New paradigms for the treatment of pediatric monogenic epilepsies:

Progressing Towards Precision Medicine

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Abstract (147 words)

Despite the availability of 28 antiseizure medications (ASMs), one-third of people with epilepsy fail to achieve sustained freedom from seizures. Clinical outcome is even poorer for children with developmental and epileptic encephalopathies (DEEs), many of which are due to single-gene mutations. Discovery of causative genes, however, has paved the way to understanding the molecular mechanism underlying these epilepsies, and to the rational application, or development, of precision treatments aimed at correcting the specific functional defects or their consequences. This article provides an overview of current progress towards precision medicine in the management of monogenic pediatric epilepsies, by focusing on four different scenarios, namely (a) rational selection of ASMs targeting specifically the underlying pathogenetic mechanisms; (b) development of targeted therapies based on novel molecules; (c) use of dietary treatments or food constituents aimed at correcting specific metabolic defects; and (d) repurposing of medications originally approved for other indications.

Abbreviations: AD, autosomal dominant; ADSHE, autosomal dominant sleep-related hypermotor epilepsy; ASD, autistic spectrum disorder; ASM, anti-seizures medication; BFIS, benign familial infantile epilepsy; BFNE, benign familial neonatal epilepsy; BZD, benzodiazepines; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; CSWS, epilepsy with continuous spike-wave during sleep; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; EIMFS, epilepsy in infancy with migrating focal seizures; ETS, ethosuximide; FFA, fenfluramine: FFEVF, familial focal epilepsy with variable foci; FIRES, febrile infection-related epilepsy syndrome; GBP, gabapentin; GEFS+, generalized epilepsy with febrile seizures plus; GLUT1, glucose transporter 1; GoF, gain-of-function; ID, intellectual disability; IGEs, idiopathic generalized epilepsies; IL-1β, Interleukin-1β; IL-1Ra, interleukin-1 receptor antagonist; KD, ketogenic diet; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LoF, loss-of-function; LTG, lamotrigine; MAE, myoclonic astatic epilepsy; NA, not applicable; NCL, neuronal ceroid lipofuscinosis; NFLE, nocturnal frontal lobe epilepsy; mTOR, mammalian target inhibitor of rapamycin; OXC, oxcarbazepine; PER, Perampanel; PNPO, pyridoxamine 5′-phosphate oxidase; PB, phenobarbital; PCDH19-FE, protocadherin 19 female-limited epilepsy; PER, perampanel; PGP, pyridoxal-5′-phosphate; PHT, phenytoin; PM, precision medicine; PRRT2, proline-rich transmembrane protein 2; RTG, retigabine; RUF, rufinamide; SELECTS, self-limited epilepsy with centro-temporal spikes; STP,

stiripentol; TPP1, tripeptidyl peptidase 1; TPM, topiramate; TSC, tuberous sclerosis complex; VGB, vigabatrin.; VPA, valproic acid; ZNS, zonisamide

1.1   Introduction

The past 30 years have seen the introduction into clinical practice of over 20 second-generation antiseizure medications (ASMs). Despite this enlarged pharmacological armamentarium, about one-third of people with epilepsy fail to achieve complete seizure control, and outcomes are even poorer for certain syndromes, such as developmental and epileptic encephalopathies (DEE)[1]. One possible reason for the inadequate response to treatment in these patients is that the large majority of currently available ASMs have been developed with the aim of suppressing symptoms (seizures), and were not designed to address the specific etiologies and mechanisms responsible for the development of the disease in individual patients [2].

The potential for a more bespoke approach to epilepsy in the form of precision medicine (PM) has been increasingly highlighted, particularly with the growing awareness of the genetic etiology of many epileptic conditions [3,4]. PM can be defined as the application of "*treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics*", and is aimed at improving clinical outcomes by tailoring treatments to the needs and characteristics of each individual [5]. When the cause of epilepsy in an individual has been identified, it may be possible to use, or to develop, a treatment which can mitigate or eliminate not only the seizures, but also comorbidities that share the same etiology.

The last decade has seen impressive advances in the discovery of gene mutations causing epilepsy, facilitated by next generation sequencing techniques. In many cases, the downstream molecular mechanisms that underlie the clinical manifestations of several monogenic epilepsies have also been deciphered, paving the way to engineered solutions specific for that gene mutation [6]. For example, if a particular epilepsy is attributable to a pathogenic variants within a gene that codes for an ion channel, it should be possible to determine first whether the encoded mutant protein results in a phenotype of loss or gain of function, and then identify a treatment capable of reversing the functional consequences [7]. This example is relatively simple and represents only one of the many directions in which PM is developing. The purpose of this article is to discuss different treatment paradigms that can be applied to the management of monogenic epilepsies with onset in childhood, and to provide examples of opportunities offered by PM-based approaches (see also Table 1). Although discussion will be focused on the treatment of monogenic epilepsies, PM approaches are being investigated also for other epilepsies, including those involving metabolic, infectious, structural and immune- or inflammatory-related etiologies [5].

2.1   Empirical treatments

The management of monogenic epilepsies still relies largely on the application of traditional, empirically identified treatments, based on historical evidence of effectiveness of individual ASMs against specific seizure types. Most monogenic epilepsies consist in DEEs, each of which is typically associated with a variety of generalized and sometimes, generalized and focal seizure types. Hence, most empirical treatments used in these epilepsies involve use of broad-spectrum ASMs such as valproate, benzodiazepines, and, depending on the specific syndrome, topiramate, lamotrigine, zonisamide, and barbiturates. Although a correlation may exist between the precise genetic etiology of the conditions being treated and response to these medications, any link between pathogenetic mechanisms in individual syndromes and a drug's mechanisms of action is generally poorly understood. Yet, targeted treatments can still be applied, based on clinical evidence of an apparent greater efficacy of certain ASMs in a specific epilepsy syndrome. For example, recognition of the value of carbamazepine in the treatment of proline-rich transmembrane protein 2 (PRRT2)-related seizures and movement disorders [8], or vigabatrin in the treatment of epileptic spasms associated with tuberous sclerosis complex (TSC) [9] was established empirically, and was not driven by the understanding of the pathogenic mechanisms responsible for epileptogenesis in these conditions.

Dravet syndrome (DS) provide an illustrative example of this paradigm. DS is the archetype of *SCN1A*-related epilepsies, which themselves display substantial phenotypic variability, ranging from simple febrile seizures or genetic epilepsy with febrile seizures plus (GEFS+) to severe DEEs [10]. To date, no PM-based treatments have been approved for DS, though use of certain ASMs has been proven to be effective in treating seizures associated with this syndrome [11]. Specifically, valproate, clobazam, and stiripentol (in combination with valproate and clobazam) are considered as first-line treatments for DS, whereas the ketogenic diet, topiramate, and cannabidiol are considered second-line, and levetiracetam, bromides, zonisamide, and vagal nerve stimulation are regarded as third-line treatments [12]. Fenfluramine, which was approved recently in the U.S. and Europe, has also been found to be effective in the add-on treatment of seizures associated with DS, with a recent case report suggesting that it could also be valuable to control non-convulsive status epilepticus in these patients [13]. Importantly, ASMs that act primarily by blocking voltage-gated sodium channels can aggravate seizures associated with DS, and are generally contraindicated in this syndrome [14]. This is explained by the fact that seizure manifestations in patients with DS are due to *SCN1A* loss-of-function mutations, resulting in impaired activity of voltage-gated sodium channels in inhibitory GABAergic interneurons. By inhibiting these channels, sodium channel blockers amplify the functional disturbance responsible for seizure generation in these patients [15].

2.1   Precision treatments

Precision treatments are based on the understanding of the function of the mutated genes, and application of interventions which are known or expected to correct the dysfunction caused by the mutated-gene products. This can occur under different scenarios, as summarized below.

3.1.1   Scenario 1 (selection of ASMs targeting specifically the pathogenetic mechanisms of the disease)

The first scenario consists in the rational application of existing ASMs to target the specific molecular dysfunction resulting from the mutated gene. For example, the classic *SCN8A*-related DEE phenotype results from a gain of function in neuronal sodium channels, and sodium channel-blocking ASMs such as phenytoin and carbamazepine can be used effectively in these patients to reduce seizure burden by attenuating the dysfunction by the affected channels [7].

Treatment responses in *SCN2A*-related epilepsies appear to be more complex, as shown by a recent retrospective study of 66 patients for whom detailed information was available [16]. Patients with early infantile epilepsies (onset at < 3 months) often achieved a clinically relevant reduction in seizure frequency or even seizure freedom with sodium channel blockers, whereas other ASMs were less effective. Conversely, for children with later-onset epilepsies, sodium-channel blockers were rarely effective and at times even worsened seizures. Correlation between ASM responses and specific mutations and their functional consequences suggested that the type of gene defect was prognostic of response to specific drugs. Specifically, only patients with later-onset epilepsies had truncating mutations, which were associated with lack of seizure improvement after administration of sodium channel blocking ASMs.

Overall, a favorable response of *SCN2A* encephalopathies with onset in the first three months of life to sodium channel blockers seems to be a common finding across available reports [4]. Early-onset cases of *SCN2A*-related epilepsies typically have gain-of-function mutations, as suggested from functional studies with four selected missense mutations and a review of literature data [4]. Relatively small gains in function were generally associated with a favorable response to sodium channel blocking ASMs. Conversely, mutations found in late-onset forms with inadequate response to sodium-channel blockers were associated with loss-of-function mutations, an observation which explains the poor response to sodium channel blocking drugs in these patients.

Carbamazepine and phenytoin are also recommended as a first-line treatment for seizures occurring in neonates and infants with *KCNQ2* encephalopathy, with most patients achieving seizure freedom

on these drugs [17]. The enigma of favorable response to these sodium-channel blockers in patients with mutated potassium channels may lie in the shared motif and close co-localization of voltage-gated Kv.7 potassium channels and sodium channels at regions of the neuronal membrane critical for action-potential generation and propagation. Based on this, mutation within the potassium channel could result in enhanced sensitivity of sodium channels to carbamazepine and other sodium-channel blocking ASMs [18].

In 2014, Orhan *et al.* made the interesting observation that the electrophysiological changes associated with a majority of *KCNQ2* mutations found in patients with encephalopathy are antagonized *in vitro* by the Kv7.2 and Kv7.3 opener, retigabine (ezogabine) [19]. Clinical evidence for potential utility of retigabine in the treatment of *KCNQ2* encephalopathies was provided by a multicenter study in 11 patients, with 3 of the 4 patients treated with retigabine before 6 months of age and 2 of the 7 treated at later times having improvements in either seizure control or development [20]. Unfortunately, the retigabine product originally approved for the treatment of focal seizures has been withdrawn from the market. To address this therapeutic gap, Xenon Pharmaceuticals is conducting a Phase 3 pivotal study (NCT04639310). with another formulation of retigabine (XEN496). This is one of the first controlled trials in children with a monogenic DEE testing a molecule that targets the specific mechanism of the disease. An open-label extension study is planned to enable longer-term assessment of changes in development and other features beyond seizures [21].

3.1.2   *Scenario 2 (development of targeted therapies based on novel molecules)*

The second scenario is the development of new drugs specifically targeting the molecular defect identified by the genetic and functional studies. One example is the design of selective sodium channel modulators addressing the functional consequences of either gain- or loss-of-function epilepsy-causative mutations. Such compounds include the Nav1.6-selective sodium channel modulators XEN901 and PRAX330, which are being developed for the management of *SCN8A*-related DEE caused by gain-of-function mutations [22]. Another drug-discovery program seeks to identify compounds that selectively activate Nav1.1 [23].

An example of innovative treatment which targets the pathogenetic mechanism and is already commercially available is represented cerliponase alfa, an enzyme replacement therapy for neuronal ceroid lipofuscinosis type 2 (CLN2 disease). CLN2 disease, a form of Batten's disease, is a genetic autosomal recessive disorder caused by mutations in the *TPP1* gene, which encodes the lysosomal

enzyme tripeptidyl peptidase 1 (TPP1). Deficiency of the enzyme leads to accumulation of lysosomal storage material in neurons in the central nervous system (CNS) and in the retina. Clinical manifestations typically appear in the late infantile period (2–4 years of age) and consist in delayed language acquisition, seizures, rapid cognitive motor decline, blindness, and early death [24]. Cerliponase alfa is a recombinant proenzyme of human TPP1 approved in the U.S. and Europe for the treatment of motor function loss associated with CLN2 disease [25,26]. Specific information on the effect of cerliponase alfa on seizure control beyond the composite measure used in the registration trials, however, is currently unavailable.

A monogenic epilepsy syndrome which represents an attractive candidate for precision medicine is protocadherin 19 (PCDH19) female-limited epilepsy (PCDH19-FE, also known as epilepsy and mental retardation limited to females). Recent evidence that the pathogenetic mechanisms involved in PCDH-19-FE may include a deficiency in neurosteroid allopregnanolone [27] in the central nervous system (CNS), led to a pilot study of ganaxolone, an analogue of allopregnanolone in the treatment of patients with this syndrome. The results of this study suggested that patients with plasma levels of allopregnanolone sulfate < 2500 pg/mL at pre-treatment show a good response to ganaxolone, whereas response does not appear to be favorable in patients with higher levels of this potential biomarker [21]. These findings are being further evaluated in a prospective randomized placebo-controlled adjunctive- therapy trial (NCT03865732) and, if confirmed, would represent an excellent example of PM being guided by a specific biomarker for prediction of efficacy.

Innovative potential precision treatments are under investigation in many other monogenic epilepsies. A notable example is represented by progressive myoclonic epilepsies [28] and especially Lafora disease, for which treatments under (mostly) preclinical investigation include CNS delivery of hydrolytic enzymes, virus-mediated gene replacement therapies, genome engineering by CRISPR-Cas9, protein inhibition by small molecules, RNA targeting by antisense oligonucleotides (ASOs) and RNA interference (RNAi) [28].

3.1.3 Scenario 3 (use of dietary treatments or food constituents to correct specific metabolic defects)

The third scenario is the use of dietary treatments or vitamins for monogenetic epilepsies resulting specific metabolic defects. Probably the best example is represented by use of the ketogenic diet to treat glucose transporter 1 (GLUT1) deficiency syndrome. This condition is caused by mutations in *SLC2A1* (which encodes GLUT1) and results in deficient glucose transport across the blood–brain barrier [29]. The ketogenic diet is a high-fat, low-carbohydrate diet that provides ketone bodies to

the brain as an alternative energy source to glucose, resulting in seizure control and improvement in associated symptoms (e.g., movement disorders and intellectual disability) [30]. Early treatment of (GLUT1) deficiency syndrome with the ketogenic diet has been shown to improve significantly long-term prognosis in affected children [31].

A similar example of this strategy is represented by the treatment of vitamin B6-dependent epilepsy. This heterogeneous group of treatable disorders is due to mutations in one of several genes (*ALDH7A1*, *PNPO*, *ALPL/ALDH4A1*, *PROSC*) and is characterized by appearance of convulsions resistant to ASMs, but controlled by daily pharmacological doses of pyridoxine or pyridoxal-5′-phosphate supplement [32].

3.1.4 Scenario 4 (repurposing of medications approved originally for other indications)

The fourth scenario consists is the targeting of the specific pathogenetic mechanisms by using drugs developed for different indications. The best example of such treatments is provided by everolimus, a mammalian target of rapamycin (mTOR) inhibitor, which was approved initially for the treatment of advanced renal cell carcinoma, and has now been approved in the U.S. and Europe for the treatment of seizures in patients with mutations in TSC genes that are causally linked to activation of the mTOR signaling cascade [33].

Another example of drug repurposing relates to the investigational use of quinidine for the treatment epilepsies secondary to *KCNT1* mutations. Phenotypes encountered in individuals with these mutations include epilepsy of infancy with migrating focal seizures (EIMFS), and severe autosomal dominant sleep-related hypermotor epilepsy (ADSHE) [34]. All gene variants evaluated to date seem to confer a gain-of-function phenotype, irrespective of the type of associated epilepsy [34]. The antiarrhythmic drug quinidine, a partial antagonist of KNa1.1, can attenuate *KCNT1*-related gain-of-function effects *in vitro*. Accordingly, Bearden *et al.* (2014) reported a marked reduction in seizure frequency together with improved cognitive development in a child with EIFMS started on quinidine [35]. However, in subsequent studies response to quinidine has been reported to differ markedly across patients [4] and to be often complicated by dose-limiting cardiac effects, particularly QT prolongation [36–40]. In the only randomized controlled trial conducted to date, quinidine was administered over 12 days to 6 individuals aged 15–54 years with severe *KCNT1*-related ADSHE [40]. The first two patients, who received starting doses of 800 and 600 mg/day, discontinued treatment after 2 days because of unexpected cardiac toxicity (T-wave flattening and significant QT interval prolongation). The remaining four patients were given 300

mg/day and showed no seizure improvement, but the blood levels of quinidine at those doses were very low or barely detectable. The reasons for the variability in response to quinidine in *KCNT1*-related epilepsies remain unclear, being possibly related to the type of mutation, the epilepsy phenotype, and the age of the individual [4]. At present, there is insufficient information to make recommendations on the use of quinidine in *KCNT1*-related epilepsies [41]. Further *in vitro* studies into the responsiveness of channel mutations to quinidine might provide clues for the design for a safer, more targeted drug.

A repurposed treatment has also been proposed for some patients with epilepsies due to *GRIN2A* mutations. These mutations seem to be associated with the 'epilepsy-aphasia' spectrum, comprising typical and atypical childhood epilepsy with centrotemporal spikes, Landau–Kleffner syndrome, and epileptic encephalopathy with continuous spike-and-wave during sleep [42]. These phenotypes often result from gain-of-function mutations, though some *GRIN2A* mutations appear to prevent expression of any functional protein. Pierson *et al.* (2014) described a *de novo* gain-of-function *GRIN2A* missense mutation in a 9-year-old boy with severe early-onset DEE. The NMDA receptors encoded by the mutated gene retained their sensitivity to memantine, which was given to the child and resulted in a marked reduction in seizure frequency [43]. Memantine has also been tried in two unrelated children with DEE caused by a gain-of-function *GRIN2D* mutation [44] and in four children with *GRIN2B*-related encephalopathy due to putative gain-of-function mutations [45]. Results on the frequency of the seizures were mixed, while improvements were reported on development, awareness and behavior, and sleep.

A severe condition for which a potential genetic contribution has been hypothesized, but not demonstrated to date [46], is febrile infection-related epilepsy syndrome (FIRES), in which abnormal immune responses and neuroinflammation seem to play a major role [47]. Following case reports suggesting a favorable response of these patients to the human recombinant form of interleukin-1 receptor antagonist (IL-1Ra) anakinra [48], a recent study provided evidence for a functional deficit of endogenous IL-1Ra in patients with FIRES and sequencing in an index patient revealed genetic variants that could be linked to this functional deficit [49]. While this example requires additional support linking genetics, pathophysiology, and therapeutic response data, it nevertheless represents an elegant example of how individual cases can guide research strategies in developing new PM approaches. In fact, the activity of IL-1Ra in various experimental models of acute seizures [50] has led to the investigational use of anakinra for the control of drug-resistant seizures in children with FIRES and other forms drug resistant epilepsy [5]. Modulation of immune-mediated and inflammatory mechanisms represents an attractive option for drug repurposing in other types of epilepsy, potential targets being represented by COX-1/2 (aspirin),

TNF (adalimumab), IL-6R (tocilizumab), alpha4 integrin (natalizumab), and microglia activation (minocycline) [5].

6.1   Conclusions and future perspectives

At present, the management of most infants and children with monogenic epilepsies still relies heavily on the use of conventional ASMs, including orphan medications which have been introduced recently, as in the case of stiripentol, cannabidiol and fenfluramine for the treatment of seizures associated with DS [51]. However, several precision treatments for many of these conditions are starting to emerge, driven by continuous advances in our understanding of the molecular mechanisms underlying these diseases [52]. In fact, some of these treatments, such as the ketogenic diet for the management of symptoms of GLUT1-deficiency syndrome, have now become established as first-line therapies, and have improved short- and long-term outcomes for affected patients [31]. For most of the severe DEEs, however, the value of different PM approaches has not yet been clearly defined, and the overall prognosis for many of these patients remains poor in terms of seizure control, intellectual disability and other comorbidities.

Efforts into the development of more effective PM approaches are being intensified, thanks to the major progress being made in characterizing the functional consequences of specific gene mutations [52]. These efforts are being facilitated by the development of new experimental models which more closely mimic the human disease, by opportunities offered by the identification of biomarkers and the possibility to analyse large sets of data through artificial intelligence tools, and by the availability of novel therapeutic tools such as ASO technology, improved CNS delivery systems, gene therapy and gene editing [6,53]. For these advances to be effectively translated into the clinic, however, a number of challenges need to be addressed.

A major challenge relates to the difficulty of conducting well designed clinical trials in diseases which are not only rare, but also heterogeneous with respect not only to underlying molecular mechanisms (e.g., precise type of mutation, and associated functional consequences) but also phenotypic manifestations. One strategy to address this challenge may involve the creation of prospective registries to collect information on the clinical course of the disease using optimized outcome measures in patients with well characterized molecular diagnoses and clinical phenotypes [54]. These registries can provide not only invaluable data on the 'natural history' of the disease in relation to well defined variables and may also identify important signals of response to interventions applied during the clinical management of these patients. Although 'natural history'

data may be sufficient to provide a control group to assess the effectiveness of a novel investigational treatment [26], efforts should also be made to improve methodologies for the conduction of randomized controlled trials in small populations, including n-of-1 trials [55].

Unfortunately, for many severe DEEs we do not currently have reliable, easily applicable tools to assess response to treatment (including long-term outcomes) not only in terms of changes in seizure frequency and severity, but also in terms of comorbid conditions and overall level of functioning and quality of life. Further efforts are needed to develop and validate improved tools for outcome assessment, prioritizing whenever feasible patient-centered outcome measures (PCOMs). Close involvement of patients and caregivers is essential to ensure success in this effort.

Another challenge in translational science relates to the need to improve early identification of affected individuals on a wide scale, by stimulating knowledge and awareness among physicians, patients and the general public, by expanding diagnostic services, and by facilitating access to affordable diagnostic tools. This is especially important in severe DEEs, because ultimate clinical outcome is dependent on the feasibility of applying effective treatment at the earliest onset of clinical manifestations, or ideally even before the appearance of symptoms [52,56].

Lastly, it is essential that appropriate incentives are provided to develop a wide range of personalized treatments, each of which is likely to benefit only a relatively small number of individuals. In that regard, it is important to emphasize that these treatments collectively can impact on the life of a large proportion of children with severe epilepsies, and bring major benefits to individuals, family members and society at large [52]. Precision treatments for orphan diseases can be developed more efficiently than empirical treatments, and regulatory requirements for these treatments are also simplified. Although incentives for development are available in terms of market exclusivity and premium prices given to these treatments, their high cost can also be a barrier to access. There is a need for legislation and other initiatives to facilitate the conduction high-quality trials academic in this area and increase funding for these studies. Addressing all the above challenges requires effective collaboration among all parties involved, including clinicians and basic scientists in industry and academia, regulators, advocacy groups, patients, caregivers, and other interested stakeholders. There are unprecedented opportunities ahead of us, which should be pursued with the highest level of commitment.

Conflict-of-interest disclosures

References

[1] Perucca E, Brodie MJ, Kwan P, Tomson T. 30 years of second-generation antiseizure medications: impact and future perspectives. Lancet Neurol 2020;19:544–56. https://doi.org/10.1016/S1474-4422(20)30035-1.

[2] Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov 2013. https://doi.org/10.1038/nrd4126.

[3] Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. Nat Rev Drug Discov 2018;17:183–96. https://doi.org/10.1038/nrd.2017.226.

[4] Perucca P, Perucca E. Identifying mutations in epilepsy genes: Impact on treatment selection. Epilepsy Res 2019. https://doi.org/10.1016/j.eplepsyres.2019.03.001.

[5] Jameson JL, Longo DL. Precision medicine--personalized, problematic, and promising. N Engl J Med 2015;372:2229–34. https://doi.org/10.1056/NEJMsb1503104.

[6] Delanty N, Cavallleri G. Genomics-Guided Precise Anti-Epileptic Drug Development. Neurochem Res 2017. https://doi.org/10.1007/s11064-017-2312-y.

[7] Musto E, Gardella E, Møller RS. Recent advances in treatment of epilepsy-related sodium channelopathies. Eur J Paediatr Neurol 2020;24:123–8. https://doi.org/10.1016/j.ejpn.2019.12.009.

[8] Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2 -associated paroxysmal diseases. Brain 2015;138:3476–95. https://doi.org/10.1093/brain/awv317.

[9] Curatolo P, Verdecchia M, Bombardieri R. Vigabatrin for tuberous sclerosis complex. Brain Dev., 2001. https://doi.org/10.1016/S0387-7604(01)00290-X.

[10] Cetica V, Chiari S, Mei D, Parrini E, Grisotto L, Marini C, et al. Clinical and genetic factors predicting Dravet syndrome in infants with SCN1A mutations. Neurology 2017;88:1037–44. https://doi.org/10.1212/WNL.0000000000003716.

[11] Cross JH, Caraballo RH, Nabbout R, Vigevano F, Guerrini R, Lagae L. Dravet syndrome: Treatment options and management of prolonged seizures. Epilepsia 2019. https://doi.org/10.1111/epi.16334.

[12] Wirrell EC, Nabbout R. Recent Advances in the Drug Treatment of Dravet Syndrome. CNS Drugs 2019;33:867–81. https://doi.org/10.1007/s40263-019-00666-8.

[13]   Specchio N, Pietrafusa N, Doccini V, Trivisano M, Darra F, Ragona F, et al. Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: A real-world study. Epilepsia 2020;61:2405–14. https://doi.org/10.1111/epi.16690.

[14]   Shi XY, Tomonoh Y, Wang WZ, Ishii A, Higurashi N, Kurahashi H, et al. Efficacy of antiepileptic drugs for the treatment of Dravet syndrome with different genotypes. Brain Dev 2016. https://doi.org/10.1016/j.braindev.2015.06.008.

[15]   Catterall WA. Dravet syndrome: a sodium channel interneuronopathy. Curr Opin Physiol 2018. https://doi.org/10.1016/j.cophys.2017.12.007.

[16]   Wolff M, Johannesen KM, Hedrich UBS, Masnada S, Rubboli G, Gardella E, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain 2017;140:1316–36. https://doi.org/10.1093/brain/awx054.

[17]   Pisano T, Numis AL, Heavin SB, Weckhuysen S, Angriman M, Suls A, et al. Early and effective treatment of KCNQ2 encephalopathy. Epilepsia 2015;56:685–91. https://doi.org/10.1111/epi.12984.

[18]   Sands TT, Balestri M, Bellini G, Mulkey SB, Danhaive O, Bakken EH, et al. Rapid and safe response to low-dose carbamazepine in neonatal epilepsy. Epilepsia 2016;57:2019–30. https://doi.org/10.1111/epi.13596.

[19]   Orhan G, Bock M, Schepers D, Ilina EI, Reichel SN, Löffler H, et al. Dominant-negative effects of KCNQ2 mutations are associated with epileptic encephalopathy. Ann Neurol 2014;75:382–94. https://doi.org/10.1002/ana.24080.

[20]   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. https://doi.org/10.1212/NXG.0000000000000096.

[21]   Bialer M, Johannessen SI, Koepp MJ, Levy RH, Perucca E, Perucca P, et al. Progress report on new antiepileptic drugs: A summary of the Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV). I. Drugs in preclinical and early clinical development. Epilepsia 2020;61:2340–64. https://doi.org/10.1111/epi.16725.

[22]   Bialer M, Johannessen SI, Koepp MJ, Levy RH, Perucca E, Tomson T, et al. Progress report on new antiepileptic drugs: A summary of the Fourteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIV). I. Drugs in preclinical and early clinical development. Epilepsia 2018. https://doi.org/10.1111/epi.14557.

[23] Frederiksen K, Lu D, Yang J, Jensen HS, Bastlund JF, Larsen PH, et al. A small molecule activator of Na v 1.1 channels increases fast-spiking interneuron excitability and GABAergic transmission in vitro and has anti-convulsive effects in vivo. Eur J Neurosci 2017;46:1887–96. https://doi.org/10.1111/ejn.13626.

[24] Williams RE, Adams HR, Blohm M, Cohen-Pfeffer JL, de Los Reyes E, Denecke J, et al. Management Strategies for CLN2 Disease. Pediatr Neurol 2017;69:102–12. https://doi.org/10.1016/j.pediatrneurol.2017.01.034.

[25] Markham A. Cerliponase Alfa: First Global Approval. Drugs 2017. https://doi.org/10.1007/s40265-017-0771-8.

[26] Schulz A, Ajayi T, Specchio N, de Los Reyes E, Gissen P, Ballon D, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. N Engl J Med 2018. https://doi.org/10.1056/nejmoa1712649.

[27] Tan C, Shard C, Ranieri E, Hynes K, Pham DH, Leach D, et al. Mutations of protocadherin 19 in female epilepsy (PCDH19-FE) lead to allopregnanolone deficiency. Hum Mol Genet 2015. https://doi.org/10.1093/hmg/ddv245.

[28] Nitschke F, Ahonen SJ, Nitschke S, Mitra S, Minassian BA. Lafora disease - from pathogenesis to treatment strategies. Nat Rev Neurol 2018;14:606–17. https://doi.org/10.1038/s41582-018-0057-0.

[29] De Giorgis V, Veggiotti P. GLUT1 deficiency syndrome 2013: Current state of the art. Seizure 2013. https://doi.org/10.1016/j.seizure.2013.07.003.

[30] Klepper J, Scheffer H, Leiendecker B, Gertsen E, Binder S, Leferink M, et al. Seizure control and acceptance of the ketogenic diet in GLUT1 deficiency syndrome: A 2- to 5-year follow-up of 15 children enrolled prospectively. Neuropediatrics 2005. https://doi.org/10.1055/s-2005-872843.

[31] Koch H, Weber YG. The glucose transporter type 1 (Glut1) syndromes. Epilepsy Behav 2019. https://doi.org/10.1016/j.yebeh.2018.06.010.

[32] Van Karnebeek CDM, Tiebout SA, Niermeijer J, Poll-The BT, Ghani A, Coughlin CR, et al. Pyridoxine-Dependent Epilepsy: An Expanding Clinical Spectrum. Pediatr Neurol 2016. https://doi.org/10.1016/j.pediatrneurol.2015.12.013.

[33] French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3):

a phase 3, randomised, double-blind, placebo-controlled study. Lancet 2016;388:2153–63. https://doi.org/10.1016/S0140-6736(16)31419-2.

[34]   Lim CX, Ricos MG, Dibbens LM, Heron SE. KCNT1 mutations in seizure disorders: The phenotypic spectrum and functional effects. J Med Genet 2016. https://doi.org/10.1136/jmedgenet-2015-103508.

[35]   Bearden D, Strong A, Ehnot J, DiGiovine M, Dlugos D, Goldberg EM. Targeted treatment of migrating partial seizures of infancy with quinidine. Ann Neurol 2014. https://doi.org/10.1002/ana.24229.

[36]   Abdelnour E, Gallentine W, McDonald M, Sachdev M, Jiang YH, 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. https://doi.org/10.1016/j.seizure.2017.11.017.

[37]   Dilena R, DiFrancesco JC, Soldovieri MV, Giacobbe A, Ambrosino P, Mosca I, et al. Early Treatment with Quinidine in 2 Patients with Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) Due to Gain-of-Function KCNT1 Mutations: Functional Studies, Clinical Responses, and Critical Issues for Personalized Therapy. Neurotherapeutics 2018;15:1112–26. https://doi.org/10.1007/s13311-018-0657-9.

[38]   Ko A, Youn SE, Kim SH, Lee JS, Kim S, Choi JR, et al. Targeted gene panel and genotype-phenotype correlation in children with developmental and epileptic encephalopathy. Epilepsy Res 2018;141:48–55. https://doi.org/10.1016/j.eplepsyres.2018.02.003.

[39]   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. https://doi.org/10.1016/j.braindev.2017.09.008.

[40]   Mullen SA, Carney PW, Roten A, Ching M, Lightfoot PA, Churilov L, et al. Precision therapy for epilepsy due to KCNT1 mutations. Neurology 2018;90:e67–72. https://doi.org/10.1212/WNL.0000000000004769.

[41]   McTague A, Nair U, Malhotra S, Meyer E, Trump N, Gazina E V., et al. Clinical and molecular characterization of KCNT1-related severe early-onset epilepsy. Neurology 2018. https://doi.org/10.1212/WNL.0000000000004762.

[42]   Reif PS, Tsai M-H, Helbig I, Rosenow F, Klein KM. Precision medicine in genetic epilepsies: break of dawn? Expert Rev Neurother 2017;17:381–92. https://doi.org/10.1080/14737175.2017.1253476.

[43] 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. https://doi.org/10.1002/acn3.39.

[44] 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;99:802–16. https://doi.org/10.1016/j.ajhg.2016.07.013.

[45] Platzer K, Yuan H, Schütz H, Winschel A, Chen W, Hu C, et al. GRIN2B encephalopathy: novel findings on phenotype, variant clustering, functional consequences and treatment aspects. J Med Genet 2017;54:460–70. https://doi.org/10.1136/jmedgenet-2016-104509.

[46] Helbig I, Barcia G, Pendziwiat M, Ganesan S, Mueller SH, Helbig KL, et al. Whole-exome and HLA sequencing in Febrile infection-related epilepsy syndrome. Ann Clin Transl Neurol 2020. https://doi.org/10.1002/acn3.51062.

[47] Rana A, Musto AE. The role of inflammation in the development of epilepsy. J Neuroinflammation 2018. https://doi.org/10.1186/s12974-018-1192-7.

[48] Dilena R, Mauri E, Aronica E, Bernasconi P, Bana C, Cappelletti C, et al. Therapeutic effect of Anakinra in the relapsing chronic phase of febrile infection–related epilepsy syndrome. Epilepsia Open 2019. https://doi.org/10.1002/epi4.12317.

[49] Clarkson BDS, LaFrance-Corey RG, Kahoud RJ, Farias-Moeller R, Payne ET, Howe CL. Functional deficiency in endogenous interleukin-1 receptor antagonist in patients with febrile infection-related epilepsy syndrome. Ann Neurol 2019;85:526–37. https://doi.org/10.1002/ana.25439.

[50] Marchi N, Fan Q, Ghosh C, Fazio V, Bertolini F, Betto G, et al. Antagonism of peripheral inflammation reduces the severity of status epilepticus. Neurobiol Dis 2009;33:171–81. https://doi.org/10.1016/j.nbd.2008.10.002.

[51] Johannessen Landmark C, Potschka H, Auvin S, Wilmshurst JM, Johannessen SI, Kasteleijn-Nolst Trenité D, et al. The role of new medical treatments for the management of developmental and epileptic encephalopathies: Novel concepts and results. Epilepsia 2021: 2021;27. https://doi.org/10.1111/epi.16849.

[52] McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol 2016.

https://doi.org/10.1016/S1474-4422(15)00250-1.

[53] Kearney H, Byrne S, Cavalleri GL, Delanty N. Tackling Epilepsy with High-definition Precision Medicine: A Review. JAMA Neurol 2019. https://doi.org/10.1001/jamaneurol.2019.2384.

[54] Rare disease registries in Europe. Orphanet Report Series, September 2020 n.d. https://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf   (accessed March 21, 2021).

[55] Samuel JP, Burgart A, Wootton SH, Magnus D, Lantos JD, Tyson JE. Randomized n -of-1 Trials: Quality Improvement, Research, or Both? Pediatrics 2016;138:e20161103. https://doi.org/10.1542/peds.2016-1103.

[56] Kotulska K, Kwiatkowski DJ, Curatolo P, Weschke B, Riney K, Jansen F, et al. Prevention of Epilepsy in Infants with Tuberous Sclerosis Complex in the EPISTOP Trial. Ann Neurol 2021. https://doi.org/10.1002/ana.25956.

[57] Specchio N, Pietrafusa N, Doccini V, Trivisano M, Darra F, Ragona F, et al. Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: A real-world study. Epilepsia 2020. https://doi.org/10.1111/epi.16690.

[58] Brunklaus A, Du J, Steckler F, Ghanty II, Johannesen KM, Fenger CD, et al. Biological concepts in human sodium channel epilepsies and their relevance in clinical practice. Epilepsia 2020. https://doi.org/10.1111/epi.16438.

[59] Howell KB, McMahon JM, Carvill GL, Tambunan D, Mackay MT, Rodriguez-Casero V, et al. SCN2A encephalopathy. Neurology 2015;85:958–66. https://doi.org/10.1212/WNL.0000000000001926.

[60] Dilena R, Striano P, Gennaro E, Bassi L, Olivotto S, Tadini L, et al. Efficacy of sodium channel blockers in SCN2A early infantile epileptic encephalopathy. Brain Dev 2017;39:345–8. https://doi.org/10.1016/j.braindev.2016.10.015.

[61] Sanders SJ, Campbell AJ, Cottrell JR, Moller RS, Wagner FF, Auldridge AL, et al. Progress in Understanding and Treating SCN2A-Mediated Disorders. Trends Neurosci 2018. https://doi.org/10.1016/j.tins.2018.03.011.

[62] Ohba C, Kato M, Takahashi S, Lerman-Sagie T, Lev D, Terashima H, et al. Early onset epileptic encephalopathy caused by de novo SCN8A mutations. Epilepsia 2014;55:994–1000. https://doi.org/10.1111/epi.12668.

[63] Boerma RS, Braun KP, van de Broek MPH, van Berkestijn FMC, Swinkels ME, Hagebeuk EO,

et al. Remarkable Phenytoin Sensitivity in 4 Children with SCN8A-related Epilepsy: A Molecular Neuropharmacological Approach. Neurotherapeutics 2016;13:192–7. https://doi.org/10.1007/s13311-015-0372-8.

[64]   McNally MA, Johnson J, Huisman TA, Poretti A, Baranano KW, Baschat AA, et al. SCN8A Epileptic Encephalopathy: Detection of Fetal Seizures Guides Multidisciplinary Approach to Diagnosis and Treatment. Pediatr Neurol 2016;64:87–91. https://doi.org/10.1016/j.pediatrneurol.2016.08.003.

[65]   Gardella E, Marini C, Trivisano M, Fitzgerald MP, Alber M, Howell KB, et al. The phenotype of SCN8A developmental and epileptic encephalopathy. Neurology 2018;91:e1112–24. https://doi.org/10.1212/WNL.0000000000006199.

[66]   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;40:229–32. https://doi.org/10.1016/j.braindev.2017.09.008.

[67]   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;39:80–3. https://doi.org/10.1016/j.braindev.2016.08.002.

[68]   Chong PF, Nakamura R, Saitsu H, Matsumoto N, Kira R. Ineffective quinidine therapy in early onset epileptic encephalopathy with KCNT 1 mutation. Ann Neurol 2016;79:502–3. https://doi.org/10.1002/ana.24598.

[69]   Gertler T, Bearden D, Bhattacharjee A, Carvill G. KCNT1-Related Epilepsy. 1993.

[70]   Yoshitomi S, Takahashi Y, Yamaguchi T, Oboshi T, Horino A, Ikeda H, et al. Quinidine therapy and therapeutic drug monitoring in four patients with KCNT1 mutations. Epileptic Disord 2019. https://doi.org/10.1684/epd.2019.1026.

[71]   Mikati MA, Jiang YH, Carboni M, Shashi V, Petrovski S, Spillmann R, et al. Quinidine in the treatment of KCNT1-positive epilepsies. Ann Neurol 2015. https://doi.org/10.1002/ana.24520.

[72]   Bearden D, Strong A, Ehnot J, DiGiovine M, Dlugos D, Goldberg EM. Targeted treatment of migrating partial seizures of infancy with quinidine. Ann Neurol 2014;76:457–61. https://doi.org/10.1002/ana.24229.

[73]   Evely KM, Pryce KD, Bhattacharjee A. The Phe932Ile mutation in KCNT1 channels associated with severe epilepsy, delayed myelination and leukoencephalopathy produces a loss-of-function

channel phenotype. Neuroscience 2017;351:65–70.
https://doi.org/10.1016/j.neuroscience.2017.03.035.

[74] Numis AL, Nair U, Datta AN, Sands TT, Oldham MS, Patel A, et al. Lack of response to
quinidine in KCNT1-related neonatal epilepsy. Epilepsia 2018. https://doi.org/10.1111/epi.14551.

[75] McTague A, Nair U, Malhotra S, Meyer E, Trump N, Gazina E V., et al. Clinical and molecular
characterization of KCNT1 -related severe early-onset epilepsy. Neurology 2018;90:e55–66.
https://doi.org/10.1212/WNL.0000000000004762.

[76] Schenzer A. Molecular Determinants of KCNQ (Kv7) K+ Channel Sensitivity to the
Anticonvulsant Retigabine. J Neurosci 2005;25:5051–60.
https://doi.org/10.1523/JNEUROSCI.0128-05.2005.

[77] Xie G, Harrison J, Clapcote SJ, Huang Y, Zhang JY, Wang LY, et al. A new Kv1.2
channelopathy underlying cerebellar ataxia. J Biol Chem 2010.
https://doi.org/10.1074/jbc.M110.153676.

[78] Orsini A, Esposito M, Perna D, Bonuccelli A, Peroni D, Striano P. Personalized medicine in
epilepsy patients. J Transl Genet Genomics 2018. https://doi.org/10.20517/jtgg.2018.14.

[79] Kotagal P. Current status of treatments for children with electrical status in slow-wave sleep
(ESES/CSWS). Epilepsy Curr 2017;17:214–6. https://doi.org/10.5698/1535-7597.17.4.214.

[80] Mullier B, Wolff C, Sands ZA, Ghisdal P, Muglia P, Kaminski RM, et al. GRIN2B gain of
function mutations are sensitive to radiprodil, a negative allosteric modulator of GluN2B-
containing NMDA receptors. Neuropharmacology 2017.
https://doi.org/10.1016/j.neuropharm.2017.05.017.

[81] Lotte J, Bast T, Borusiak P, Coppola A, Cross JH, Dimova P, et al. Effectiveness of antiepileptic
therapy in patients with PCDH19 mutations. Seizure 2016.
https://doi.org/10.1016/j.seizure.2016.01.006.

[82] Stamberger H, Weckhuysen S, De Jonghe P. STXBP1 as a therapeutic target for epileptic
encephalopathy. Expert Opin Ther Targets 2017.
https://doi.org/10.1080/14728222.2017.1386175.

[83] Stamberger H, Nikanorova M, Willemsen MH, Accorsi P, Angriman M, Baier H, et al. STXBP1
encephalopathy: A neurodevelopmental disorder including epilepsy. Neurology 2016.

[84] Mignot C, Moutard M-L, Trouillard O, Gourfinkel-An I, Jacquette A, Arveiler B, et al. STXBP1-

related encephalopathy presenting as infantile spasms and generalized tremor in three patients. Epilepsia 2011;52:1820–7. https://doi.org/10.1111/j.1528-1167.2011.03163.x.

[85] Dilena R, Striano P, Traverso M, Viri M, Cristofori G, Tadini L, et al. Dramatic effect of levetiracetam in early-onset epileptic encephalopathy due to STXBP1 mutation. Brain Dev 2016;38:128–31. https://doi.org/10.1016/j.braindev.2015.07.002.

[86] Vlaskamp DRM, Shaw BJ, Burgess R, Mei D, Montomoli M, Xie H, et al. SYNGAP1 encephalopathy: A distinctive generalized developmental and epileptic encephalopathy. Neurology 2019. https://doi.org/10.1212/WNL.0000000000006729.

[87] Billakota S, Andresen JM, Gay BC, Stewart GR, Fedorov NB, Gerlach AC, et al. Personalized medicine: Vinpocetine to reverse effects of GABRB3 mutation. Epilepsia 2019. https://doi.org/10.1111/epi.16394.

[88] Byers HM, Beatty CW, Hahn SH, Gospe SM. Dramatic response after lamotrigine in a patient with epileptic encephalopathy and a de Novo CACNA1A Variant. Pediatr Neurol 2016. https://doi.org/10.1016/j.pediatrneurol.2016.03.012.

[89] Klepper J. Glucose transporter deficiency syndrome (GLUT1DS) and the ketogenic diet. Epilepsia, 2008. https://doi.org/10.1111/j.1528-1167.2008.01833.x.

[90] Klepper J, Flörcken A, Fischbarg J, Voit T. Effects of anticonvulsants on GLUT1-mediated glucose transport in GLUT1 deficiency syndrome in vitro. Eur J Pediatr 2003. https://doi.org/10.1007/s00431-002-1112-8.

[91] Daci A, Bozalija A, Jashari F, Krasniqi S. Individualizing Treatment Approaches for Epileptic Patients with Glucose Transporter Type1 (GLUT-1) Deficiency. Int J Mol Sci 2018;19. https://doi.org/10.3390/ijms19010122.

[92] Orsini A, Valetto A, Bertini V, Esposito M, Carli N, Minassian BA, et al. The best evidence for progressive myoclonic epilepsy: A pathway to precision therapy. Seizure 2019. https://doi.org/10.1016/j.seizure.2019.08.012.

[93] Hoffmann GF, Schmitt B, Windfuhr M, Wagner N, Strehl H, Bagci S, et al. Pyridoxal 5′-phosphate may be curative in early-onset epileptic encephalopathy. J Inherit Metab Dis 2007. https://doi.org/10.1007/s10545-006-0508-4.

[94] Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Everolimus for treatment-refractory seizures in TSC. Neurol Clin Pract 2018;8:412–20.

https://doi.org/10.1212/CPJ.0000000000000514.

[95] Yuskaitis CJ, Rossitto L-A, Gurnani S, Bainbridge E, Poduri A, Sahin M. Chronic mTORC1 inhibition rescues behavioral and biochemical deficits resulting from neuronal Depdc5 loss in mice. Hum Mol Genet 2019;28:2952–64. https://doi.org/10.1093/hmg/ddz123.

[96] de Calbiac H, Dabacan A, Marsan E, Tostivint H, Devienne G, Ishida S, et al. Depdc5 knockdown causes mTOR-dependent motor hyperactivity in zebrafish. Ann Clin Transl Neurol 2018;5:510–23. https://doi.org/10.1002/acn3.542.

[97] Dutchak PA, Laxman S, Estill SJ, Wang C, Wang Y, Wang Y, et al. Regulation of Hematopoiesis and Methionine Homeostasis by mTORC1 Inhibitor NPRL2. Cell Rep 2015. https://doi.org/10.1016/j.celrep.2015.06.042.

[98] Vawter-Lee M, Franz DN, Fuller CE, Greiner HM. Clinical Letter: A case report of targeted therapy with sirolimus for NPRL3 epilepsy. Seizure 2019. https://doi.org/10.1016/j.seizure.2019.10.007.

[99] Kenney-Jung DL, Vezzani A, Kahoud RJ, LaFrance-Corey RG, Ho M-L, Muskardin TW, et al. Febrile infection-related epilepsy syndrome treated with anakinra. Ann Neurol 2016;80:939–45. https://doi.org/10.1002/ana.24806.

[100] Specchio N, Pietrafusa N. New-onset refractory status epilepticus and febrile infection-related epilepsy syndrome. Dev Med Child Neurol 2020. https://doi.org/10.1111/dmcn.14553.

Table 1. Examples of epilepsy syndromes for which targeted treatments are available or are being developed.

Causative mutated gene	Specific target	Related syndromes	Targeted (precision) treatments	Commonly used empirical treatments	References
Sodium channels					
SCN1A	LoF in Nav1.1	DS	None currently available for clinical use	VPA, CLB, TPM, STP, CLB, FFA	[12,57]
SCN2A	GoF in Nav1.2	BFNE; DEE; EIMFS; symptom onset <3 months of age	CBZ, OXC, PHT or LTG	NA	[16,58–60]
SCN2A	LoF in Nav1.2	ASD/ID and childhood-onset seizures	None currently available for clinical use	VPA, BZD, LEV	[61]
SCN8A	GoF in Nav1.6	DEE; familial myoclonic epilepsy; BFNE; EIMFS	CBZ, OXC, PHT, (XEN901)	NA	[21,62–65]
Potassium channels					
KCNT1	GoF	AD-NFLE, EIMFS; NFLE; DEE	Quinidine	STP + BZD (CLB, CZP), LEV, KD	[36–38,40,66–75]
KCNQ2	Kv7.2 LoF	DEE; BFNE	CBZ, PHT, RTG (XEN496)	NA	[20,21,76]
KCNQ3	Kv7.3 LoF	DEE; BFNE	CBZ, PHT, RTG (XEN496)	NA	[76]
KCNA2	GoF	DEE, severe ataxia, milder familial epilepsy	4-Aminopyridine	acetazolamide	[77,78]
NMDA receptors					
GRIN2A	NMDA sub 2a GoF	Atypical SELECTS; CSWS; Landau–Kleffner syndrome; DEE	Memantine	BDZ, VPA, ETS	[43,79]
GRIN2B	NMDA sub 2b GoF	West syndrome; LGS; DEE	Memantine, radiprodil	NA	[80]
GRIN2D	NMDA sub 2d GoF	DEE	Ketamine, memantine	NA	[44]
Other genetic targets					
PCDH19	Allopregnanolone deficiency?	PCDH19-FE	Ganaxolone	CLB, Bromide	[21,22,81]
STXBP1	NA	DEE	None currently available for clinical use	VGB, VPA, LEV	[82–85]
CDKL5	NA	CDKL5 deficiency disorder	Ganaxolone		[22]
SYNGAP1	NA	Generalized epilepsy with eyelid myoclonia with absences and myoclonic-atonic seizures, seizures triggered by eating, and developmental delay/intellectual disability	None currently available for clinical use	VPA, LTG	[86]
GABRB3	NA	LGS	Vinpocetine	NA	[87]
PRRT2	NA	Familial infantile convulsions with paroxysmal choreoathetosis, BFIS	None currently available for clinical use	CBZ, OXC	
CACNA1A	GoF in Cav2.1	West syndrome; DEE; IGEs	None currently available for clinical use	ETS or LTG	[88]
Metabolic-genetic targets					
SLC2A1	NA	GLUT1 deficiency syndrome	Ketogenic diet	Acetazolamide, TPM, ZNS, PHT, CBZ	[89–91]
EPM2A / EPM2B	Malin/laforin deficiency and	Lafora disease	None currently available for clinical use	VPA, PB, TPM, ZNS, BZD, PER	[92]

	accumulation of polyglucosans				
TPP1	TPP1 deficiency	NCL type 2	Cerliponase alfa	VPA, CLB	[26]
ALDH7A1	B6 deficiency	Pyridoxine-dependent epilepsy	Pyridoxine	NA	[32]
PNPO	P5P deficiency	PNPO deficiency	Pyridoxal-5-phosphate	NA	[93]
mTOR signalling pathways					
TSC1 and 2	TSC1 and 2	TSC; focal dysplasia	Everolimus	VGB	[94]
DEPDC5	GATOR1 complex subunit	FFEVF; familial mesial temporal lobe epilepsy; West syndrome	Everolimus	NA	[95,96]
NPRL2/NPRL3	GATOR1 complex subunit	FFEVF	Everolimus	NA	[97,98]
Neuroinflammation pathways					
NA	IL-1β	FIRES	Anakinra	Anesthetics, Immunotherapy, KD	[21,99,100]

Abbreviations: AD, autosomal dominant; ASD, autistic spectrum disorder; BFIS, benign familial infantile epilepsy; BFNE, benign familial neonatal epilepsy; BZD, benzodiazepines; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; CSWS, epilepsy with continuous spike-wave during sleep; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; EIMFS, epilepsy in infancy with migrating focal seizures; ETS, ethosuximide; FFA, fenfluramine: FFEVF, familial focal epilepsy with variable foci; FIRES, febrile infection-related epilepsy syndrome; GBP, gabapentin; GEFS+, generalized epilepsy with febrile seizures plus; GLUT1, glucose transporter 1; GoF, gain-of-function; ID, intellectual disability; IGEs, idiopathic generalized epilepsies; IL-1β, Interleukin-1β; KD, ketogenic diet; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LoF, loss-of-function; LTG, lamotrigine; MAE, myoclonic astatic epilepsy; NA, not applicable; NCL, neuronal ceroid lipofuscinosis; NFLE, nocturnal frontal lobe epilepsy; OXC, oxcarbazepine; PER, Perampanel; PNPO, pyridoxamine 5′-phosphate oxidase; PB, phenobarbital; PCDH19-FE, protocadherin 19 female-limited epilepsy; PER, perampanel; PGP, pyridoxal-5′-phosphate; PHT, phenytoin; RTG, retigabine; RUF, rufinamide; SELECTS, self-limited epilepsy with centro-temporal spikes; STP, stiripentol; TPP1, tripeptidyl peptidase 1; TPM, topiramate; TSC, tuberous sclerosis complex; VGB, vigabatrin.; VPA, valproic acid; ZNS, zonisamide