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REVIEW

Rational Small Molecule Treatment for Genetic Epilepsies

Ethan M. Goldberg[1,2]

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Abstract
Genetic testing has yielded major advances in our understanding of the causes of epilepsy. Seizures remain resistant to treatment in a significant proportion of cases, particularly in severe, childhood-onset epilepsy, the patient population in which an underlying causative genetic variant is most likely to be identified. A genetic diagnosis can be explanatory as to etiology, and, in some cases, might suggest a therapeutic approach; yet, a clear path from genetic diagnosis to treatment remains unclear in most cases. Here, we discuss theoretical considerations behind the attempted use of small molecules for the treatment of genetic epilepsies, which is but one among various approaches currently under development. We explore a few salient examples and consider the future of the small molecule approach for genetic epilepsies. We conclude that significant additional work is required to understand how genetic variation leads to dysfunction of epilepsy-associated protein targets, and how this impacts the function of diverse subtypes of neurons embedded within distributed brain circuits to yield epilepsy and epilepsy-associated comorbidities. A syndrome- or even variant-specific approach may be required to achieve progress. Advances in the field will require improved methods for large-scale target validation, compound identification and optimization, and the development of accurate model systems that reflect the core features of human epilepsy syndromes, as well as novel approaches towards clinical trials of such compounds in small rare disease cohorts.

Keywords Neurogenetics · Ion channels · Precision medicine · Epilepsy

Introduction

Advances in genetic testing have revealed that epilepsy in many patients — including up to half or more of children [1] — has a genetic basis, with a causative variant more likely to be identified in severe, early-onset cases. This has driven increasing efforts to leverage such information to drive the development of "precision" treatments directed at or based on these genetically defined targets. However, advances in therapy have lagged behind achievements of diagnostic testing. The concept of "precision" treatment for epilepsy using small molecules is largely predicated upon the basic idea that variants causing "gain of function" (increased activity) could be approached using an antagonist of the protein product of the gene in question (typically an ion channel or neurotransmitter receptor), while "loss of function" (decreased activity) could be approached using a small molecule activator. We call this the "block gain/activate loss" approach, of which multiple examples exist in the literature [2–7].

While new anti-seizure medications (ASM) continue to enter clinical use, overall rates of pharmacoresistance in epilepsy remain high, with only 70% of patients being seizure-free even with prescription of appropriately selected AMSs [8, 9]. Many of the ASMs prescribed today are small molecules that have been in medical use for over 50 years. Valproate, synthesized in the late nineteenth century, first prescribed in 1962 and FDA approved in 1978, and which is associated with significant toxicity, is still the most commonly prescribed anti-seizure medication today, and constitutes 20% or more of prescriptions of anti-seizure medications in various cohorts [10–14]. Approximately 15% of patients with epilepsy in the USA — over 2 million patients — are prescribed phenytoin [15], which has been used for the treatment of epilepsy since its introduction by Merritt and Putnam in 1937 [16]. However, such ASMs were developed naïve to

✉ Ethan M. Goldberg
goldberge@chop.edu

[1] Department of Pediatrics, Division of Neurology, Abramson Research Center, The Epilepsy Neurogenetics Initiative, The Children's Hospital of Philadelphia, Abramson Research Center Room 502A, 19104 Philadelphia, PA, USA

[2] Departments of Neurology and Neuroscience, The University of Pennsylvania Perelman School of Medicine, 19104 Philadelphia, PA, USA

their mechanism of action, and the biological activity of such compounds is not directly related (at least so far as is/was known at the time) to the cause of epilepsy. It is interesting to note that phenytoin and other ASMs with a prominent mechanism of action of sodium (Na+) channel blockade are now being reintroduced as "precision" therapeutics in the context of Na+ channelopathies that act via gain of function. The hope is that genomics can inform the development of improved mechanistically oriented small molecule therapeutics and other gene-driven treatments.

Small molecules are one major class of FDA-approved prescription drugs, and generally refer to compounds that are (a) chemically synthesized and (b) small, having a molecular weight below 1 kDa. Most FDA-approved ASMs are small molecules. This is in contrast to the other major classes of drugs, the biologics, which includes proteins (such as monoclonal antibodies, or insulin) and living cells (e.g., CAR-T cells). A full discussion of this distinction is beyond the scope of this review. Briefly, a relative advantage of the small molecules is their size, which allows access to extracellular and intracellular targets for modulation of discrete protein functions, such as ion channel gating. In addition, these compounds are more readily synthesized and can be more easily produced in large quantities at a lower cost.

A basic methodology in modern drug discovery is to identify a disease target, validate that target, identify a compound(s) with therapeutic potential, develop and optimize the compound, and then perform preclinical and clinical trials, culminating in a clinical trial (ideally, a large-scale double-blind placebo-controlled trial), to prove safety and efficacy. Undertaking such an endeavor is a time-consuming and costly process and success at outset is far from guaranteed. In the genetic epilepsies, identification of candidate compounds has also been based on neurobiological insight and application of the "block gain/activate loss" approach, rather than via rigorous compound screening followed by drug optimization. Testing has been undertaken in the form of $N=1$ observational case reports, or is based on clinical experience in small patient cohorts, in many cases with little or no functional validation of the approach, limited or no long-term follow-up, and a narrow definition of success restricted to qualitative measures or impressions such as patient/parent report of seizure frequency.

There are many more reviews about precision medicine in epilepsy than there are papers reporting its implementation, let alone its success. As of May 30, 2021, a PubMed search with key words of "Precision medicine" AND "Epilepsy" in the Title/Abstract fields yielded 309 publications. In this invited commentary, we attempt to briefly summarize the state of the field and suggest a path forward.

What's in a Name?

There is ongoing semantic debate as to the meaning of various terms in the field. Attempts at practical definitions are provided below, although these may not conform to consensus opinion, for which the reader is referred to expert reports and panels on the topic [17–19].

Gain/Loss of Function

This is an important concept for targeted/precision therapy for epilepsy, as it forms the basis of an approach that is often taken in the field (the "block gain/activate loss" approach). Yet, what is meant by gain or loss of function is not always clear. Such terms were initially developed in the field of *Drosophila* genetics by the Nobel laureate Hermann J. Muller [20]. Amorphic (complete loss of gene function; "null") or hypomorphic (partial loss) mutations lead to absence of or decrease in protein function by disrupting transcriptional or translational processes. An example of a human disease with a loss of function mechanism might be glycogen storage disease type 5 (GSDV; McArdle disease) due to loss of function variants in the gene *PYGM* encoding muscle-associated glycogen phosphorylase (myophosphorylase) which breaks down glycogen in muscle to gluose-1-phosphate. Patients with GSDV have glycogen accumulation in muscle with exercise leading to exercise intolerance, cramps, and muscle breakdown. In this case, increasing levels of myophosphorylase, or reducing its substrate, are rational, targeted approaches to therapy. On the other hand, hypermorphic mutations lead to gain of function via increases in normal gene activity, such as due to increased gene dosage, mutations that confer constitutive activation, or via other mechanisms. Examples in neurology include Huntington's disease or the various spinocerebellar ataxias due to CAG triplet repeat expansion, which cause cellular toxicity due to gain-of-function. In such cases, while the exact pathophysiology may not be entirely understood, the path forward is more clear, with efforts under development to decrease accumulation of the toxic protein product. Hence, such disorders are considered as potentially targetable diseases either via small molecule or genetics-based approaches (gene therapy or antisense oligonucleotide-based therapy).

The genetic epilepsies represent a different category of disease. Consider a pathogenic variant in a voltage-gated Na+ channel gene associated with epilepsy. Na+ channel function is defined across various biophysical parameters, such as single-channel conductance, the voltage dependence and kinetics of channel gating, and other measures that govern channel behavior, such that prediction of gain

or loss of function based solely on knowledge of a particular missense variant is not possible. Determination of gain/loss of function has classically been undertaken via heterologous expression in *Xenopus* oocytes or a mammalian cell line such as CHO or HEK-293 cells. However, voltage-gated Na + channels are macromolecular complexes composed of a pore-forming (α) and accessory β subunits, along with other interacting proteins including 14–3-3, ankyrin, fibroblast growth factors, and other molecules, which cannot be accurately reconstituted in heterologous systems. Expression, trafficking, and function of Na + channels are regulated by phosphorylation and other post-translational modifications. Furthermore, such heterologous cell systems are of course not neurons, and hence lack a polarized morphology with axon, axon initial segment, soma, and dendrite, which normally exhibit compartment-specific Na + channel localization and regulation. Finally, there are of course many different types of neurons, including excitatory and various defined subsets of GABAergic inhibitory interneurons, each with cell type–specific developmentally regulated Na + channel expression profiles. Given this, it is perhaps not surprising that our simplified model systems imperfectly reflect the impact of a given genetic variant at other, more complex, levels of analysis.

For example, a given *SCNXA* (i.e., *SCN1A*, *2A*, etc.) variant when co-expressed in a heterologous system with β subunits may yield a complex or mixed pattern of effects that cannot be easily defined as gain or loss of function, because its impact on the parameters listed above suggests competing or opposite effects on the overall activity of the channel (such as decreased current density with a left/hyperpolarized shift in voltage dependence of activation). Things become even more complicated as we attempt to understand the impact of ion channel variants on neuronal function. A given Na + channel variant might cause apparent loss of function at the gene or ion channel level via decreased protein production through disruption of translation (such as a variant that introduces a premature termination codon in *SCN1A*), yet this variant produces hyperexcitability in the network and epilepsy presumably due to the fact that *SCN1A* is selectively or preferentially expressed in GABAergic inhibitory interneurons. Some variants in *SCN1A*, *8A*, and *9A* have been shown to produce gain of function at the ion channel level in heterologous systems through a variety of mechanisms [21–24] including hyperpolarizing/left shifts in the voltage dependence of activation and increased slowly inactivating/persistent current, which might paradoxically lead to loss of neuron function by accelerating entrance into depolarization block. Hence, a pathogenic variant could be a *gain* of function at the level of gene or ion channel but *loss* of function at the level of an individual neuron. A pathogenic variant could be a *loss* of function at the level of gene or ion channel yet lead to *gain* of function at the level of the circuit/network.

It is important to note that, in general, it is easier to address gain-of-function disorders with a small molecule approach than it is to address loss of function. Of all rare Mendelian genetic disorders (including neurological disorders), only an estimated 6% have a currently FDA-approved orphan drug; however, this figure is 12% of the total (i.e., twice as many) when considering those with a known or predicted gain-of-function mechanism [25]. Only a small number of Mendelian genetic disorders with presumptive loss-of-function mechanisms have known activators. Why this is the case likely relates to how drug discovery and repurposing pipelines operate as well as the fact that it is simply more difficult to compensate for the absence of a protein via pharmacologic means than to block its excess using a small molecule approach. With regard to genetic epilepsies, this probably also relates to the basic biology of the targets in question and the requirements that, for example, a specific channel isoform might need to be targeted while avoiding its highly paralogous family or subfamily members (for example, making an Nav1.2- or Nav1.6-specific antagonist).

Precision Medicine

This term best refers to a medical treatment or preventative measure directed towards individual patients classified based on data reflecting some discrete feature of their underlying biology (such as, in the present context, a pathogenic variant in a specific disease-associated gene). A goal of precision medicine is to leverage data (often genetic) to select the most or develop a more efficacious treatment and/or avoid potential complications of a treatment. Such a treatment is then directed at the biology suggested or informed by a biomarker: in this case, the use of a small molecule with a known mechanism of action directed at a molecular target encoded by an epilepsy-associated gene for the purposes of treating seizures or non-seizure comorbidities caused by the pathogenic variant.

Illustrative Examples

Quinidine for KCNT1-Related Epilepsy

This is the infamous example in the field and has been discussed extensively in the literature. *KCNT1* encodes the sodium-activated potassium (K +) channel subunit $K_{Na}1.1/K_{Ca}4.1$/Slo2.2, also known as Slack. This subunit forms heterotetrameric high conductance delayed rectifier K + channels that are weakly voltage dependent and activated by intracellular sodium [26]. Pathogenic variants in *KCNT1* have been identified as a cause of a range of epilepsy

syndromes including epilepsy of infancy with migrating focal seizures (EIMFS; previously malignant migrating partial seizures of infancy), a form of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), Ohtahara syndrome, and others [27–29]. EIMFS is a developmental and epileptic encephalopathy [30] with a clear genetic basis yet is associated with genetic heterogeneity, although *KCNT1* is the gene most frequently implicated [31]. Such variants had been shown to act via the so-called gain of function at the ion channel level [32, 33], with increased conductance via cooperative gating, enhanced open probability, and/or enhanced sensitivity to sodium [34, 35]. Based on the "block gain/activate loss" paradigm described above, our group piloted the use of quinidine for the treatment of EIMFS due to a de novo heterozygous pathogenic variant in *KCNT1*:c.1283G > A (p.Arg428Gln) identified via trio whole exome sequencing analysis [2]. Based on this genetic diagnosis and the existing literature on the subject at the time, we considered available compounds with activity against Slack channels. This search revealed quinidine as an FDA-approved compound with known activity as a Slack antagonist [36, 37]. However, quinidine in healthy individuals is thought to lower seizure threshold [38] rather than exerting anticonvulsant action, and can also be associated with toxicity including prolonged QTc with cases of sudden cardiac death reported in adults, particularly if delivered intravenously. In this case, administration of quinidine was undertaken while the patient was admitted to the hospital under telemetry monitoring. Up-titration of quinidine to over 40 mg/kg/day achieved serum quinidine levels between 1.5 and 4 µg/mL, which led to a complete cessation of seizures for a period of many months [2].

It should be noted that quinidine of course is a nonspecific pharmacologic agent used as a class I antiarrhythmic and anti-malarial. It blocks a range of ion channels including Nav1.5 and various K + channels including its action as a pore blocker of the voltage-gated K + channel subunits Kv1.4 [39] and ERG [40] as well as other actions including inhibition of the drug transport protein P-glycoprotein [41]. In this sense, it is less specific for Slack than for example phenytoin is for Nav1.6, but the rationale overall was similar to other approaches that have been attempted subsequently in the field. Furthermore, it is known that quinidine traverses the blood–brain barrier, albeit with relatively poor CNS penetration (with a CSF-to-serum ratio of on average 16% in a small cohort of healthy human control subjects [42]). So, if the reduction in seizures in this case was due to quinidine at all, this may or may not have been due to activity of quinidine against Slack. Subsequent reports showed a less dramatic or little to no clinical efficacy of quinidine [43, 44]. An observational study of 43 patients from an international collaborative patient registry suggested that adjunctive quinidine produced significant (50%) seizure reduction in only a subset of patients, with a small number of patients exhibiting seizure freedom [45]. In an observational study involving 27 patients, nearly half of patients displayed a marked (> 50%) or some (25–50%) improvement in seizure frequency with quinidine [46]. A separate report suggested that response to quinidine might be age-dependent: among patients with EIMFS due to gain-of-function pathogenic variants in *KCNT1*, 4/4 (100%) of those younger than age 4 years responded to quinidine, while none (0/4) of the patients older than age 4 responded [47], an interesting observation also made by others [48]. It should again be noted that it is difficult to evaluate such heterogeneous data systematically, given the various ages of the patients involved, different dosing regimens, variable protocols for monitoring of serum drug concentrations, and other considerations, including the fact that patients were all concurrently taking one or more conventional anti-seizure medications at the time that quinidine was introduced.

So is quinidine a precision medicine for epilepsy? At the time, we were careful to not use that term, opting instead to use "Targeted." First of all, it remains unclear if quinidine has anti-seizure effects in *KCNT1*-associated epilepsy at all (or in any epilepsy). Second, quinidine is not specific for Slack and there is no evidence that any efficacy in *KCNT1*-associated epilepsy — if real — is due to block of Slack channels. A further requirement for a therapy to qualify as precision medicine might be that it actually works, and that it works because of successful action on a proposed and rational target. Nevertheless, despite its limitations, this initial effort contributed to a wave of excitement that drove additional efforts in this field, including generation of induced pluripotent stem (iPS) cells [49] and mouse models [50, 51], creation of an International Patient Registry with currently over 100 patients that is the basis of a natural history study that could support future clinical trials, the formation of active patient/family organizations (such as KCNT1 Epilepsy; www.kcnt1epilepsy.org), efforts to develop ASO-based therapies in experimental systems [52], and attempts to develop a "better quinidine" (Jenkins, Gribkoff, Kaczmarek. Soc Neurosci Abstr 375.01).

Quinidine for *KCNT1* epilepsy captured the imagination of many in the field yet led to significant controversy. As of 2021, the story is far from over. The field could be driven forward by the generation of improved and more accurate models of *KCNT1* epilepsy; a greater ion channel, cellular, and circuit understanding of how pathogenic variants in *KCNT1* lead to disease; development of small molecules that might be a "better" quinidine (more potent; more selective; better CNS penetration; etc.); and support for clinical investigation that leverages the energy and involvement of patient and family groups.

SCN8A Epilepsy

The use of Na + channel blocking ASMs for treatment of *SCN8A*-related epilepsy has already been mentioned above and has been reviewed previously [53–56]. This example is an implementation of the "block gain/activate loss" paradigm in which heterozygous pathogenic variants in *SCN8A* were identified as a cause of epilepsy [57], the impact of this variant on the function of Nav1.6-containing Na + channels was determined to act via gain of function, and compounds were identified that act on or partially normalized this presumed pathology in various model systems including heterologous cells, transfected primary neurons in culture, iPS cell–derived neurons from patients with *SCN8A* encephalopathy, and in experimental animal models [24, 58–61]. Phenytoin and other Na + channel blocking ASMs have been shown to reduce seizures in patients with *SCN8A*-related epilepsy [5, 59].

We performed a study on a small cohort of patients with *SCN8A*-related epilepsy at our institution and found that a patient with a dramatic response to high-dose oxcarbazepine harbored a de novo pathogenic variant that also exhibited strong response to this drug in a heterologous cell system in vitro, with oxcarbazepine producing a near-complete normalization of the slowly inactivating/persistent current component [59]. However, patients with treatment-resistant epilepsy including lack of response to Na + channel blockers held what we called "complex" variants exhibiting increased persistent current as well as abnormal gating that could not be normalized by the Na + channel blocking agents tested, which included phenytoin, oxcarbazepine, lacosamide, and GS-967. This result highlights that the response to a particular targeted therapeutic may be variant- or patient-specific.

Phenytoin is an FDA-approved anti-seizure medication with a prominent mechanism of action as pore blocker of voltage-gated sodium (Na +) channels [62–64], yet acts on Na + channels composed of any/all voltage-gated Na + channel subunits [65, 66] and is not specific for Nav1.6-containing Na + channels. Further improvements on a small molecule approach to *SCN8A* epilepsy have been made. The novel Na + channel modulator GS-458967 (GS-967/Prax330), which acts preferentially on slowly inactivating/persistent current over transient current, was shown to reduce persistent and resurgent Na + current and normalize cellular hyperexcitability in neurons in a mouse model of *SCN8A* encephalopathy (*Scn8a*-N1768D mice) and to be an effective treatment for epilepsy in the mouse model in vivo [58, 67, 68]. The compound NBI-921352 (formerly XEN901, developed by Xenon Pharmaceuticals), an Nav1.6-selective blocker, is currently undergoing planning for a phase II clinical trial in patients with *SCN8A* encephalopathy.

Dravet Syndrome

Dravet syndrome is due to heterozygous pathogenic loss of function variants in *SCN1A* encoding the neuronal voltage-gated Na+ channel α subunit Nav1.1. The dominant hypothesis as to Dravet syndrome pathogenesis is the "interneuron hypothesis" whereby haploinsufficiency for Nav1.1 preferentially impacts GABAergic inhibitory interneurons of cerebral cortex, leading to a relative impairment of interneurons, impaired synaptic inhibition, altered excitatory:inhibitory balance in cerebral cortex circuits, and hyperexcitability leading to epilepsy. This model, combined with prior clinical experience in the field suggesting that lamotrigine aggravated seizures [69], has led to the dogma that Na + channel blocking ASMs should be avoided in Dravet syndrome.

However, recent work in experimental animal models of Dravet syndrome (*Scn1a+/-* mice) showed that the impaired excitability of parvalbumin-immunoreactive fast-spiking basket cell interneurons seen previously in developing *Scn1a+/-* mice [70–72] is in fact transient and limited to early developmental time points; these same interneurons largely recover intrinsic excitability by young adulthood [73]. Other preclinical work demonstrated efficacy of GS-967 in a mouse model of Dravet syndrome [74], and reduction of *Scn8a* transcript using an antisense oligonucleotide also extended survival in *Scn1a+/-* mice [75] demonstrating that inhibiting Na + channel activity may be efficacious in the treatment of Dravet syndrome in the chronic phase. The basis for these results is unclear but suggests the potential opportunity for the development of small molecule Na + channel modulators for the treatment of Dravet syndrome. Interestingly, lamotrigine has been shown to have efficacy in some cases of Dravet syndrome if prescribed in older patients [76, 77].

At 1 in 15,000 individuals [78], Dravet syndrome is the most common epileptic encephalopathy and can be viewed as the canonical genetic epilepsy. Yet, much is still left to be learned about the pathogenesis of this syndrome and the challenges of linking from human genetic variant (*SCN1A*) to impact on ion channel function (Nav1.1-containing Na + channels), to Nav1.1-expressing neurons (parvalbumin-positive GABAergic interneurons and other cells), to cerebral cortex microcircuits and intact experimental animals, to understand epilepsy and non-seizure comorbidities in human patients.

The *Scn1a+/-* mouse model of Dravet syndrome recapitulates core features of the human disease including temperature-sensitive seizures, epilepsy, status epilepticus, sudden death, as well as various behavioral deficits that represent endophenotypes of autism spectrum disorder [70, 79, 80]. This mouse model has been critical to the development of the precision therapeutic STK-001 (an antisense oligonucleotide-based approach) by Stoke Therapeutics, which increases expression of *Scn1a* and

reduces seizures and SUDEP in *Scn1a+/-* mice [81] and is undergoing a Phase 1/2a open-label study in children with Dravet syndrome due to pathogenic variants in *SCN1A*. Drug screening in a zebrafish Nav1.1 mutant (*scn1Lab*) led to identification of clemizole, which inhibits seizures in this model [82, 83]. EpyGenix Therapeutics is currently enrolling in a Phase II, multicenter, randomized, double-blind placebo-controlled trial of EPX-100 (clemizole hydrochloride) for the treatment of Dravet syndrome. These developments reinforce the importance of basic neuroscience, experimental model systems, and target validation, in the development of potential new therapies for genetic epilepsies. Other biologics are in the planning stages including ETX-101 from Encoded Therapeutics, which is an AAV-based therapy targeting *SCN1A* expression in GABAergic interneurons.

Key Questions in the Field

There are many challenges in the field of small molecule therapeutics for genetic epilepsies. One obvious barrier is the complexity of the human brain. Therapeutic targets are expressed dynamically across development in discrete subcellular compartments of various neuronal cell types; this expression pattern itself might be altered by the genetic lesion, with pathology interacting with ongoing development and compensatory plasticity in poorly understood ways. What was or may have initially been a gain/loss of function at the level of an ion channel or neuron may not manifest as such later in development, due to compensatory reorganization or plasticity, such that we are chasing a "moving target."

An obvious question is whether rare or ultrarare genetic epilepsy syndromes can be successfully prevented, treated, and/or cured. To answer this, we need to define benchmarks for what success might look like. For a developmental and epileptic encephalopathy, does this mean a 50% decrease in seizures? 90% decrease? complete cessation of seizures? cessation of seizures with successful discontinuation of other ASMs? Slowing further developmental regression? Accelerating or recovering neurocognitive development? Complete cessation of seizures and normalization of neurocognitive development with amelioration and elimination of all syndrome-associated comorbidities? When might treatment need to be initiated to achieve such outcomes?

Are there common themes such as pathways that can be targeted, or a basic logic to solving the genetic epilepsies (a "new logic" beyond our "block gain/activate loss" approach)? Or will each epilepsy syndrome (each variant? each individual patient?) need to be approached independently? Candidate compounds may have variant- or even patient-specific effects.

The Path Forward

The development of small molecules for precision medicine in epilepsy has perhaps not proceeded at the pace we had hoped. Further progress requires a redoubling of our efforts fueled by better models, improved screening tools, novel clinical trial methodologies, and enhanced partnership and interaction with industry, as well as an influx of new ideas from the next generation of neuroscience and epilepsy researchers. We need a greater understanding of how genetic variation leads to epilepsy, which involves the hard work of linking from human genetic variation, to the impact of genetic variation on protein function, to how altered function at the level of a given protein target impacts the activity of diverse subtypes of neurons to influence brain networks to produce epilepsy and epilepsy-associated comorbidities including developmental delay/intellectual disability, autism spectrum disorder, and SUDEP risk. This hard work will need to be done for each and every epilepsy syndrome and perhaps for specific variants.

Model Systems

From the discussion above, it is clear that robust preclinical models can drive forward the development of novel candidate therapies in the genetic epilepsies. However, among the top 10 most frequently identified epilepsy genes on NextGen sequencing panels [84], we only have highly robust mouse models for perhaps three: Dravet syndrome, *GABRG2*-related epilepsy [85], and *SCN8A* encephalopathy [58, 86].

The field requires improved high-throughput screening tools to determine the impact of genetic variation on protein target function and the effects of candidate compounds. High-throughput electrophysiological assays [87] and imaging-based approaches [88] allow for the recording of hundreds of cells or neurons simultaneously and facilitate larger-scale screening of candidate compounds against many variants. We need improved models to accurately predict the cellular impact of genetic variants and how altered ion channel and neurotransmitter receptor function manifests at the level of neurons [24, 89, 90].

We require more and improved experimental animal models, including Drosophila, zebrafish, mice, and other organisms, that recapitulate core features of human epilepsy syndromes, including epilepsy, epilepsy-associated cognitive comorbidities, and SUDEP, to validate and optimize the compounds identified via screening platforms. Further advances in mouse genetics will make it faster, easier, and cheaper to generate transgenic mice harboring conditional (e.g., Cre-dependent) missense variants which allows for the control of variant expression in space and time [58, 91], and facilitates the investigation of cell type–specific roles in pathology.

We require a greater understanding of the developmental trajectory of the expression of epilepsy-associated genes and therapeutic targets. Advances in single-cell biology have provided novel insights into cell type–specific transcriptomic profiles. It will be critical to develop a single-cell transcriptomic atlas of the developing human brain [92] and understand how this profile changes in epilepsy.

Clinical Trials

There are many limitations of $N=1$ trials, including difficulty in the selection and validation of the reliability of outcome measures, difficulty in or inability to apply randomization, lack of statistical analysis, lack of internal validity (a measure of the degree to which the intervention is actually responsible for the outcome), and the scope of inference (applicability of findings to other patients). There may be value in the further development of methodologies to turn $N=1$ case reports into $N=1$ trials, despite the challenges; such trials retain importance particularly in the field of rare or ultrarare neurodevelopmental disorders [93, 94]. But we need to pick the right small molecules to pilot in such trials. And we need to develop new methods and the infrastructure and support to bridge from $N=1$ or small clinical trials to larger, more powerful trials, informed by natural history studies that better define the trajectory of rare epilepsy syndromes. Yet, there have been very few true double-blind randomized control trials in pediatric epilepsy in general, and most are for adjunctive treatment of the more common epilepsy syndromes, such as recent clinical trials of small molecules fenfluramine and cannabidiol for treatment of Dravet syndrome [95–97]. Other genetic epilepsies may simply be too rare for the types of studies that require hundreds of patients.

Conclusion

Genetics provides a proximate mechanism as to the cause of disease that could, in theory, be leveraged towards the development of novel, targeted therapies for genetic epilepsies. In practice, this has been and will continue to be no easy task. Novel advances in model systems, compound screening, and clinical trial methodologies in neurodevelopmental disorders offer promise for clinicians and researchers as well as patients and their families living with what are in many cases completely untreatable and incurable diseases.

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Declarations

Conflict of Interest The author declares no competing interests.

References

1. Guerrini R, Noebels J. How can advances in epilepsy genetics lead to better treatments and cures? Adv Exp Med Biol. 2014;813:309–17.
2. Bearden D, Strong A, Ehnot J, DiGiovine M, Dlugos D, Goldberg EM. Targeted treatment of migrating partial seizures of infancy with quinidine. Annals of Neurology. 2014;76(3).
3. Li D, Yuan H, Ortiz-Gonzalez XR, Marsh ED, Tian L, McCormick EM, et al. GRIN2D Recurrent De Novo Dominant Mutation Causes a Severe Epileptic Encephalopathy Treatable with NMDA Receptor Channel Blockers. Am J Hum Genet. 2016 Oct 6;99(4):802–16.
4. Pierson TM, Yuan H, Marsh ED, Fuentes-Fajardo K, Adams DR, Markello T, et al. GRIN2A mutation and early-onset epileptic encephalopathy: personalized therapy with memantine. Ann Clin Transl Neurol. 2014 Mar 1;1(3):190–8.
5. Boerma RS, Braun KP, van den Broek MPH, van de Broek MPH, van Berkestijn FMC, Swinkels ME, et al. Remarkable Phenytoin Sensitivity in 4 Children with SCN8A-related Epilepsy: A Molecular Neuropharmacological Approach. Neurotherapeutics. 2016 Jan;13(1):192–7.
6. Millichap JJ, Park KL, Tsuchida T, Ben-Zeev B, Carmant L, Flamini R, et al. KCNQ2 encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients. Neurol Genet. 2016 Oct;2(5):e96.
7. Welzel T, Ziesenitz VC, Waldvogel S, Scheidegger S, Weber P, van den Anker JN, et al. Use of a personalized phenytoin dosing approach to manage difficult to control seizures in an infant with a SCN2A mutation. Eur J Clin Pharmacol. 2019 May;75(5):737–9.
8. Berg AT, Rychlik K. The course of childhood-onset epilepsy over the first two decades: A prospective, longitudinal study. Epilepsia. 2015 Jan 1;56(1):40–8.
9. Geerts AT, Arts WF, Stroink H, Peeters E, Brouwer O, Peters B, et al. Course and outcome of childhood epilepsy: A 15-year follow-up of the Dutch Study of Epilepsy in Childhood. Epilepsia. 2010 Jul;51(7):1189–97.
10. Chen S, Yoshida S, Matsumoto R, Ikeda A, Kawakami K. Prescription patterns of antiepileptic drugs for adult patients with newly diagnosed focal epilepsy from 2006 to 2017 in Japan. Epilepsy Research. 2021 Jan 1;169.
11. Weijenberg A, Bos JHJ, Schuiling-Veninga CCM, Brouwer OF, Callenbach PMC. Antiepileptic drug prescription in Dutch children from 2006–2014 using pharmacy-dispensing data. Epilepsy Research. 2018 Oct 1;146:21–7.
12. Van De Vrie-Hoekstra NW, De Vries TW, Van Den Berg PB, Brouwer OF, De Jong-Van Den Berg LTW. Antiepileptic drug utilization in children from 1997–2005 - A study from the Netherlands. European Journal of Clinical Pharmacology. 2008 Oct;64(10):1013–20.
13. Groth A, Wilke T, Borghs S, Gille P, Joeres L. Analyse von Routinedaten zur medikamentösen Therapie von erwachsenen Patienten mit fokaler Epilepsie in Deutschland: Eine Längsund Querschnittsanalyse neu zugelassener Antiepileptika. GMS German Medical Science. 2017 Jun 12;15:1–17.
14. Nicholas JM, Ridsdale L, Richardson MP, Ashworth M, Gulliford MC. Trends in antiepileptic drug utilisation in UK primary care 1993-2008: Cohort study using the General Practice Research Database. Seizure. 2012 Jul;21(6):466–70.

15. Sirven JI, Shafer PO, Kalilani L, Wild I, Fishman J, Owens S. Current state of the union of epilepsy care in the United States: Antiepileptic drugs — An introduction to the Connectors Project. Epilepsy and Behavior. 2018 Mar 1;80:98–103.
16. Putnam TJ, Merritt HH. EXPERIMENTAL DETERMINATION OF THE ANTICONVULSANT PROPERTIES OF SOME PHENYL DERIVATIVES. Science. 1937 May 28;85(2213):525–6.
17. Toward precision medicine: Building a knowledge network for biomedical research and a new taxonomy of disease. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. National Academies Press; 2012. 1–128 p.
18. Ellis CA, Petrovski S, Berkovic SF. Epilepsy genetics: clinical impacts and biological insights. The Lancet Neurology. 2020 Jan;19(1):93–100.
19. EpiPM Consortium. A roadmap for precision medicine in the epilepsies. The Lancet Neurology. 2015 Dec;14(12):1219–28.
20. Muller HJ. Further studies on the nature and causes of gene mutations. Inernational Congress of Genetics. 1932;213–55.
21. Huang J, Vanoye CG, Cutts A, Goldberg YP, Dib-Hajj SD, Cohen CJ, et al. Sodium channel NaV1.9 mutations associated with insensitivity to pain dampen neuronal excitability. J Clin Invest. 2017 Jun 30;127(7):2805–14.
22. Wengert ER, Wedgwood KCA, Wagley PK, Strohm SM, Panchal PS, Majidi AI, et al. Somatostatin-positive Interneurons Contribute to Seizures in *SCN8A* Epileptic Encephalopathy [Internet]. Neuroscience; 2021 Feb [cited 2021 Jun 1]. Available from: https://doi.org/10.1101/2021.02.05.429987
23. Berecki G, Bryson A, Terhag J, Maljevic S, Gazina EV, Hill SL, et al. SCN1A gain of function in early infantile encephalopathy. Ann Neurol. 2019 Apr;85(4):514–25.
24. Liu Y, Schubert J, Sonnenberg L, Helbig KL, Hoei-Hansen CE, Koko M, et al. Neuronal mechanisms of mutations in SCN8A causing epilepsy or intellectual disability. Brain. 2019 Feb 1;142(2):376–90.
25. Chen B, Altman RB. Opportunities for developing therapies for rare genetic diseases: focus on gain-of-function and allostery. Orphanet J Rare Dis. 2017 Apr 17;12(1):61.
26. Yuan A, Santi CM, Wei A, Wang ZW, Pollak K, Nonet M, et al. The sodium-activated potassium channel is encoded by a member of the Slo gene family. Neuron. 2003 Mar 6;37(5):765–73.
27. Møller RS, Heron SE, Larsen LHG, Lim CX, Ricos MG, Bayly MA, et al. Mutations in KCNT1 cause a spectrum of focal epilepsies. Epilepsia. 2015 Sep 1;56(9):e114–20.
28. Barcia G, Fleming MR, Deligniere A, Gazula V-R, Brown MR, Langouet M, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet. 2012 Nov;44(11):1255–9.
29. Heron SE, Smith KR, Bahlo M, Nobili L, Kahana E, Licchetta L, et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 2012 Nov;44(11):1188–90.
30. Coppola G, Plouin P, Chiron C, Robain O, Dulac O. Migrating partial seizures in infancy: a malignant disorder with developmental arrest. Epilepsia. 1995 Oct;36(10):1017–24.
31. Burgess R, Wang S, McTague A, Boysen KE, Yang X, Zeng Q, et al. The Genetic Landscape of Epilepsy of Infancy with Migrating Focal Seizures. Annals of Neurology. 2019 Dec 1;86(6):821–31.
32. Barcia G, Fleming MR, Deligniere A, Gazula V-R, Brown MR, Langouet M, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nature Genetics. 2012 Oct 21;44(11):1255–9.
33. Heron SE, Smith KR, Bahlo M, Nobili L, Kahana E, Licchetta L, et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. Nature Genetics. 2012 Nov;44(11):1188–90.
34. Kim GE, Kronengold J, Barcia G, Quraishi IH, Martin HC, Blair E, et al. Human Slack Potassium Channel Mutations Increase Positive Cooperativity between Individual Channels. Cell Reports. 2014 Dec 11;9(5):1661–72.
35. Tang Q-Y, Zhang F-F, Xu J, Wang R, Chen J, Logothetis DE, et al. Epilepsy-Related Slack Channel Mutants Lead to Channel Over-Activity by Two Different Mechanisms. Cell Reports. 2016 Jan 5;14(1):129–39.
36. Bhattacharjee A, Joiner WJ, Wu M, Yang Y, Sigworth FJ, Kaczmarek LK. Slick (Slo2.1), a rapidly-gating sodium-activated potassium channel inhibited by ATP. J Neurosci. 2003 Dec 17;23(37):11681–91.
37. Yang B, Gribkoff VK, Pan J, Damagnez V, Dworetzky SI, Boissard CG, et al. Pharmacological activation and inhibition of Slack (Slo2.2) channels. Neuropharmacology. 2006 Sep;51(4):896–906.
38. Kerr F, Kenoyer G, Bilitch M. Quinidine overdose. Neurological and cardiovascular toxicity in a normal person. Br Heart J. 1971 Jul;33(4):629–31.
39. Yamagishi T, Ishii K, Taira N. Antiarrhythmic and bradycardic drugs inhibit currents of cloned K+ channels, KV1.2 and KV1.4. Eur J Pharmacol. 1995 Aug 4;281(2):151–9.
40. Gessner G, Zacharias M, Bechstedt S, Schönherr R, Heinemann SH. Molecular determinants for high-affinity block of human EAG potassium channels by antiarrhythmic agents. Mol Pharmacol. 2004 May;65(5):1120–9.
41. Fromm MF, Kim RB, Stein CM, Wilkinson GR, Roden DM. Inhibition of P-glycoprotein-mediated drug transport: A unifying mechanism to explain the interaction between digoxin and quinidine [seecomments]. Circulation. 1999 Feb 2;99(4):552–7.
42. Ochs HR, Greenblatt DJ, Lloyd BL, Woo E, Sonntag M, Smith TW. Entry of quinidine into cerebrospinal fluid. Am Heart J. 1980 Sep;100(3):341–6.
43. Chong PF, Nakamura R, Saitsu H, Matsumoto N, Kira R. Ineffective quinidine therapy in early onset epileptic encephalopathy with KCNT1 mutation. Ann Neurol. 2016 Mar;79(3):502–3.
44. Madaan P, Jauhari P, Gupta A, Chakrabarty B, Gulati S. A quinidine non responsive novel KCNT1 mutation in an Indian infant with epilepsy of infancy with migrating focal seizures. Brain Dev. 2018 Mar;40(3):229–32.
45. Fitzgerald MP, Fiannacca M, Smith DM, Gertler TS, Gunning B, Syrbe S, et al. Treatment Responsiveness in KCNT1-Related Epilepsy. Neurotherapeutics. 2019 Jul;16(3):848–57.
46. Borlot F, Abushama A, Morrison-Levy N, Jain P, Puthenveettil Vinayan K, Abukhalid M, et al. KCNT1-related epilepsy: An international multicenter cohort of 27 pediatric cases. Epilepsia. 2020 Apr;61(4):679–92.
47. Abdelnour E, Gallentine W, McDonald M, Sachdev M, Jiang Y-H, Mikati MA. Does age affect response to quinidine in patients with KCNT1 mutations? Report of three new cases and review of the literature. Seizure. 2018 Feb;55:1–3.
48. Fukuoka M, Kuki I, Kawawaki H, Okazaki S, Kim K, Hattori Y, et al. Quinidine therapy for West syndrome with KCNTI mutation: A case report. Brain Dev. 2017 Jan;39(1):80–3.
49. Quraishi IH, Stern S, Mangan KP, Zhang Y, Ali SR, Mercier MR, et al. An Epilepsy-Associated KCNT1 Mutation Enhances Excitability of Human iPSC-Derived Neurons by Increasing Slack KNa Currents. J Neurosci. 2019 Sep 11;39(37):7438–49.
50. Shore AN, Colombo S, Tobin WF, Petri S, Cullen ER, Dominguez S, et al. Reduced GABAergic Neuron Excitability, Altered Synaptic Connectivity, and Seizures in a KCNT1 Gain-of-Function Mouse Model of Childhood Epilepsy. Cell Rep. 2020 Oct 27;33(4):108303.
51. Quraishi IH, Mercier MR, McClure H, Couture RL, Schwartz ML, Lukowski R, et al. Impaired motor skill learning and altered seizure susceptibility in mice with loss or gain of function of the Kcnt1 gene encoding Slack (KNa1.1) Na+-activated K+ channels. Sci Rep. 2020 Feb 21;10(1):3213.

52. Burbano LE, Li M, Jancovski N, Jafar-Nejad P, Richards K, Sedo A, et al. Antisense oligonucleotide therapy for *KCNT1* encephalopathy [Internet]. Neuroscience; 2020 Nov [cited 2021 Jun 1]. Available from: https://doi.org/10.1101/2020.11.12.379164
53. Brunklaus A, Lal D. Sodium channel epilepsies and neurodevelopmental disorders: from disease mechanisms to clinical application. Dev Med Child Neurol. 2020 Jul;62(7):784–92.
54. Brunklaus A. Precision medicine in sodium channelopathies - Moving beyond seizure control towards disease modification. Eur J Paediatr Neurol. 2020 Jan;24:7.
55. Møller RS, Johannesen KM. Precision Medicine: SCN8A Encephalopathy Treated with Sodium Channel Blockers. Neurotherapeutics. 2016 Jan;13(1):190–1.
56. Gardella E, Møller RS. Phenotypic and genetic spectrum of SCN8A-related disorders, treatment options, and outcomes. Epilepsia. 2019 Dec;60 Suppl 3:S77–85.
57. Veeramah KR, O'Brien JE, Meisler MH, Cheng X, Dib-Hajj SD, Waxman SG, et al. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am J Hum Genet. 2012 Mar 9;90(3):502–10.
58. Bunton-Stasyshyn RKA, Wagnon JL, Wengert ER, Barker BS, Faulkner A, Wagley PK, et al. Prominent role of forebrain excitatory neurons in SCN8A encephalopathy. Brain. 2019 Feb 1;142(2):362–75.
59. Zaman T, Abou Tayoun A, Goldberg EM. A single-center SCN8A-related epilepsy cohort: clinical, genetic, and physiologic characterization. Ann Clin Transl Neurol. 2019 Aug;6(8):1445–55.
60. Tidball AM, Lopez-Santiago LF, Yuan Y, Glenn TW, Margolis JL, Clayton Walker J, et al. Variant-specific changes in persistent or resurgent sodium current in SCN8A-related epilepsy patient-derived neurons. Brain. 2020 Oct 1;143(10):3025–40.
61. Estacion M, O'Brien JE, Conravey A, Hammer MF, Waxman SG, Dib-Hajj SD, et al. A novel de novo mutation of SCN8A (Nav1.6) with enhanced channel activation in a child with epileptic encephalopathy. Neurobiol Dis. 2014 Sep;69:117–23.
62. Mantegazza M, Curia G, Biagini G, Ragsdale DS, Avoli M. Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. The Lancet Neurology. 2010 Apr;9(4):413–24.
63. Ragsdale DS, Scheuer T, Catterall WA. Frequency and voltage-dependent inhibition of type IIA Na+ channels, expressed in a mammalian cell line, by local anesthetic, antiarrhythmic, and anticonvulsant drugs. Molecular pharmacology. 1991 Nov;40(5):756–65.
64. Ragsdale DS, Mcphee JC, Scheuer T, Catterall WA. Common molecular determinants of local anesthetic, antiarrhythmic, and anticonvulsant block of voltage-gated Na+ channels. Proceedings of the National Academy of Sciences of the United States of America. 1996 Aug 20;93(17):9270–5.
65. Ragsdale DS, Scheuer T, Catterall WA. Frequency and voltage-dependent inhibition of type IIA Na+ channels, expressed in a mammalian cell line, by local anesthetic, antiarrhythmic, and anticonvulsant drugs. Mol Pharmacol. 1991 Nov;40(5):756–65.
66. Ragsdale DS, McPhee JC, Scheuer T, Catterall WA. Common molecular determinants of local anesthetic, antiarrhythmic, and anticonvulsant block of voltage-gated Na+ channels. Proc Natl Acad Sci U S A. 1996 Aug 20;93(17):9270–5.
67. Wengert ER, Saga AU, Panchal PS, Barker BS, Patel MK. Prax330 reduces persistent and resurgent sodium channel currents and neuronal hyperexcitability of subiculum neurons in a mouse model of SCN8A epileptic encephalopathy. Neuropharmacology. 2019 Nov 1;158:107699.
68. Baker EM, Thompson CH, Hawkins NA, Wagnon JL, Wengert ER, Patel MK, et al. The novel sodium channel modulator GS-458967 (GS967) is an effective treatment in a mouse model of SCN8A encephalopathy. Epilepsia. 2018 Jun;59(6):1166–76.
69. Guerrini R, Dravet C, Genton P, Belmonte A, Kaminska A, Dulac O. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia. 1998 May;39(5):508–12.
70. Ogiwara I, Miyamoto H, Morita N, Atapour N, Mazaki E, Inoue I, et al. Nav1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. J Neurosci. 2007 May 30;27(22):5903–14.
71. Tai C, Abe Y, Westenbroek RE, Scheuer T, Catterall WA. Impaired excitability of somatostatin- and parvalbumin-expressing cortical interneurons in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A. 2014 Jul 29;111(30):E3139-3148.
72. De Stasi AM, Farisello P, Marcon I, Cavallari S, Forli A, Vecchia D, et al. Unaltered Network Activity and Interneuronal Firing During Spontaneous Cortical Dynamics In Vivo in a Mouse Model of Severe Myoclonic Epilepsy of Infancy. Cereb Cortex. 2016 Apr;26(4):1778–94.
73. Favero M, Sotuyo NP, Lopez E, Kearney JA, Goldberg EM. A Transient Developmental Window of Fast-Spiking Interneuron Dysfunction in a Mouse Model of Dravet Syndrome. J Neurosci. 2018 Sep 5;38(36):7912–27.
74. Anderson LL, Hawkins NA, Thompson CH, Kearney JA, George AL. Unexpected Efficacy of a Novel Sodium Channel Modulator in Dravet Syndrome. Sci Rep. 2017 May 10;7(1):1682.
75. Lenk GM, Jafar-Nejad P, Hill SF, Huffman LD, Smolen CE, Wagnon JL, et al. Scn8a Antisense Oligonucleotide Is Protective in Mouse Models of SCN8A Encephalopathy and Dravet Syndrome. Ann Neurol. 2020 Mar;87(3):339–46.
76. Dalic L, Mullen SA, Roulet Perez E, Scheffer I. Lamotrigine can be beneficial in patients with Dravet syndrome. Dev Med Child Neurol. 2015 Feb;57(2):200–2.
77. Andrade DM. Dravet syndrome, lamotrigine, and personalized medicine. Dev Med Child Neurol. 2015 Feb;57(2):118–9.
78. Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, et al. Incidence of Dravet Syndrome in a US Population. Pediatrics. 2015 Nov;136(5):e1310-1315.
79. Mistry AM, Thompson CH, Miller AR, Vanoye CG, George AL, Kearney JA. Strain- and age-dependent hippocampal neuron sodium currents correlate with epilepsy severity in Dravet syndrome mice. Neurobiol Dis. 2014 May;65:1–11.
80. Yu FH, Mantegazza M, Westenbroek RE, Robbins CA, Kalume F, Burton KA, et al. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nat Neurosci. 2006 Sep;9(9):1142–9.
81. Han Z, Chen C, Christiansen A, Ji S, Lin Q, Anumonwo C, et al. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. Sci Transl Med. 2020 Aug 26;12(558).
82. Griffin A, Hamling KR, Knupp K, Hong S, Lee LP, Baraban SC. Clemizole and modulators of serotonin signalling suppress seizures in Dravet syndrome. Brain. 2017 Mar 1;140(3):669–83.
83. Baraban SC, Dinday MT, Hortopan GA. Drug screening in Scn1a zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment. Nat Commun. 2013;4:2410.
84. Lindy AS, Stosser MB, Butler E, Downtain-Pickersgill C, Shanmugham A, Retterer K, et al. Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. Epilepsia. 2018 May;59(5):1062–71.
85. Kang J-Q, Shen W, Zhou C, Xu D, Macdonald RL. The human epilepsy mutation GABRG2(Q390X) causes chronic subunit accumulation and neurodegeneration. Nat Neurosci. 2015 Jul;18(7):988–96.
86. Wagnon JL, Korn MJ, Parent R, Tarpey TA, Jones JM, Hammer MF, et al. Convulsive seizures and SUDEP in a mouse model of SCN8A epileptic encephalopathy. Hum Mol Genet. 2015 Jan 15;24(2):506–15.

87. Kang SK, Vanoye CG, Misra SN, Echevarria DM, Calhoun JD, O'Connor JB, et al. Spectrum of KV 2.1 Dysfunction in KCNB1-Associated Neurodevelopmental Disorders. Ann Neurol. 2019 Dec;86(6):899–912.
88. Atkin TA, Maher CM, Gerlach AC, Gay BC, Antonio BM, Santos SC, et al. A comprehensive approach to identifying repurposed drugs to treat SCN8A epilepsy. Epilepsia. 2018 Apr;59(4):802–13.
89. Berecki G, Howell KB, Deerasooriya YH, Cilio MR, Oliva MK, Kaplan D, et al. Dynamic action potential clamp predicts functional separation in mild familial and severe de novo forms of SCN2A epilepsy. Proc Natl Acad Sci U S A. 2018 Jun 12;115(24):E5516–25.
90. Ben-Shalom R, Keeshen CM, Berrios KN, An JY, Sanders SJ, Bender KJ. Opposing Effects on NaV1.2 Function Underlie Differences Between SCN2A Variants Observed in Individuals With Autism Spectrum Disorder or Infantile Seizures. Biol Psychiatry. 2017 Aug 1;82(3):224–32.
91. Gilet JG, Ivanova EL, Trofimova D, Rudolf G, Meziane H, Broix L, et al. Conditional switching of KIF2A mutation provides new insights into cortical malformation pathogeny. Hum Mol Genet. 2020 Mar 27;29(5):766–84.
92. Taylor DM, Aronow BJ, Tan K, Bernt K, Salomonis N, Greene CS, et al. The Pediatric Cell Atlas: Defining the Growth Phase of Human Development at Single-Cell Resolution. Dev Cell. 2019 Apr 8;49(1):10–29.
93. Hartman AL. N-of-1 Trials in Rare Genetic Neurodevelopmental Disorders: Opportunities for Improvement. Neurology. 2021 Mar 16;96(11):513–4.
94. Müller AR, Brands MMMG, van de Ven PM, Roes KCB, Cornel MC, van Karnebeek CDM, et al. Systematic Review of N-of-1 Studies in Rare Genetic Neurodevelopmental Disorders: The Power of 1. Neurology. 2021 Mar 16;96(11):529–40.
95. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019 Dec 21;394(10216):2243–54.
96. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017 May 25;376(21):2011–20.
97. Ceulemans B, Boel M, Leyssens K, Van Rossem C, Neels P, Jorens PG, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia. 2012 Jul;53(7):1131–9.