**Review Article**

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# Treatment strategies targeting specific genetic etiologies in epilepsy

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Recent genetic advances allow for identification of the genetic etiologies of epilepsy within individual patients earlier and more frequently than ever. Specific targeted treatments have emerged from improvements in understanding of the underlying epileptogenic pathophysiology. These targeted treatment strategies include modifications of ion channels or other cellular receptors and their function, mechanistic target of rapamycin signaling pathways, and substitutive therapies in hereditary metabolic epilepsies. In this review, we explore targeted treatments based on underlying pathophysiologic mechanisms in specific genetic epilepsies.

**Key words:** Epilepsy, Genetics, Precision medicine.

## Introduction

With scientific advances, understanding of epilepsies and their underlying mechanisms have evolved. Epilepsy is classified based on seizure type, epilepsy type, and epilepsy syndrome. Along with this classification, an etiologic diagnosis should be considered in each individual epilepsy patient at each step of diagnosis, as it often carries significant treatment implications [1]. In patients with developmental and epileptic encephalopathy, targeted gene panels commonly used in clinical settings provide identification of specific genetic etiologies. Increasing data about genetic epilepsy provide knowledge about phenotypes, prognosis, and targeted treatment of the epilepsy. This evolution of knowledge is shifting paradigms in epilepsy treatment from a population approach, based on epilepsy type or syndrome, to an individually targeted approach, based not only on epilepsy syndrome, but on the underlying pathophysiologic mechanism. In this review, we present the current state of this ongoing paradigm shift and focus on specific genetic epilepsies with specific targeted treatments important for clinicians to know for proper disease management.

## Current Approaches to Genetic Epilepsy

Of the more than 100 genes implicated in epilepsy [2], most affect ion channels, cellular receptors, signaling pathways, or metabolic pathways [3]. Identification of these genes allowed for design of evidence-based treatment approaches to target these pathways within individual patients. Here, we review the genetic causes of epilepsy that have targeted treatments within each category (Table 1).

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**Table 1.** Targeted therapies for genetic epilepsies

| Gene | Phenotype | Specific target | Targeted therapy | Status of therapy |
|---|---|---|---|---|
| Sodium channel | | | | |
| *SCN1A* | Dravet syndrome | Na$_v$1.1 LoF | Avoid SCBs | Established |
| *SCN2A* | Ohtahara syndrome, West syndrome, EIMFS, onset <3 months of age, benign familial neonatal/infantile seizures | Na$_v$1.2 GoF | SCBs | Potential |
| | Seizures with autism, onset >3 months of age | Na$_v$1.2 LoF | - | - |
| *SCN8A* | Onset from neonate to 18 months with diverse seizure types including focal seizures, spasms or non-convulsive status epilepticus | Na$_v$1.6 GoF | SCBs | Potential |
| | Cognitive disability without epilepsy | Na$_v$1.6 LoF | - | - |
| Potassium channel | | | | |
| *KCNQ2* | Ohtahara syndrome, neonatal onset focal seizures, benign familial neonatal epilepsy | K$_v$7.2 LoF | SCBs<br>Retigabine | Established<br>Potential |
| *KCNT1* | EIMFS, nocturnal frontal lobe epilepsy | Slack GoF | Quinidine | Potential |
| NMDA receptor | | | | |
| *GRIN2A* | Continuous spike-and-wave during sleep, Landau–Kleffner syndrome | NMDA GoF | Memantine | Hypothetical |
| | | NMDA LoF | - | - |
| *GRIN2B* | West syndrome, Lennox–Gastaut syndrome | NMDA GoF | Memantine | Hypothetical |
| | | NMDA LoF | - | - |
| mTOR signaling pathways | | | | |
| *DEPDC5/NPRL2/NPRL3* | Familial focal epilepsy with variable foci, West syndrome | GATOR1 complex subunit | mTOR inhibitors | Hypothetical |
| *TSC1/TSC2* | Tuberous sclerosis, focal cortical dysplasia | TSC1/TSC2 | mTOR inhibitors | Hypothetical |
| Glucose transporter | | | | |
| *SLC2A1* | GLUT1 deficiency | Glucose transporter type 1 | Ketogenic diet | Established |
| Pyridoxine metabolic pathway | | | | |
| *ALDH7A1* | Pyridoxine dependent epilepsy | Pyridoxine metabolic pathway | Pyridoxine | Established |

Status of therapies were assessed as follows:'established': in routine clinical use, 'potential': some case reports on its use in patients available, 'hypothetical': only based on theoretical considerations, data from animal models or single case reports in humans.
LoF, loss of function; SCB, sodium channel blocker; EIMFS, epilepsy of infancy with migrating focal seizures; GoF, gain of function; Slack, sodium-activated potassium channel subfamily T member 1; NMDA, N-methyl-D-aspartate; mTOR, mechanistic target of rapamycin; GATOR1, gap activity toward rags 1; TSC, tuberous sclerosis complex; GLUT1, glucose transporter 1; -, not available.

### 1. Modifying functions of ion channels or receptors

#### 1) Sodium channel

*SCN1A* encodes the $\alpha$1 subunit of the voltage-gated sodium channel Na$_v$1.1 [4]. Dravet syndrome is caused by a *de novo* loss-of-function mutation within *SCN1A*, which results in reduced sodium current in GABAergic interneurons [5,6]. As this mutation increases overall excitability via reduced activity of inhibitory interneurons, sodium channel blockers should be avoided in Dravet syndrome patients, including carbamazepine, lamotrigine, and phenytoin [7]. Conversely, stripentol which increases GABAergic effect is recommended for use adding to valproic acid and clobazam [8].

Although the phenotype and treatment of Dravet syndrome have been well established, data for epilepsies associated with *SCN2A* and *SCN8A* only recently have increased. *SCN2A* encodes Na$_v$1.2, the type II $\alpha$-subunit of voltage-gated sodium channels [9]. In addition to benign familial neonatal/infantile seizures (BFNIS) [10], mutations of *SCN2A* cause developmental and epileptic encephalopathies (DEE) or intellectual disability and/or autism with/without epilepsy [11-14]. Phenotypes of DEE in *SCN2A* mutations include Ohtahara syndrome, West syndrome, epilepsy of infancy with migrating focal seizures (EIMFS), and unclassified severe epilepsy [11,12]. There are two distinct groups in *SCN2A*-related DEE. The first group is characterized by neonatal and early infantile-onset epilepsy (<3 months of age), missense mutations with gain-of-function effects, and a good response to sodium channel blockers. The second group is characterized by late infantile or childhood-onset epilepsy (>3 months of age), loss-of-function mutations, mainly truncating mutations, and relatively poor response to sodium channel blockers [13]. Sodium channel blockers, including phenytoin, carbamazepine, oxcarbazepine, lamotrigine, and topiramate, are effective in treating neonatal and early infantile-onset *SCN2A*-related DEE [11,12,15,16]. In contrast, sodium channel blockers proved either not effective, or even aggravated seizures, in patients with late infantile or childhood-onset DEE or intellectual disability and/or autism [13]. Sodium channel blockers were also effective in patients with BFNIS [13]. In deciding whether to treat patients with *SCN2A*-related epilepsy with a sodium channel blocker, clinicians should first identify the phenotype and next consider whether the variant might be gain-of-function or loss-of-function.

*SCN8A* encodes the voltage-gated sodium channel $Na_v1.6$, which plays a role in regulation of neuronal excitability in the brain [17]. *SCN8A* mutations present in a wide spectrum of epilepsy phenotypes, ranging from benign familial infantile epilepsy to severe DEE [18-23]. Also, *SCN8A* mutations associate with movement disorders including hypotonia, dystonia, choreoathetosis, and ataxia in addition to sudden unexpected death in epilepsy patients [21,24-26]. First identified in 2012, *SCN8A* DEE, also known as early infantile epileptic encephalopathy type 13, is defined as a severe developmental epileptic encephalopathy syndrome caused by *de novo* gain-of-function mutations of *SCN8A* [27]. Onset of seizures in *SCN8A* DEE patients ranges from the neonatal period to 18 months of age. Focal seizures or spasms are predominant seizure types. They present West syndrome, neonatal status epilepticus, or non-convulsive status epilepticus [28]. As *SCN8A* DEE is caused by gain-of-function mutation, sodium channel blockers, such as phenytoin, carbamazepine, and oxcarbazepine, are effective for seizure control [18,28]. Recent studies showed benign epilepsy associates with intermediate gain-of-function *SCN8A* mutations, while severe epilepsy associates with severe gain-of-function mutations [29]. Furthermore, *SCN8A* mutations linked with cognitive disability without epilepsy are loss-of-function [29]. Pathophysiological considerations supported by clinical data suggest that sodium channel blockers are effective and should be considered as a treatment option in *SCN8A* DEE patients.

### 2) Potassium channel

*KCNQ2* encodes the voltage-gated potassium channel subunit $K_v7.2$. *KCNQ2* mutations were traditionally identified in benign familial neonatal epilepsy (BFNE) which were autosomal dominantly inherited [30,31]. BFNE presents seizures during the first week after birth which remit spontaneously with normal development [31,32]. Recently, *de novo KCNQ2* mutations have been identified in patients with neonatal DEE [33-40]. *KCNQ2* encephalopathy also presents with seizure onset during the first week after birth. However, these seizures are intractable, usually tonic, with burst suppression EEG pattern and accompany severe developmental delay [33-36,40]. Functional studies demonstrate that *KCNQ2* mutations seen in BFNE are haploinsufficient, whereas mutations in *KCNQ2* encephalopathy are dominant negative and result in a more severe reduction of channel current [31,41]. However, in rare cases, some *KCNQ2* mutations in encephalopathy show an increase of channel current [42].

One targeted treatment approach for loss-of-function *KCNQ2* mutations is retigabine. Retigabine, first introduced as an add-on therapy in focal epilepsy in adults, opens the voltage-gated potassium channel $K_v7.2/K_v7.3$ [43]. Retigabine attenuates seizures in knock-in mice with *KCNQ2* mutations [44]. A recent study reported improvement of seizures and development in 5 of 11 patients with *KCNQ2* encephalopathy, 3 of 4 patients treated before the age of 6 months, and 2 of 7 patients treated at an older age [38]. Although successful in treating seizures, retigabine was withdrawn from the market because of serious side effects, such as loss of vision and blue discoloration of both the skin and retina [45]. Interestingly, clinical observations have suggested sodium channel blockers are effective against *KCNQ2* encephalopathy [35,36]. Numerous successful reports support the recommendation of sodium channel blockers as a first-line treatment in *KCNQ2* encephalopathy [37]. A systemic review of 133 patients with *KCNQ2* related BFNE and 84 patients with *KCNQ2* encephalopathy determined that sodium channel blockers are appropriate for both groups and suggested that phenobarbital be considered in *KCNQ2* related BFNE [46]. The therapeutic effect of sodium channel blockers against *KCNQ2* mutations could be explained by the colocalization of voltage-gated sodium channels and KCNQ potassium channels on neuronal membranes. The modulation of the sodium channel may significantly affect the function of the whole channel complex [37].

*KCNT1* encodes the sodium-activated potassium channel subfamily T member 1, also called Slack. It is widely expressed in the frontal cortex and is responsible for slow hyperpolarization of neurons [47]. The clinical spectrum of *KCNT1* mutations include autosomal dominant nocturnal frontal lobe epilepsy and EIMFS [47,48]. As the mutations of *KCNT1* typically have gain-of-function effect [48,49], potassium channel blockers are proposed as a treatment. Quinidine, an inhibitor of potassium channels including *KCNT1*, is used as an antiarrhythmic and antimalarial drug [50]. Clinical trials of quinidine showed mixed results. Some studies suggested significant seizure reduction but treatment failures were also reported [51-57]. Proposed explanations for the lack of response to treatment include low drug levels in the brain associated with interindividual variability in crossing the blood-brain barrier, limitations on dosage due to prolongation of QT interval, or other additional unrecognized pathophysiological factors [51,55]. Quinidine is a promising treatment option in some patients with *KCNT1*-related epilepsy, but further larger studies are necessary to clarify the effectiveness.

### 3) N-methyl-D-aspartate receptor

N-methyl-D-aspartate (NMDA) receptors are ligand-gated ion channels involved in fast excitatory neurotransmission and play a role in both synaptogenesis and synaptic plasticity [58]. *GRIN2A* and *GRIN2B* encode the GluN1 and GluN2 subunits of the NMDA receptor. Mutations in *GRIN2A* and *GRIN2B* present diverse neurologic or psychologic disorders including epilepsy, intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder, and schizophrenia [58-61]. Epilepsies caused by *GRIN2A* mutations range from mild syndromes, such as childhood epilepsy with centrotemporal spikes, to severe syndromes, such as Landau–Kleffner syndrome or epileptic encephalopathy with continuous spike-and-wave during sleep [62]. Epilepsies caused by *GRIN2B* mutations include West syndrome, Lennox–Gastaut syndrome, and other DEE [58]. A functional study of a missense mutation of *GRIN2A* (c.2434C>A; p.L812M) revealed enhanced agonist potency; decreased sensitivity to negative modulators, including magnesium, protons, and zinc; prolonged synaptic response time course; and increased single-channel open probability. Taken together, the mutation causes overactivation of NMDA receptors and drives neuronal hyperexcitability [63]. Memantine, an NMDA-receptor antagonist approved for treating Alzheimer's dementia, reduced seizure burden in a patient with a *GRIN2A* mutation (p.L812M) [64]. However, memantine use in another patient with a different *GRIN2A* mutation (p.N615K) showed a contrasting result [64]. Therefore, specific electrophysiological evaluation of each *GRIN2A* mutation is needed to evaluate its response to NMDA-receptor antagonists.

## 2. Modifying mechanistic target of rapamycin signaling pathways

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by loss-of-function mutations in one of two genes: TSC1 or TSC2. It affects multiorgan systems including tumors of the brain, skin, heart, lungs, and kidneys. The brain abnormalities include tubers and subependymal giant cell astrocytomas (SEGA). Multiple tubers cause intractable seizures, autism spectrum disorder, and intellectual disability [65]. The TSC protein complex acts as an inhibitor of the mechanistic target of rapamycin (mTOR) signaling pathway. The mTOR inhibitor, everolimus, is approved for the treatment of renal angiomyolipoma and SEGA [65]. Everolimus reduces both tumor size and seizure burden. Data from the EXIST-3 trial support that everolimus leads to a significant seizure reduction in TSC patients with refractory epilepsy [66-68]. Furthermore, preventive antiepileptic treatment in TSC patients is recommended to modify the natural history of epilepsy [69], as epilepsy develops in 70% to 90% of TSC patients and is often resistant to medication. EPISTOP, a clinical trial designed to compare preventive versus conventional antiepileptic treatment in TSC infants, demonstrated that preventive treatment with vigabatrin was safe, modified the natural history of seizures in TSC, and reduced the risk and severity of epilepsy [69].

Germline loss-of-function mutations in *DEPDC5* have emerged as a major cause of familial focal epilepsy with variable foci [70,71]. *DEPDC5*-related familial focal epilepsy also present with focal cortical dysplasia (FCD) [72,73]. Recent studies demonstrate that the GATOR1 protein complex, comprised of *DEPDC5*, *NPRL3*, and *NPRL2*, plays a pivotal role in regulating mTOR signaling in response to cellular amino acid levels [74]. Additionally, mutations in *DEPDC5*, *NPRL3*, or *NPRL2* are linked to FCD, hemimegalencephaly, and seizures [74]. Recent studies demonstrate that a biallelic 2-hit mutational mechanism in *DEPDC5*, defined as mutations in both somatic brain tissue and germline cells, causes focal epilepsy with FCD [75]. Furthermore, the role of the GATOR1 proteins in regulating mTOR signaling suggest possible options for mTOR inhibition in the treatment of epilepsy associated with mutations in *DEPDC5*, *NPRL3*, or *NPRL2* [74].

## 3. Substitutive therapies in inherited metabolic diseases

*SLC2A1* encodes the glucose transporter, GLUT1, required to transport glucose across the blood-brain barrier. Mutations in *SLC2A1* result in GLUT1 deficiency [76]. Classical GLUT1 deficiency is characterized by early-onset severe developmental delay with microcephaly and medication refractory seizures [77]. The current standard treatment for GLUT1 deficiency is the ketogenic diet, a high fat diet that raises levels of ketone bodies in the blood to make them available to the brain [78]. Therefore, the ketogenic diet provides an alternative energy supply to the brain.

Pyridoxine-dependent epilepsy is an autosomal recessive disease caused by biallelic *ALDH7A1* mutations. *ALDH7A1* encodes the $\alpha$-aminoadipic semialdehyde ($\alpha$-AASA) dehydrogenase, a key enzyme in lysine oxidation [79]. *ALDH7A1* mutations result in accumulation of pipecolic acid, $\alpha$-AASA, and its cyclic equilibrium partner $\Delta$1-piperideine-6-carboxylate ($\Delta$1-P6C) [80]. The accumulated $\Delta$1-P6C is postulated to bind the active vitamer of pyridoxine (pyridoxal 5′-phosphate) and cause pyridoxine-dependent epilepsy [80]. Classical pyridoxine-dependent epilepsy presents as neonatal-onset treatment-resistant seizures that dramatically respond to pharmacological dosages of pyridoxine. However, lifelong supplementation of pyridoxine fails to prevent the developmental and cognitive disabilities in >75% of patients with pyridoxine-dependent epilepsy [81,82]. The current consensus guidelines recommend a lysine-restricted diet and competitive inhibition of lysine transport through the use of pharmacologic doses of arginine as an adjunct therapy with pyridoxine [80]. Triple therapy with pyridoxine, arginine and dietary lysine restriction is suggested to treat seizures and intellectual disability [80].

## Conclusion

We reviewed the current state of targeted treatment for epilepsies based on underlying pathophysiologic mechanisms of specific genetic mutations. In epilepsies caused by pathogenic variants of genes that lead to a gain or loss of function of ion channels or receptors, therapies that modify the function of the ion channels or receptors have shown success. The phenotypes caused by different mutations in the same gene can vary based on the function of the specific channels or receptors. For example, pathogenic gain-of-function mutations of *SCN2A* associate with early-onset DEE or BFNIS, whereas loss-of-function mutations of *SCN2A* associate with intellectual disability and/or autism or childhood-onset epilepsy. Successful therapies would increase channel conductance in patients with loss-of-function mutations or decrease channel conductance in patients with gain-of-function mutations. Modifications of the mTOR signaling pathways target specific proteins associated with epileptogenesis. Substitutive therapies treat hereditary metabolic diseases by supplying essential metabolites to compensate for defective metabolic pathways, such as use of the ketogenic diet in GLUT1 deficiency and pyridoxine in pyridoxine-dependent epilepsy.

The fundamental treatment goal of genetic epilepsies is either to correct the pathogenic variant of the gene or to modulate the expression of the mutated gene to compensate for the impact of the variant. Although gene therapy is not yet approved for clinical use, some preclinical studies have shown positive results using antisense oligonucleotides to decrease the function in a gain-of-function mutation of *SCN8A* and to increase $Na_v1.1$ function in Dravet syndrome [83,84].

The current treatment paradigm in genetic epilepsies is shifting towards precision medicine and personalized treatment to target specific etiologies. Meeting this demand for precision medicine requires functional studies of individual patients with specific therapies.

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## Authors' Contributions

Conception and design: HCK. Acquisition of data: HJK, HCK. Analysis and interpretation of data: HJK. Drafting the article: HJK. Critical revision of the article:HCK. Final approval of the version to be published: HJK, HCK.

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