.

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