New paradigms for the treatment of pediatric monogenic epilepsies:

Progressing Towards Precision Medicine

Nicola Specchio¹, Nicola Pietrafusa¹, Emilio Perucca² and Helen Cross³

¹ Rare and Complex Epilepsy Unit, Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Member of European Reference Network EpiCARE, 00165 - Rome, Italy.
² Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy
³ UCL NIHR BRC Great Ormond Street Institute of Child Health, and Great Ormond Street Hospital for Children, London, UK

Number of text pages: 25
Number of words: 3691
Number of references: 100
Number of figures: 0
Number of tables: 1

*Corresponding Author:

Nicola Specchio, MD, PhD

Rare and Complex Epilepsy Unit, Department of Neuroscience, Bambino Gesù Children’s Hospital, IRCCS, Rome

P.zza S. Onofrio 4, 00165, Rome, Italy, Tel. +39 68592645; fax +390668592463

e-mail: nicola.specchio@opbg.net
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.

Keywords: Drug resistant epilepsy, monogenic epilepsies, children, precision medicine, seizure disorder, epileptic encephalopathy, review

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.[6]

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 lipofuscinosi 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 epilepsy 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.

Acknowledgments

We would like to thank Dr. David Macari for English editing of the text.
Conflict-of-interest disclosures

NS has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus and Takeda; has received speaker honoraria from Eisai, Biomarin, Livanova, Sanofi; has served as an investigator for Zogenix, Marinus, Biomarin, UCB, Roche.

NP received speaker honoraria from Zogenix.

EP has received speaker’s or consultancy fees from Arvelle, Biogen, Corlieve, Eisai, GW Pharma, Sanofi, Sun Pharma, UCB Pharma, Xenon Pharma and Zogenix.

JHC has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo and Marinus. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. Her research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital. She holds an endowed chair at UCL Great Ormond Street Institute of Child Health; she holds grants from NIHR, EPSRC, GOSH Charity, ERUK, and the Waterloo Foundation.
References


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


[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


<table>
<thead>
<tr>
<th>Causative mutated gene</th>
<th>Specific target</th>
<th>Related syndromes</th>
<th>Targeted (precision) treatments</th>
<th>Commonly used empirical treatments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium channels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN1A</td>
<td>LoF in Nav1.1</td>
<td>DS</td>
<td>None currently available for clinical use</td>
<td>VPA, CLB, TPM, STP, CLB, FFA</td>
<td>[12,57]</td>
</tr>
<tr>
<td>SCN2A</td>
<td>GoF in Nav1.2</td>
<td>BFNE; DEE; EIMFS; symptom onset &lt;3 months of age</td>
<td>CBZ, OXC, PHT or LTG</td>
<td>NA</td>
<td>[16,58–60]</td>
</tr>
<tr>
<td>SCN2A</td>
<td>LoF in Nav1.2</td>
<td>ASD/ID and childhood-onset seizures</td>
<td>None currently available for clinical use</td>
<td>VPA, BZD, LEV</td>
<td>[61]</td>
</tr>
<tr>
<td>SCN8A</td>
<td>GoF in Nav1.6</td>
<td>DEE; familial myoclonic epilepsy; BFNE; EIMFS</td>
<td>CBZ, OXC, PHT, (XEN901)</td>
<td>NA</td>
<td>[21,62–65]</td>
</tr>
<tr>
<td>Potassium channels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCNT1</td>
<td>GoF</td>
<td>AD-NFLE, EIMFS; NFLE; DEE</td>
<td>Quinidine</td>
<td>STP + BZD (CLB, CZP), LEV, KD</td>
<td>[36–38,40,66–75]</td>
</tr>
<tr>
<td>KCNQ2</td>
<td>Kv7.2 LoF</td>
<td>DEE; BFNE</td>
<td>CBZ, PHT, RTG (XEN496)</td>
<td>NA</td>
<td>[20,21,76]</td>
</tr>
<tr>
<td>KCNQ3</td>
<td>Kv7.3 LoF</td>
<td>DEE; BFNE</td>
<td>CBZ, PHT, RTG (XEN496)</td>
<td>NA</td>
<td>[76]</td>
</tr>
<tr>
<td>KCNA2</td>
<td>GoF</td>
<td>DEE, severe ataxia, milder familial epilepsy</td>
<td>4-Aminopyridine</td>
<td>acetazolamide</td>
<td>[77,78]</td>
</tr>
<tr>
<td>NMDA receptors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRIN2A</td>
<td>NMDA sub 2a GoF</td>
<td>Atypical SELECTS; CSWS; Landau–Kleffner syndrome; DEE</td>
<td>Memantine</td>
<td>BDZ, VPA, ETS</td>
<td>[43,79]</td>
</tr>
<tr>
<td>GRIN2B</td>
<td>NMDA sub 2b GoF</td>
<td>West syndrome; LGS; DEE</td>
<td>Memantine, radiprodil</td>
<td>NA</td>
<td>[80]</td>
</tr>
<tr>
<td>GRIN2D</td>
<td>NMDA sub 2d GoF</td>
<td>DEE</td>
<td>Ketamine, memantine</td>
<td>NA</td>
<td>[44]</td>
</tr>
<tr>
<td>Other genetic targets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCDH19</td>
<td>Allopregnanolone deficiency?</td>
<td>PCDH19-FE</td>
<td>Ganaxolone</td>
<td>CLB, Bromide</td>
<td>[21,22,81]</td>
</tr>
<tr>
<td>STXBP1</td>
<td>NA</td>
<td>DEE</td>
<td>None currently available for clinical use</td>
<td>VGB, VPA, LEV</td>
<td>[82–85]</td>
</tr>
<tr>
<td>CDKL5</td>
<td>NA</td>
<td>CDKL5 deficiency disorder</td>
<td>Ganaxolone</td>
<td>NA</td>
<td>[22]</td>
</tr>
<tr>
<td>SYNGAP1</td>
<td>NA</td>
<td>Generalized epilepsy with eyelid myoclonia with absences and myoclonic-atonic seizures, seizures triggered by eating, and developmental delay/intellectual disability</td>
<td>None currently available for clinical use</td>
<td>VPA, LTG</td>
<td>[86]</td>
</tr>
<tr>
<td>GABRB3</td>
<td>NA</td>
<td>LGS</td>
<td>Vinpocetine</td>
<td>NA</td>
<td>[87]</td>
</tr>
<tr>
<td>PRRT2</td>
<td>NA</td>
<td>Familial infantile convulsions with paroxysmal choreoathetosis, BFIS</td>
<td>None currently available for clinical use</td>
<td>CBZ, OXC</td>
<td></td>
</tr>
<tr>
<td>CACNA1A</td>
<td>GoF in Cav2.1</td>
<td>West syndrome; DEE; IGEs</td>
<td>None currently available for clinical use</td>
<td>ETS or LTG</td>
<td>[88]</td>
</tr>
<tr>
<td>Metabolic-genetic targets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC2A1</td>
<td>NA</td>
<td>GLUT1 deficiency syndrome</td>
<td>Ketogenic diet</td>
<td>Acetazolamide, TPM, ZNS, PHT, CBZ</td>
<td>[89–91]</td>
</tr>
<tr>
<td>EPM2A / EPM2B</td>
<td>Malin/laforin deficiency and</td>
<td>Lafora disease</td>
<td>None currently available for clinical use</td>
<td>VPA, PB, TPM, ZNS, BZD, PER</td>
<td>[92]</td>
</tr>
<tr>
<td>TPP1</td>
<td>TPP1 deficiency</td>
<td>NCL type 2</td>
<td>Cerliponase alfa</td>
<td>VPA, CLB</td>
<td>[26]</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>ALDH7A1</td>
<td>B6 deficiency</td>
<td>Pyridoxine-dependent epilepsy</td>
<td>Pyridoxine</td>
<td>NA</td>
<td>[32]</td>
</tr>
<tr>
<td>PNPO</td>
<td>P5P deficiency</td>
<td>PNPO deficiency</td>
<td>Pyridoxal-5-phosphate</td>
<td>NA</td>
<td>[93]</td>
</tr>
</tbody>
</table>

### mTOR signalling pathways

<table>
<thead>
<tr>
<th>TSC1 and 2</th>
<th>TSC1 and 2</th>
<th>TSC; focal dysplasia</th>
<th>Everolimus</th>
<th>VGB</th>
<th>[94]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEPDC5</td>
<td>GATOR1 complex subunit</td>
<td>FFEVF; familial mesial temporal lobe epilepsy; West syndrome</td>
<td>Everolimus</td>
<td>NA</td>
<td>[95,96]</td>
</tr>
<tr>
<td>NPRL2/NPRL3</td>
<td>GATOR1 complex subunit</td>
<td>FFEVF</td>
<td>Everolimus</td>
<td>NA</td>
<td>[97,98]</td>
</tr>
</tbody>
</table>

### 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.