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Review article

Identifying mutations in epilepsy genes: Impact on treatment selection

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ABSTRACT

The last decade saw impressive advances not only in the discovery of gene mutations causing epilepsy, but also in unraveling the molecular mechanisms underlying the clinical manifestations of the disease. Increasing evidence is emerging that understanding these mechanisms is relevant for selection of the most appropriate treatment in the affected individual(s). The present article discusses the therapeutic implications of epilepsy-causing variants affecting a broad range of targets, from ion channels to genes controlling cellular metabolism and cell signaling pathways. Identification of a precise genetic etiology can direct physicians to (i) prescribe treatments that correct specific metabolic defects (e.g., the ketogenic diet for GLUT1 deficiency, or pyridoxine for pyridoxine-dependent epilepsies); (ii) avoid antiepileptic drugs (AEDs) that can aggravate the pathogenic defect (e.g., sodium channel blocking drugs in *SCN1A*-related Dravet syndrome), or (iii) select AEDs that counteract the functional disturbance caused by the gene mutation (e.g., sodium channel blockers for epilepsies due to gain-of-function *SCN8A* mutations). In some instances, different pathogenic variants of the same gene can have opposite functional effects, which determines whether certain treatments can be beneficial or deleterious (e.g., gain-of-function versus loss-of-function variants in *SCN2A* determine whether sodium channel blockers improve or worsen seizure control). There are also cases where functional disturbances caused by the gene defect may not be corrected by existing AEDs, but can be countered by medications already available in the market for other indications (e.g., memantine has been used to treat the epileptic encephalopathy caused by a specific gain-of-function *GRIN2A* mutation), thus making 'drug repurposing' a valuable tool for personalized epilepsy therapies. As our understanding of pathogenic mechanisms improve, opportunities arise for development of treatments targeting the specific gene defect or its consequences. Everolimus, an mTOR inhibitor approved for the treatment of focal seizures associated with tuberous sclerosis complex, is an example of a medication targeting the etiological mechanisms of the disease. Several treatments aimed at correcting specific pathogenic defects responsible for rare genetic epilepsies are currently in development, and range from traditional small molecules to novel approaches involving peptides, antisense oligonucleotides, and gene therapy.

1. Introduction

Since the historical finding of a *CHRNA4* mutation causing autosomal dominat sleep-related hypermotor epilepsy (formerly known as autosomal dominant nocturnal frontal lobe epilepsy) in 1995 (Steinlein et al., 1995), discoveries of epilepsy genes have advanced greatly and accelerated further with the advent of next generation sequencing (Helbig et al., 2016; Perucca, 2018). Initially, identification of a pathogenic variant in an individual with epilepsy was considered to have primarily implications for diagnosis, prognosis, and counseling (Weber et al., 2014). Increasingly, however, evidence is emerging that characterizing specific gene mutations is relevant for treatment selection. To some extent, this relates to accumulation of studies assessing genotype-phenotype correlations and providing empyrical observations on how certain genotypes influence response to specific treatments. More relevantly, however, therapeutic implications emerge from understanding the function of the mutated gene, a crucial step which permits the selection, or the development, of treatments which target the molecular defect or its consequences (EpiPM Consortium, 2015). We are now entering the era of genomics-driven personalized medicine, whereby novel treatments can be designed which are not solely symptomatic, but address the underlying cause of the epilepsy in the

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individual person and offer opportunities for truly disease modifying effects (Delanty and Cavelleri, 2017).

The present article will discuss several examples of how identifying the mutated gene or, more precisely, the specific gene variant permits rational treatment selection, either by prescribing the most appropriate intervention or by avoiding medications which can paradoxically worsen the disease. To illustrate the broad therapeutic impact of genetic knowledge, the chosen examples are drawn from epilepsies caused by mutations affecting a wide variety of targets, from ion channels to genes controlling cellular metabolism and cell signaling pathways. While this article will focus on treatments for Mendelian epilepsies, it should be emphasized that important therapeutic clues or opportunities to develop novel treatments may also derive from improved understanding of polygenic epilepsies, and epilepsy susceptibility genes (Ferraro, 2012; International League against Epilepsy Consortium on Complex Epilepsies, 2018).

2. Epilepsies due to mutations in sodium channel genes

Voltage-gated sodium channels are involved in action potential generation and propagation, and their antagonism is a primary mechanism of action of many currently available antiepileptic drugs (AEDs). Mutations in sodium channel genes, including *SCN1A*, *SCN1B*, *SCN2A*, *SCN3A*, *SCN8A*, and *SCN9A* are collectively responsible for a considerable proportion of cases of drug-resistant genetic epilepsies with onset in infancy and childhood (Parrini et al. (2017)). The three most common among these genes, *SCN1A*, *SCN2A*, and *SCN8A*, illustrate the therapeutic implications of understanding the causative gene variant, and its functional consequences.

2.1. SCN1A-related epilepsies

SCN1A is the most relevant epilepsy gene, and *SCN1A*-related seizure disorders show remarkable phenotypic heterogeneity. The archetypes of *SCN1A*-related epilepsies are Dravet syndrome and genetic epilepsy with febrile seizures plus (GEFS+), which itself displays substantial phenotypic variability, ranging from simple febrile seizures or febrile seizures plus to severe epileptic encephalopathies (Miller and Sotero de Menezes, 2018; Myers et al., 2018). Other phenotypes associated with *SCN1A* mutations include familial simple febrile seizures, focal epilepsies, and an early infantile epileptic encephalopathy (Mantegazza et al., 2005; Miller and Sotero de Menezes, 2018; Sadleir et al., 2017). *SCN1A* mutations have also been found to increase the risk for mesial temporal lobe epilepsy with hippocampal sclerosis and febrile seizures (Kasperaviciute et al., 2013). As an indication of the heterogeneity in clinical expression, clinical phenotypes vary even among family members with the same pathogenic variant, probably as a result of variation in other genes (Escayg and Goldin, 2010).

The functional mechanisms underlying *SCN1A*-related epilepsies, and their implications for treatment selection, have been most extensively investigated in Dravet syndrome.

2.1.1. Dravet syndrome

Heterozygous loss-of-function mutations in *SCN1A* are responsible for the majority of cases of Dravet syndrome (Catterall et al., 2018), a condition that affects 1 in 15,700 to 1 in 40,000 livebirths (Hurst, 1990; Wu et al., 2015). Studies in rodent models carrying the defective gene have demonstrated that the mutation impairs the excitability of inhibitory interneurons in the hippocampus, cortex, cerebellum and thalamus, without affecting the function of excitatory neurons (Yu et al., 2006; Catterall et al., 2010; Chea et al., 2012; Tsai et al., 2015); similar findings have also been reported in neurons derived from induced pluripotent stem cells (iPSCs) obtained from patients with Dravet syndrome (Sun et al., 2016). The resulting pattern is an unbalance between inhibition and excitation, which explains the low seizure threshold in these patients.

Because the mechanism underlying epileptogenesis in *SCN1A*-associated Dravet syndrome is a loss-of-function in sodium channels in inhibitory interneurons, it is not suprising that sodium channel blocking AEDs, such as carbamazepine, oxcarbazepine, phenytoin and lamotrigine, are usually ineffective and can even aggravate seizures in these patients (Guerrini et al., 1998; Xu et al., 2014; Shi et al., 2016). As a result, sodium channel blocking drugs should be generally avoided when managing patients with Dravet syndrome due to *SCN1A* mutations (Wirrell et al., 2017; Perucca et al., 2018). Alternative treatments that can be of value in these patients include valproate and benzodiazepines (Wirrell et al., 2017), stiripentol (Chiron et al., 2000), cannabinoids (Devinsky et al., 2017) and the ketogenic diet (Ko et al., 2018a). Fenfluramine has also shown promising anti-seizure efficacy in a recent clinical trial (Bialer et al., 2018a).

The elucidation of the mechanisms responsible for *SCN1A*-related Dravet syndrome has stimulated innovative research into precision treatments aimed at correcting the underlying molecular or functional defect. Strategies being pursued include the development of antisense oligonucleotides which can restore functional SCN1A mRNA and $Na_V1.1$ levels (Stoke Therapeutics, 2018), or peptides such as Hm1 which activate selectively $Na_V1.1$ in inhibitory interneurons without affecting firing in excitatory neurons (Richards et al., 2018). In early studies, both these treatments have been found to be effective in suppressing seizures and prolonging survival in rodent models of Dravet syndrome (Richards et al., 2018; Stoke Therapeutics, 2018).

Additional genes which have been indentified in cases with a Dravet syndrome-like phenotype include *PCDH19*, *GABRA1*, *SCN1B*, *CHD2*, *STXBP1*, *SCN8A*, *GABRG2*, *HCN1*, and *KCNA*2 (Steel et al., 2017). Therefore, Dravet syndrome represents a good example of how defining the phenotype may not provide all the information needed for optimal management, and how genetic testing can guide pathophysiologic understanding and therapeutic strategy. Apart from predicting adverse responses to sodium channel blockers, genetic characterization might also inform about outcomes with other therapies (Shi et al., 2016). In a recent retrospective study, stiripentol added on to valproate was found to have better efficacy in Dravet syndrome patients with *SCN1A* mutations than in those with variants of unknown significance or benign variants in *SCN1A* (Cho et al., 2018). In the same study, the effectiveness of stiripentol was also greater in individuals with missense mutations in *SCN1A* (87.5% reduction in seizure frequency) than in those with truncation mutations (70.5% reduction in seizure frequency). These findings require confirmation in well designed prospective studies.

2.1.2. Other SCN1A-related epilepsies

For other *SCN1A*-related epilepsies, the implications of a genetic diagnosis for treatment selection have not been well characterized. In particular, patient selection for clinical trials has been typically based on phenotype, and variability in drug response in relation to genetic diagnosis (and genetic variant) has not been evaluated. Functional effects may vary depending on the specific pathogenic variant. For example, in the case of GEFS+-causing mutations, effects observed in heterologous expression systems were considered to be predictive of either increase or decrease in sodium channel activity depending on the gene variant assessed (Escayg and Goldin, 2010). Results in mouse models, however, suggest that, similarly to Dravet syndrome, the primary functional defect in GEFS+, and probably other *SCN1A*-related epilepsies, is loss-of-function leading to decreased activity of GABAergic inhibitory neurons. Based on these data, it has been suggested that sodium channel blocking AEDs should preferably be avoided in these epilepsies (Miller and Sotero de Menezes, 2018). Anecdotal observations suggest that response to sodium channel blockers may be unfavorable even in patients with *SCN1A*-related focal epilepsy (Perucca et al., 2017).

2.2. SCN2A-related epilepsies

SCN2A encodes the voltage-gated sodium channel Nav1.2. Mutations in *SCN2A* have been associated initially with rare cases of benign familial neonatal-infantile epilepsy and later, more prominently, with a broad range of early-onset infantile (< 3 months of age) and later-onset infantile/childhood epileptic and developmental encephalopathies. *SCN2A*-related epilepsies include West syndrome, Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, myoclonic-atonic epilepsy, Lennox-Gastaut syndrome, and focal epilepsies with an electrical status epilepticus during slow sleep-like EEG pattern (Wolff et al., 2017). *SCN2A* mutations can also have a pathogenic role in some cases of autism spectrum disorder, with or without associated seizures (Sanders et al., 2018).

Howell et al.(2015) reported the clinical features of 11 patients with *SCN2A*-related encephalopathies, 10 of whom had seizure onset in the first 6 weeks of life. In 9 patients, seizures were significantly improved with sodium channel blocking AEDs, with 5 patients requiring relatively high serum phenytoin concentrations. Treatment responses in *SCN2A*-related epilepsies have been evaluated in a recent retrospective study of 66 patients for whom detailed information was available (Wolff et al., 2017). 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 such as phenytoin and carbamazepine, whereas other AEDs were less effective. Conversely, sodium channel blockers were rarely effective and at times even worsened seizures in children with later-onset epilepsies. Assessment of the correlation between AED response and specific mutations and their functional consequences suggested the type of gene variant allows to predict how patients will do on specific drugs. Specifically, truncating mutations were found only in patients with later-onset epilepsies and no seizure improvement after administration of sodium channel blockers. Functional studies with four selected missense mutations and a review of literature data suggested that early-onset cases had gain-of-function mutations, and that relatively small gains-of-function were generally associated with a favorable response to sodium channel blocking AEDs. Conversely, mutations found in late-onset forms with inadequate response to sodium channel blockers were associated with loss-of-function effects. 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 literature reports (Howell et al., 2015; Dilena et al., 2017; Flor-Hirsch et al., 2018; Ko et al., 2018b; Sanders et al., 2018).

Based on the data discussed above, *SCN2A*-related epilepsies provide a good example on how pathogenic variants in the same gene can affect the gene product function in opposite directions, with important implications for response to specific AEDs (Weber et al., 2014). A detailed review of available data on *SCN2A* mutations causing gain-of-function, loss-of-function, or mixed effects, and their relationship with clinical phenotypes and response to treatment has recently been published (Sanders et al., 2018).

2.3. SCN8A-related epilepsies

SCN8A-related epilepsies are typically associated with severe encephalopathies with seizure onset in the first 18 months of life and multiple seizure types (focal seizures, afebrile generalized tonic-clonic seizures, infantile spasms, and myoclonic and absence seizures) (Larsen et al., 2015a; Hammer et al., 2016; Gardella et al., 2018). Phenotypes can include Lennox-Gastaut syndrome, West syndrome, and several other epileptic encephalopathies (Hammer et al., 2016). Psychomotor development varies from normal prior to seizure onset (with subsequent slowing or regression after seizure onset) to delayed from birth. Patients typically develop intellectual disability, ranging from mild to severe. Movement disorders, cortical blindness, and startle and sleep problems may also be present (Larsen et al., 2015a; Hammer et al., 2016; Gardella et al., 2018).

The *SCN8A* gene encodes the voltage gated sodium channel Nav 1.6, and most epilepsy-causing variants reported seem to have an activating effect on channel activity (Wagnon et al., 2015; Barker et al., 2016; Ottolini et al., 2017; Atkin et al., 2018; Liu et al., Brain 2019). This may explain why seizures associated with *SCN8A*-related epilepsies generally respond favorably to sodium channel blocking AEDs such as phenytoin, carbamazepine, oxcarbazepine, lacosamide, lamotrigine, rufinamide, and oxcarbazepine, though response is often incomplete (for review, see Hammer et al., 2016).

Phenytoin can be particularly effective in suppressing seizures in some children with *SCN8A*-related epilepsies (Boerma et al., 2016; Braakman et al., 2017), but it can produce significant adverse effects during maintenance treatment (Braakman et al., 2017). This stimulated efforts to identify more selective treatments for these epilepsies, either by repurposing already existing medications (Atkin et al., 2018) or by developing novel chemical entities. Among the latter, the investigational drug XEN901, a potent and highly selective $Na_V1.6$ sodium channel inhibitor, is being currently developed as a precision treatment for early infantile epileptic encephalopathies associated with gain-of-function mutations in *SCN8A* (Bialer et al., 2018b). Another novel promising compound is GS458967, a sodium channel modulator which inhibits preferentially the persistent sodium current and has shown seizure protecting effects in a mouse model of *SCN8A* epileptic encephalopathy (Baker et al., 2018).

It should be noted that mutations in *SCN8A* can also cause developmental delay, intellectual disability or autism without epilepsy. As opposed to most epilepsy-causing *SCN8A* variants, these mutations have loss-of-function effects, thus potentially requiring different targeted therapeutic approaches (Liu et al., 2019).

3. Epilepsies due to mutations in potassium channel genes

Potassium channels play an important role in regulation of neuronal excitability. Not surpringly, mutations in several potassium channel genes (*KCNA2*, *KCNB1*, *KCNC1*, *KCND2*, *KCND3*, *KCNH1*, *KCNH2*, *KCNH5*, *KCNJ10*, *KCNMA1*, *KCNQ2*, *KCNQ3*, and *KCNT1*) have been associated with a variety of epilepsy phenotypes. Activation of potassium channels is expected to reduce neuronal excitability, which explains why many of these epileptogenic mutations are loss-of-function (Wei et al., 2017). Yet, as best demonstrated in the case of *KCNT1*-related epilepsies, there are examples of gain-of-function mutations also causing epilepsy, a situation that has been descrived as an 'unresolved paradox' (Niday and Tzingounis, 2018). Possible explanations for the paradox may relate to a prevailing impact of the mutation on inhibitory interneurons, or to complex interactions between potassium channels and other ion channels, though other mechanisms may also be at play (Niday and Tzingounis, 2018). In the next sections we will focus on *KCNQ2*-, *KCNQ3*- and *KCNT1*-related epilepsies, which provide examples of how identification of the genetic defect can have important implications not only for drug selection but also for the development of innovative, more effective treatments.

3.1. KCNQ2- and KCNQ3-related epilepsies

3.1.1. Benign familial neonatal epilepsy (BFNE)

Mutations in *KCNQ2* and *KCNQ3*, which encode potassium channels Kv7.2 and Kv7.3, cause BFNE, a condition characterized by onset of seizures (most typically, clusters of focal seizures with alternating laterality) in the first few days of life, associated with a normal interictal EEG, normal imaging findings and, often, a family history of seizures in the neonatal period (Weber et al., 2014; Sands et al., 2016). The terms "benign" or, more appropriately, 'self-limiting' reflect the fact that in most affected infants the seizures are limited to the first year of life and neurologic development is normal. The underlying pathogenic mechanism seems to involve loss-of-function with haploinsufficiency,

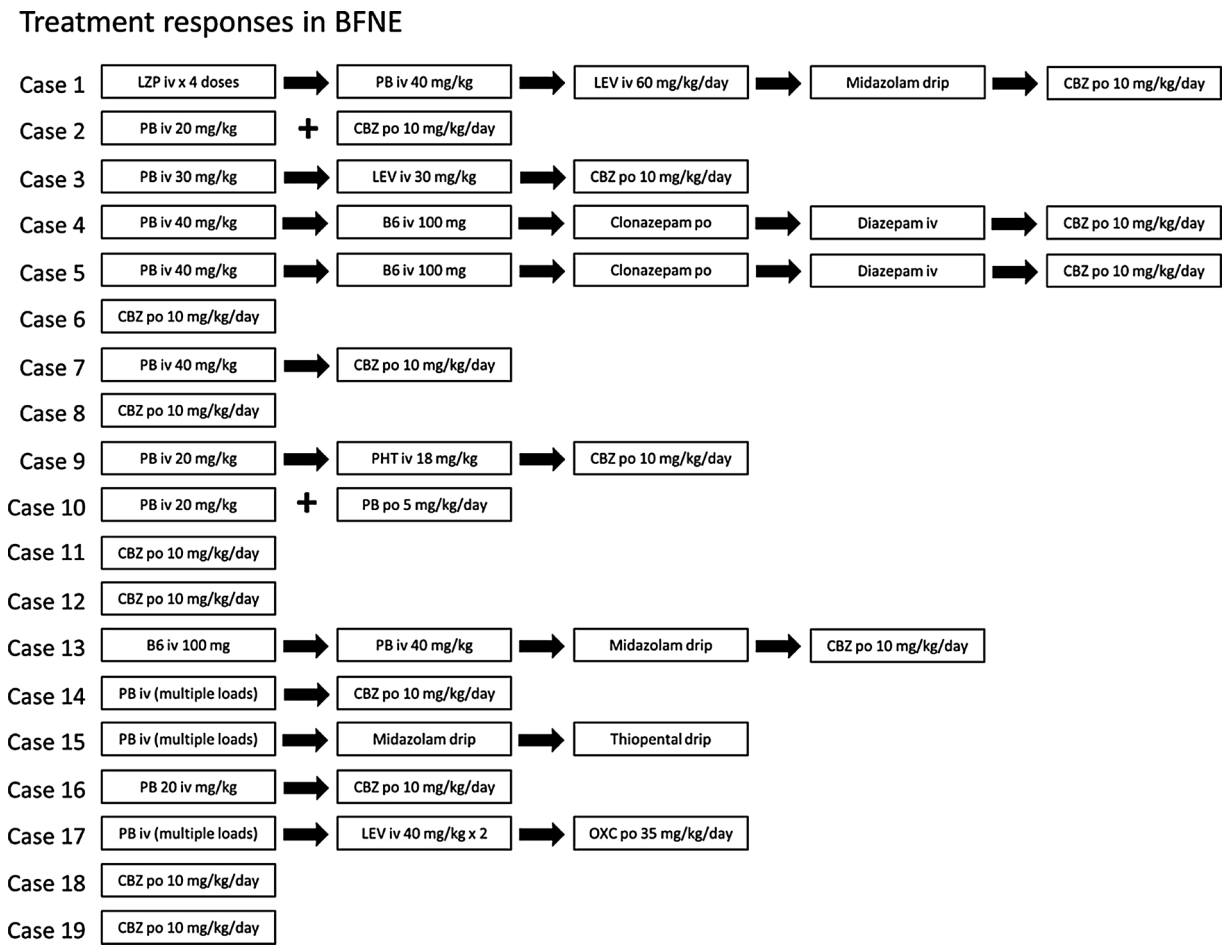

Fig. 1. Responses to antiepileptic drug therapy in 19 newborns with benign familial neonatal epilepsy. Drugs are shown in the order in which they were administered and the last treatment was associated with cessation of seizures. In case 9, seizures ceased after administration of phenytoin (PHT), but recurred with weaning and carbamazepine (CBZ) was started without further recurrence. LEV, levetiracetam; LZP, lorazepam; OXC, oxcarbazepine; PB, phenobarbital.
Reproduced from Sands et al., 2016, with permission.

resulting in subthreshold membrane depolarization and increased neuronal firing (Maljevic et al., 2010). Dysfunction of interneurons leading to potentiation of excitatory transmission has also been suggested as a causative mechanism (Soh et al., 2018).

BFNE have been traditionally treated with phenobarbital, but other AEDs may also be used (Miceli et al., 2018a). Recent reports have provided evidence that BFNE usually responds well to carbamazepine, and potentially to other sodium channel blockers (Sands et al., 2016; Vilan et al., 2017). In a recent multicenter retrospective study, 16 of 19 patients with BFNE were found to harbor mutations or deletions in *KCNQ2* and *KCNQ3* (Sands et al., 2016). Of the 14 patients with *KCNQ2*-associated BFNE, 12 responded to carbamazepine and two, in whom carbamazepine was not tried, responded to oxcarbazepine (n = 1) and phenobarbital (n = 1). Of the two patients with *KCNQ3* mutations, one responded to carbamazepine and one, in whom carbamazepine was not tried, responded to i.v. thiopental. Interestingly, 7 of the carbamazepine-responsive patients had previously failed to respond to other AEDs, including phenobarbital (Fig. 1), and a delay in implementing carbamazepine treatment was associated with more prolonged hospitalizations. Early recognition of BFNE, which can be aided by genetic testing, is essential for rapid implementation of effective therapy, and avoidance of medications like i.v. barbiturates which are not always effective and can be associated with sedation, hypotonia and feeding difficulties. Use of carbamazepine in these infants has been found to be well tolerated, with a good response being generally obtained at low doses (Sands et al., 2016).

The favorable response to the sodium channel blocker carbamazepine is intriguing because the primary genetic defect underlying BFNE affects the function of potassium channels. A possible explanation may lie in the close co-localization, and sharing of a common motif, of voltage-gated Kv.7 potassium channels and sodium channels at regions of the neuronal membrane critical for action potential generation and propagation (Pan et al., 2006; Sands et al., 2016). This could result in enhanced sensitivity of the sodium channel to carbamazepine and other sodium channel blockers. Results of structure-activity studies confirm that modulation of voltage-gated potassium channels can affect the function of closely associated sodium channels (Nguyen et al., 2012).

3.1.2. *KCNQ2 and KCNQ3 encephalopathies*

Remarkably, mutations in *KCNQ2* and *KCNQ3* can also cause severe phenotypes (Miceli et al., 2017, 2018a). Most studies have focused on *KCNQ2* encephalopathy, which like BFNE has neonatal onset but, unlike BFNE, results in cognitive decline and sometimes refractory epilepsy resembling the electroclinical phenotype of Otahara syndrome (Miceli et al., 2018a). Early brain MRI can show abnormalities (i.e. basal ganglia and thalamic hyperintensities) which later resolve. *KCNQ2* encephalopthy is usually caused by *de novo* mutagenesis (Pisano et al., 2018). A study by Orhan et al.(2014) showed that most mutations responsible for *KCNQ2* encephalopathy show a striking dominant-negative effect on wild-type Kv 7.2 or Kv 7.3 subunits.

Similarly to BNFE, seizures associated with *KCNQ2* encephalopathy may respond to carbamazepine and other sodium channel blockers (Weckhuysen et al., 2013; Numis et al., 2014; Pisano et al., 2018; Vilan

Table 1
Summary of reported findings with the use of quinidine in KCNT1-related epilepsies. Abbreviations: EIMFS, epilepsy of infancy with migrating focal seizures; EOE, early onset encephalopathy (not classified); SHE, sleep hypermotor epilepsy (formerly known as nocturnal frontal lobe epilepsy); ADSHE, autosomal dominant sleep hypermotor epilepsy (formerly known as autosomal dominant nocturnal frontal lobe epilepsy).

Reference	Diagnosis	Age quinidine started	*KCNT1* mutation	Outcome of quinidine treatment
Bearden et al., 2014	EIMFS	25 months	c.1283 G > A, p.R428Q[a]	Striking improvement in seizures, with long periods of seizure freedom. Improved cognition (quinidine levels 1.5 to 4 μg/mL)
Mikati et al., 2015	Atypical SHE	11 years	c.2386 T > C, p.Y796H[a]	No improvement in seizures (quinidine levels up to 2.4 μg/mL)
	EIMFS	3 years	c.1887 G > C, p.K629N[b]	80% reduction in seizure frequency (quinidine levels: 0.6 to 1.1 μg/mL)
Chong et al., 2016	EOE	5 years	c.1283 G > A, p.R428Q	No improvement in seizures (quinidine levels: 3 to 5 μg/mL)
Fukuoka et al., 2017	West syndrome	2.5 years	c.1955 G > T, p.G652V	60 to 80% reduction in seizure frequency and improved development (quinidine levels: 2.7-4.8 μg/mL)
Abdelnour et al., 2018	Focal seizures	13 years	c.1421 G > A, p.R474H	Worsening of seizures (quinidine levels of 1.1 to 2.6 μg/mL)
	EIMFS	3 months	c.2965 G > T, p.?	70% reduction in seizure frequency (quinidine level of 0.4 μg/mL)
	Focal seizures	9 years	c.1193 G > A, p.R398Q	Worsening of seizures (quinidine levels of 0.4 to 3.2 μg/mL)
Dilena et al., 2018	EIMFS	3 months	c.2849 G > A, p.R950Q[a]	About 90% reduction in seizure frequency, no impact on neurodevelopment (quinidine level of 2.7 μg/mL)
	EIMFS	6 months	c.2677 G > A, p.E893K[a]	About 90% reduction in seizure frequency, no impact on neurodevelopment (quinidine level of 3.5 μg/mL)
Ko et al., 2018b	EIMFS (2 cases)	Not specified	See note[†]	No seizure improvement. In one case, 'therapeutic' levels of quinidine were achieved. In the second case, quinidine was withdrawn at 'subtherapeutic' levels due to QT prolongation.
Madaan et al., 2018	EIMFS	6 months	c.808C > G, p.Q270E	No improvement in seizures at doses up to 35 mg/kg (quinidine levels not reported)
McTague et al., 2018	EIMFS	Not specified	c.820C > A, p.L274I[b]	No improvement in seizure frequency at 40 mg/kg/day (quinidine levels not reported)
	EIMFS	Not specified	c.1504 T > G, p.F502V[a]	Marked reduction in seizure frequency at 40 mg/kg/day (quinidine levels not reported)
	EIMFS	Not specified	c.2687 T > A, p.M896K[a]	Transient reduction in seizure frequency at 30/mg/kg/day (quinidine levels not reported)
Mullen et al., 2018[†]	ADSHE	17 years	See note[††]	No seizure improvement on low-dose (300 mg/day, quinidine levels < 0.15 μg/mL)
	ADSHE	15 years	See note[††]	No improvement in seizures on low-dose quinidine (300 mg/day, quinidine levels < 0.15 μg/mL)
	ADSHE	30 years	See note[††]	No improvement in seizures on low-dose quinidine (300 mg/day, quinidine levels < 0.15 μg/mL)
	ADSHE	28 years	See note[††]	No improvement in seizures on low-dose quinidine (300 mg/day, quinidine levels < 0.15 μg/mL)
Numis et al., 2018	EIMFS	5 months	c.1649-1651delAGC, p.Del550[c]	No improvement in seizures (quinidine levels up to 1 μg/mL)
	EIMFS	2.5 years	c.776C > A, p.A259D[c]	No improvement in seizures (quinidine levels up to 2 μg/mL)
	EIMFS	2 months	c.1546° > G, M516V[a]	No improvement in seizures (quinidine levels up yo 4.6 μg/mL)
	EIMFS	1.5 months	c.1283 G > A, p.R428Q[a]	No improvement in seizures (quinidine levels up to 1.3 μg/mL)

(a) responsive *in vitro* to quinidine; (b) slightly responsive *in vitro* to quinidine; (c) unresponsive *in vitro* to quinidine. Results should be interpreted cautiously because in many studies quinidine was tested at high concentrations (300 μM).

[†] There were 3 cases with EIMFS due to *KCNT1* mutations (first case with c.1421 G > A, p.R474 H; second case with c.2800 G > A, p.A934 T; third c.1038C > G, p.F346 L): the 2 cases treated with quinidine were not specified. [††]Mutations (either c.2782C > T, p.R928C or c.2849 G > A, p.R950Q) were quinidine-responsive. Two other patients given higher doses (600 or 900 mg/day) were not assessable for efficacy because cardiac toxicity led to early discontinuation.

et al., 2017), although there are patients who may respond to other AEDs. Carbamazepine and phenytoin have been recommended as first-line drugs for the treatment of seizures in neonates and infants with *KCNQ2* encephalopathy, including those presenting with status epilepticus, and most patients achieve seizure freedom on these drugs (Pisano et al., 2018). It has been suggested that early seizure control may also improve neurodevelopmental outcome (Pisano et al., 2018), even though this may not be always the case (Numis et al., 2014). In patients resistant to carbamazepine or other sodium channel blockers, the ketogenic diet has been reported to be often effective (Ko et al., 2018a).

In an elegant study, Orhan et al. (2014) found that the electrophysiological changes associated with a majority of *KCNQ2* mutations found in patients with encephalopathy are antagonized i*n vitro* by the Kv7.2 and Kv7.3 opener retigabine (ezogabine). Clinical evidence for a potential usefulness of retigabine in the treatment of *KCNQ2* encephalopaties was provided by a multicenter study in 11 patients. Improvement in seizures or development, as assessed by treating physicians and parents, was reported in 3 of the 4 patients treated with retigabine before 6 months of age, and in 2 of the 7 treated at later times (Millichap et al., 2016). Unfortunately, the retigabine preparation originally approved for the treatment of focal seizures has been withdrawn from the market. An investigational retigabine-based product (XEN496), however, is being developed specifically for KCNQ2 encephalopathy, with a Phase III clinical trial scheduled to start in mid-2019 (Xenon Pharma, 2018).

It should be emphasized that not all *KCNQ2* mutations are loss-of-function, and that there are *KCNQ2* encephalopathies caused by gain-of-function variants (Devaux et al., 2016; Millichap et al., 2017). Therefore, evaluation of the specific variant is important for treatment selection, because Kv7.2/3 activators such as retigabine could be aggravating when used in patients with gain-of-function mutations. Extensive research is ongoing to identify novel molecules endowed with different actions on potassium channels. A recent review highlighted a remarkable heterogeneity in the molecular scaffolds exploitable to develop Kv7.2/3 modulators, and predicted a 'bright future' for candidate drugs targeting in different ways the function of these channels (Miceli et al., 2018b).

3.2. *KCNT1- and KCNT2-related epilepsies*

3.2.1. *KCNT1-related epilepsies*

Autosomal dominant causative variants in *KCNT1*, which encodes the potassium channel KNa1.1, play a causative role in a wide spectrum of seizure disorders. Phenotypes encountered in individuals with *KCNT1* mutations include epilepsy of infancy with migrating focal seizures (EIMFS), severe ADSHE and, less commonly, West syndrome, Ohtahara syndrome, early myoclonic encephalopathy, leukodystrophy and/or leukoencephalopathy, focal epilepsy, and multifocal epilepsy (Lim et al., 2016; Gertler et al., 2018). All gene variants evaluated to date seem to confer a gain-of-function phenotype, irrespective of the type of associated epilepsy (Lim et al., 2016; Gertler et al., 2018; McTague et al., 2018). Seizures associated with *KCNT1*-related epilepsies are often severe and drug-resistant. Treatments often used in the management of these syndromes include stiripentol, benzodiazepines (clobazam, clonazepam and nitrazepam), levetiracetam, bromides and the ketogenic diet, but response is typically poor (Lim et al., 2016; Gertler et al., 2018; McTague et al., 2018).

The antiarrhythmic drug quinidine, a partial antagonist of KNa1.1, can attenuate *in vitro* the channel's gain-of-function associated with *KCNT1*-related epilepsies, although responsiveness to the drug in these studies seems to vary across the examined gene variants (Milligan et al., 2014; McTague et al., 2018). Interest in the use of quinidine for the treatment of these epilepsies spiked when Bearden et al. (2014) reported a marked reduction in seizure frequency together with improved cognitive development in a child with EIFMS started on the drug (Bearden et al., 2014). Subsequent reports, however, showed that response to quinidine differs markedly across patients (Table 1), and that use of the drug in these patients is often complicated by dose-limiting cardiac effects, particularly QT prolongation (Abdelnour et al., 2018; Dilena et al., 2018; Ko et al., 2018b; Madaan et al., 2018; Mullen et al., 2018). In the only controlled trial conducted to date, quinidine was administered to 6 individuals with severe *KCNT1*-related ADSHE aged 15–54 years, according to an in-patient 12-day double-blind, placebo controlled design (Mullen et al., 2018). The first two patients discontinued treatment after 2 days because of unexpected cardiac toxicity (T-wave flattening and significant QT interval prolongation) at starting doses of 800 and 600 mg/day. The remaining four patients were only tested at 300 mg/day and showed no seizure improvement, but their blood level of quinidine was very low or barely detectable.

The reason for the variable response to quinidine in *KCNT1*-related epilepsies is unclear. Possible explanations include limitations in reaching effective serum drug concentrations due to dose-limiting cardiac effects; variable responsiveness of the gene variant to the drug; interindividual differences in penetration of the drug across the blood-brain barrier, possibly due to variable expression of efflux transporters; the developmental age window in which quinidine is given; and the influence of neuronal damage resulting from prolonged exposure to severe seizures (Mikati et al., 2015). Inspection of available case reports suggests that response tends to be more favorable when quinidine is started below 4 years of age (Abdelnour et al., 2018), but a recent report failed to identify young age as a positive prognostic factor (Numis et al., 2018).

At present, there is insufficient information to make recommendations on the use of quinidine in *KCNT1*-related epilepsies, and further studies are required to evaluate its potential effectiveness and possible predictors of clinical response, including *in vitro* responsiveness of the gene variant to quinidine. Based on available evidence, there seems to be no indication for using quinidine in adolescents and adults with *KCNT1*-related ADSHE (Mullen et al., 2018). A cautious trial may be justified in infants and young children with *KCNT1*-related epilepsies unresponsive to conventional AEDs or the ketogenic diet. If the drug is used in these patients, it should be titrated cautiously under close ECG monitoring and careful clinical observation, preferably in a hospital setting.

3.2.2. *KCNT2-related epilepsies*

Mutations in *KCNT2* can also cause an early-onset epileptic encephalopathy (Gururaj et al., 2017). Ambrosino et al.(2018) recently reported two children with *de novo KCNT2* mutations, a 9-year old girl whose initial West syndrome had evolved to Lennox-Gastaut syndrome, and a 14-year-old girl with EIMFS. Both children were found to have a gain-of-function mutation which was responsive *in vitro* to quinidine. The girl with Lennox-Gastaut syndrome was treated with quinidine (33 mg/kg/day; serum level, 0.7 μg/mL) in addition to her pre-existing AED therapy, with some improvement in seizure frequency and cognition. The reduction in seizure frequency was no longer present after 3 months, but the improvement in alertness persisted. An attempt to increase the dose of quinidine dose resulted in unacceptable QT prolongation.

4. Epilepsies due to mutations in N-methyl-D-aspartate (NMDA) receptor genes

Glutamate-mediated excitatory neurotransmission is partly mediated by activation of NMDA receptors. These cation channel-receptors are made up of two GluN1 subunits (obligatory), together with auxiliary GluN2(A–D) or GluN3(A,B) subunits. Mutations of *GRIN1*, *GRIN2A*, *GRIN2B*, and *GRIN2D* genes, which encode the GluN1, GluN2A, GluN2B, and GluN2D subunits, respectively, have all been associated with epileptic phenotypes (Wei et al., 2017).

Much attention has been given to the association between *GRIN2A*

mutations and 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 (Myers and Scheffer, 2016; Reif et al., 2017). These phenotypes often result from gain-of-function mutations, though some *GRIN2A* mutations appear to prevent expression of a functional protein. While the epileptogenic effect of gain-of-function mutations can be explained in terms of excessive NMDA-mediated excitation, the pathogenic mechanisms of destructive mutations are unclear. It has been suggested that destructive mutations can result in substitution of the unexpressed GluN2A subunit with other, functionally different subunits (Wei et al., 2017), but this hypothesis does not appear to be supported by recently published findings (Strehlow et al., 2019).

In an elegant study, Pierson et al. (2014) described a *de novo* gain-of-function *GRIN2A* missense mutation in a 9-year old boy with severe early-onset epileptic encephalopathy. The NMDA receptors associated with the boy's variant and with a previously reported gain-of-function mutation were expressed in *Xenopus laevis* oocytes, and their sensitivity to marketed drugs possessing NMDA-receptor activity (memantine, dextromethorphan and amantadine) was assessed. Interestingly, the two variants assessed had different effects on the receptor's sensitivity to the tested drugs. The NMDA receptors encoded by the boy's mutated gene retained their sensitivity to memantine, and memantine was subsequently tried in this patient resulting in a marked reduction in seizure frequency. Felbamate also has some NMDA-blocking activity (De Sarro et al., 1994), but its potency at NMDA receptors associated with different gain-of-function *GRIN2A* variants does not appear to have been evaluated (Reif et al., 2017). Novel NMDA receptor blockers selective for receptors containing the Glu2A subunit are being developed (Volkmann et al., 2016).While there seems to be a rationale for testing NMDA receptor antagonists in patients with gain-of-function variants encoding receptors with retained or enhanced sensitivity to these drugs, a benefit from the use of these agents is considered to be unlikely in patients carrying variants leading to complete or partial loss of channel function (Strehlow et al., 2019). Strehlow et al.(2019) suggested that the latter patients might respond to positive allosteric modulators of the NMDA receptors (Zhu and Paoletti, 2015; Addis et al., 2017).

Interestingly, memantine has also been tried in two unrelated children with epileptic encephalopathy caused by a gain-of-function *GRIN2D* mutation (Li et al., 2016). In prior experiments, the mutated receptor had been found to retain some sensitivity *in vitro* to NMDA-receptor antagonists, including memantine itself, ketamine and magnesium. Introduction of memantime was associated with a reduction in seizure frequency in a 2.5-year-old girl, whereas a 6.5-year-old-boy showed little or no seizure improvement. Both children had reportedly some developmental improvements. Several months after discontinuing memantine, the older child developed subclinical status epilepticus refractory to midazolam- and pentobarbital-induced coma, but responsive to ketamine and magnesium. It was suggested that the incomplete or poor response to memantime was related to its 10-fold lower *in vitro* potency on the mutant receptor compared with the wild-type receptor, whereas for ketamine and magnesium the difference in sensitivity between the mutated and the wild type receptor was much less.

In a more recent study, Platzer et al.(2017) reported on 4 patients with *GRIN2B*-related encephalopathy due to putative gain-of-function mutations, who were also treated with memantine. There were parental reports of improved awareness and behaviour and sleep, but none of the patients showed a reduction in seizure frequency despite the fact that in two of them *in vitro* responsiveness of the receptor to memantine was actually increased compared with the wild-type receptor. The authors' conclusion that "options for personalised therapy in *GRIN2B* encephalopathy still require more systematic and thorough evidence best through double-blinded prospective trials" is also applicable to other *GRIN*-related epilepsies.

5. Epilepsies related to mTOR pathway mutations

The mechanistic target of rapamycin (mTOR) signalling pathway is involved in the modulation of many functions, including lipid and protein synthesis, cell growth and survival, cell motility and cell proliferation. It plays a key role in brain development, and its hyperexpression can lead to epileptogenic malformations of cortical development, such as tuberous sclerosis complex (TSC), focal cortical dysplasias, and hemimegalencephaly. The molecular genetics of these disorders have been reviewed, and may involve mutations in *MTOR*, *AKT3*, *PIK3CA*, *TSC1*, *TSC2* and *PTEN* genes, as well as in the GATOR1 (GAP Activity Toward Rags complex 1) complex genes *DEPDC5*, *NPRL2* and *NPRL3* (Marsan and Baulac, 2018; Baldassari et al., 2019). Understanding the mTOR-related pathophysiology of these disorders is relevant for the development of potential new treatments, and for TSC-associated seizures etiology-driven treatments are already a reality.

5.1. Seizures associated with TSC

TSC is an autosomal dominant genetic neurocutaneous disorder, which occurs with an incidence of 1 in 5800 livebirths (Osborne et al., 1991). It is caused by inactivating pathogenic variants in either the *TSC1* or the *TSC2* gene, resulting in hyperactivation of the mTOR pathway (Randle, 2017). Elucidation of the mechanism underlying TSC provided the rationale for testing mTOR inibitors as potential treatment, first in animal models and subsequently in patients (Schubert-Bast et al., 2018). Ultimately, these studies led to the regulatory approval of mTOR inhibitors for the management of TSC-associated giant cell astrocytoma, angiomyolipoma, lymphangioleiomyomatosis, and focal seizures (Franz and Krueger, 2018). In the controlled trial that demonstrated the efficacy of everolimus as add-on treatment for focal seizures associated with TSC, reductions in seizure frequency during treatment became progressively greater over time, suggesting that the compound might also have a disease-modifying effect (French et al., 2016). Whether early treatment with everolimus can prevent the development of epilepsy, and whether this compound (or related agents with improved brain penetration) can be of benefit in epilepsies related to other neurological disorders resulting from dysregulation of the mTOR pathway ('mTORopathies') remains to be established in well controlled trials.

Vigabatrin, which is considered to be most effective AED in controlling infantile spasms associated with TSC, has been recently reported to partially inhibit the mTOR pathway and glial proliferation in a knock-out mouse model of TSC, and to also inhibit mTOR pathway activation in cultured astrocytes from both knock-out and control mice (Zhang et al. (2013)). These findings are intriguing, particularly because the efficacy of vigabatrin in these patients was discovered well before elucidation of the pathogenic role of mTOR activation. Equally intriguing, preliminary findings suggest that vigabatrin might also prevent the development epilepsy if administered before seizure onset in infants with TSC (Jóźwiak et al., 2011). A randomized trial to investigate the potentially antiepileptogenic effects of vigabatrin in TSC is currently ongoing as part of the EU-funded EPISTOP collaboration (Schubert-Bast et al., 2018).

6. Epilepsies due to inborn errors of metabolism

Mutations affecting genes that control the intermediary metabolism of carbohydrates, lipids, amino acids, vitamins, and energy metabolism, result in a many rare syndromes associated with early-onset seizure disorders. Prompt identification of the underlying cause is important, because the clinical manifestations, including long-term outcome, can be managed succesfully with precision treatments. A detailed review of the pathophysiological, diagnostics and therapeutic aspects of these

epilepsies can be found in a recent review (Campistol and Plecko, 2015), and only two examples are discussed below.

6.1. Glucose transporter 1 (GLUT1) deficiency syndrome

Epilepsies associated with GLUT1 deficiency syndrome, a condition occurring with an extimated incidence of 1 in 83,000 livebirths (Larsen et al., 2015b), represent a prime example of how identifying the genetic etiology is essential for selection of an effective treatment. GLUT1 deficiency syndromes encompass several phenotypes, and their heterogeneous manifestations can delay its recognition (De Giorgis and Veggiotti, 2013). The classical syndrome consists in an early-onset encephalopathy with typically drug-resistant infantile seizures, developmental delay, microcephaly and a complex movement disorder consisting of ataxia and dystonia. Other phenotypes include paroxysmal exercise-induced dyskinesia, episodic choreoathetosis and spasticity, early-onset absence epilepsy, childhood absence epilepsy, myoclonic astatic epilepsy, and focal epilepsy (Koch and Weber, 2019).

The manifestations of GLUT1 deficiency are caused by mutations of the solute carrier family 2 (facilitated glucose transporter) member 1 (*SLC2A1*) gene, which encodes the transporter responsible for transferring glucose across the blood-brain barrier (Seidner et al., 1998). The resulting defect impairs the availability of glucose to the brain, and the resulting shortage of the primary energy supply in the CNS leads to neuronal dysfunction. The manifestations of the disease can be prevented or controlled by providing the brain with an alternative source of energy, such as ketone bodies, whose access to the brain is not dependent on a functional GLUT1 (Klepper et al. (2005)). While mild forms of GLUT1 deficiency syndrome can respond favorably to conventional AEDs, severe GLUT1-related epilepsies require use of the ketogenic diet to achieve an adequate therapeutic effect (Koch and Weber, 2019). In fact, the diet should be regarded as the first-line treatment for these patients.

6.2. Pyridoxine and pyridoxal-5′-phosphate-dependent epilepsies

Pyridoxine-dependent epilepsy is a rare autosomal recessive disorder which occurs at an estimated incidence of 1 in 20,000 to 1 in 700,000 livebirths (Baxter, 1999; Ebinger et al., 1999). It is associated with a highly variable phenotypic spectrum, one hallmark of which is the appearance of AED-refractory neonatal- or early infantile-onset seizures responsive to high doses of pyridoxine (vitamin B6)(Van Karnebeek et al., 2016). Prognosis for seizure control is generally favorable, but some degree of developmental delay often persists even in patients receiving early treatment. Pyridoxine-dependent epilepsy is caused by a mutation in the *ALDH7A1* gene, which encodes alpha-aminoadipic semialdehyde dehydrogenase (antiquitin), a critical enzyme in the lysine degradation pathway. The enzyme defect leads to chemical inactivation of pyridoxal phosphate and, consequently, to a wide range of metabolic and functional abnormalities.

Early recognition of pyridoxine-dependent epilepsy is important because timely implementation of pyridoxine treatment impacts positively on seizures and, in some cases, on neurodevelopment (Van Karnebeek et al., 2012). Recognizing that the condition is probably underdiagnosed, many centres include pyridoxine as part of their treatment protocol for neonatal seizures (Mei et al., 2017). There have been reports of some of these epilepsies also benefiting from a trial of folinic acid, and the suggestion has been made that in neonates with seizures and an incomplete response to pyridoxine, add-on administration of folinic acid should be considered (Campistol and Plecko, 2015). Patients with pyridoxine-dependent epilepsy generally require lifelong pyridoxine therapy. Additional treatments that have been suggested, particularly to improve cognitive outcomes, include lysine-restricted diets and high-dose arginine supplementation (Van Karnebeek et al., 2012; Campistol and Plecko, 2015).

Pyridox(am)ine 5′-phosphate oxidase (PNPO) deficiency is an autosomal recessive disorder caused by mutations in the *PNPO* gene, and is typically associated with a neonatal- or infantile-onset epileptic encephalopathy treatable with pyridoxal- 5′-phosphate or, in some cases, with pyridoxine (Plecko, 2013; Mills et al., 2014; Plecko et al., 2014). Failure to recognize and treat this condition effectively can result in death or severe developmental impairment, but outcome is considerably improved when early treatment is implemented (Campistol and Plecko, 2015). Similarly to pyridoxine, the first administration of pyridoxal- 5′-phosphate can result in severe apnoea, and therefore resuscitation equipment should be at hand.

6.3. Neuronal ceroid lipofuscinosis type 2 (CLN2)

Neuronal ceroid lipofuscinosis type 2 (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 CNS neurons and in the retina. Clinical manifestations typically appear in the late infantile period (2–4 yeas of age) and consist in delayed language acquisition, seizures, rapid cognitive motor decline, blindness, and early death (Williams et al., 2017). Discovery of the genetic defect underlying CLN2 disease led to the development of cerliponase alfa, a recombinant proenzyme of human tripeptidyl peptidase 1, as an enzyme replacement therapy. Cerliponase alfa was initially tested by intrathecal administration in young dogs homozygous for TPP1 deficiency, and found to be effective in preventing the progression of the disease (Katz et al., 2014). Based on these findings, the compound was given by intraventricular infusion every 2 weeks in 23 children with CLN2 disease aged 3–16 years, and found to be associated with a slower rate of decline in motor and language function compared with historical controls (Schulz et al. (2018)). In the latter trial, cerliponase alfa-treated children had relatively stable scores on the CLN2 Rating Scale, which combine scores for all four CLN2 domains (motor, language, vision, and seizure domains), whereas historical controls showed progressive deterioration on this measure. Although the four-domain score includes a seizure domain, specific data on the effect of treatment on seizures were not reported. The trial has led to regulatory approval of cerliponase alfa in the U.S. and Europe for the treatment of motor function loss associated with CLN2 disease (Markham, 2017).

7. Conclusions and future perspectives

As discussed above, an increasing body of evidence indicates that identifying the pathogenic variant in individual patients with genetic epilepsies is relevant not only for diagnosis and prognosis, but also for treatment selection (Mei et al., 2017; Reif et al., 2017). This finding is not surprising, because responses to specific treatments can vary depending on the disease's underlying mechanisms which, in turn, may differ even across individuals sharing the same phenotype (McTague et al., 2016). In fact, reports are now starting to emerge that results of genetic testing do impact on clinical management, with beneficial effects of improved seizure control and reduced health care costs (Perucca et al., 2017; Peng et al., 2019).

Admittedly, evidence on the value of gene defects as predictors of response to specific treatments is still limited, and only a relatively small number of pathogenic mutations involve genes 'actionable' with current therapeutic tools. Moreover, most of the available information on genotype-response relationships originates from retrospective studies that evaluated treatment responses in patients with specific syndromes or specific gene defects (Müller et al., 2016; Pisano et al., 2018; Lim et al., 2017; Gardella et al., 2018; Ko et al., 2018a). In some instances, as in the case of sodium channel blocker-induced seizure aggravation in patients with Dravet syndrome, correlations with treatment effects were discovered even before the genetic cause of the disease was identified (Guerrini et al., 1998). Limitations of most

studies conducted to date include potential bias due to retrospective assessment, and failure to analyse data in relation to specific variants that can affect in different ways the function of the mutated gene. These confounders may contribute to some of the conflicting nature of some findings. For example, in two recent retrospective studies of patients with *CDKL5*-related epilepsy, the ketogenic diet was reported to be either completely ineffective (Ko et al., 2018a) or to produce favorable antiseizure effects in more than half of the patients, at least in the short term (Lim et al., 2017). In the future, genotype-treatment response correlations should be preferentially evaluated in prospective studies in patients carefully characterized with respect to phenotype as well as type of pathogenic variants. These studies should incorporate available information on the functional consequences of the specific gene variants (e.g., gain-of-function versus loss-of function) and, whenever possible, their sensitivity to the tested treatment in *in vitro* or *in vivo* models. Development of reliable algorithms to predict treatment responses may require not only information on mutations and the patient's phenotype, but also other variables such as modifier gene profiles, concomitant medications, and comorbidities. Prospective registries organised within networks of centres of excellence such as the European EpiCARE (https://www.epilepsyallianceeurope.org/programmes/epicare/) could provide an ideal setting for these studies.

With advances in our understanding of the molecular mechanisms leading to the development of epilepsy and its comorbidities, patients' management is going to be increasingly influenced by application of truly personalised therapies. Rather than relying on empyrical observations relating genotypes to response to specific drugs, future prevailing paradigms will involve starting with the characterization of the functional consequences of the pathogenic gene variant, and searching thereafter for available treatments that could correct the specific dysfunction responsible for the manifestations of the disease in the individual patient. If no available treatment is identified, then new treatments may be designed and developed to address the pathogenic defect or the resulting functional abnormalities (Franco and Perucca, 2015; McTague et al., 2016; Delanty and Cavalleri, 2017). It should be noted, however, that applying or developing these precision-based approaches is not without hurdles. Results obtained so far suggest that it may be unrealistic to expect complete reversal of the constellation of manifestations defining each genetic disease, particularly when these therapies are not started early in life. Furthermore, developing new treatments for these rare to very rare diseases is financially challenging, and suitable economic models need to be developed to ensure not only reasonable returns from investments, but also broad access to these therapies at costs affordable by health insurance systems and individuals.

The search for potentially useful personalized medications already available in the market can utilise different approaches. One consists in interrogating chemical/drug libraries or databases such as the Library of Integrated Network-based Cellular Signatures (LINCS). For example, a recent study used published data and software to characterize the transcriptomic signature of chronic temporal lobe epilepsy, and to search for prescribable drugs with the potential to reverse it (Mirza et al., 2017). This result in identification of 36 potentially useful compounds, including 11 medications for which there is already evidence for an antiepileptic efficacy in animal models or in humans. In a publicly accessible database listing 173 prescribable non-epilepsy drugs with published evidence of antiepileptic efficacy in animal models, medications that target proteins of known causal human epilepsy genes are highly overpresented, an observation that reinforces the potential of drug repurposing as a source of personalized therapies for genetic epilepsies (Sivapalarajah et al., 2018). If database searches do not yield attractive candidates for repurposing, already available drugs with potentially useful activities can be identified through high throughput screening models. This approach was used in a recent study where a specific gain-of-function mutation in a girl with *SCN8A*-related epileptic encephalopathy was introduced in a HEK293 cell line suitable for high throughput screening (Atkin et al., 2018). The cells bearing the girl's mutation were used to screen 1320 small molecules, resulting in identification of 90 already marketed compounds which reversed the functional defect, including 4 lead drug candidates (amitriptyline, carvedilol, nilvadipine and carbamazepine). It should be emphasised that identification of attractive candidate compounds through database searches or high throughput screening is only a first step in developing a personalized therapy. Further preclinical experiments including, whenever appropriate, rodent models reproducing the genetic defect of interest, are generally required to assess in greater detail the therapeutic potential of candidate treatment(s). Clinical safety and pharmacokinetic data may also be needed, particularly when the compound is not approved for use in the population of interest, such as young children. Ultimately, formal efficacy testing will have to be conducted under carefully controlled clinical conditions. It should be understood that, despite promising results in *in vitro* and *in vivo* models, the expected clinical outcome may not necessarily materialize, and unpredictable toxicity could also emerge (Mullen et al., 2018). The conflicting results with the use of quinidine in *KNCT1*-related epilepsy provide a good example of the difficulties in trying to extrapolate preclinical data to the clinical setting, and of the need for caution in interpreting anecdotal case reports.

The alternative to drug repurposing consists in developing totally novel treatments, which can be designed once the mechanisms of the disease have been sufficiently characterized. The development of effective therapies for genetic CNS disorders is facilitated by advances in gene therapies, sense and antisense oligonucleotides, and other innovative therapeutics (McTague et al., 2016; Tiwari et al., 2018; Wykes and Lignani, 2018). Applied research in this area also benefits from improved understanding of structure-activity relationships, and from access to 3D structural information on thousands of protein molecules through the Protein Data Bank (Westbrook and Burley (2019)). The availability of animal models which reproduce the targeted genetic defect is highly valuable to streamline preclinical development (Fuchs et al., 2018; Richards et al., 2018). Several examples of novel treatments being developed as potential precision therapies for monogenic epilepsies have been mentioned in this article. Of course, development of novel therapies tend to be more costly than developing a drug through repurposing, but expedite review and approval pathways and other incentives exist for treatments targeting orphan indications, particularly when they are associated with prominent clinical benefit (Kesselheim et al., 2015).

Conflicts of interest

EP received speaker's or consultancy fees from Axovant, Biogen, Eisai, GW Pharma, Sanofi, Takeda, UCB Pharma and Xenon Pharma. PP has received honoraria from Eisai.

Author contributions

Both authors contributed equally to this work.

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