Treatment of epileptic encephalopathies

Simona Balestrini, MD,[a,b] Sanjay M Sisodiya, PhD, FRCP.[a]

[a]NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, and Epilepsy Society, Chalfont-St-Peter, Bucks, United Kingdom;

[b]Neuroscience Department, Polytechnic University of Marche, Ancona, Italy.

Corresponding author:

Simona Balestrini

Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

+44 20 3448 8612 (telephone) +44 20 3448 8615 (fax)

s.balestrini@ucl.ac.uk

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Abstract

Background. Epileptic encephalopathies represent the most severe epilepsies, with onset in infancy and childhood and seizures continuing in adulthood in most cases. New genetic causes are being identified at a rapid rate. Treatment is challenging and the overall outcome remains poor. Available targeted treatments, based on the precision medicine approach, are currently few.

Objective. To provide an overview of the treatment of epileptic encephalopathies with known genetic determinants, including established treatment, anecdotal reports of specific treatment, and potential tailored precision medicine strategies.

Method. Genes known to be associated to epileptic encephalopathy were selected. Genes where the association was uncertain or with no reports of details on treatment, were not included. Although some of the genes included are associated with multiple epilepsy phenotypes or other organ involvement, we have mainly focused on the epileptic encephalopathies and their antiepileptic treatments.

Results. Most epileptic encephalopathies show genotypic and phenotypic heterogeneity. The treatment of seizures is difficult in most cases. The available evidence may provide some guidance for treatment: for example, ACTH seems to be effective in controlling infantile spams in a number of genetic epileptic encephalopathies. There are potentially effective tailored precision medicine strategies available for some of the encephalopathies, and therapies with currently unexplained effectiveness in others.

Conclusions. Understanding the effect of the mutation is crucial for targeted treatment. There is a broad range of disease mechanisms underlying epileptic encephalopathies, and this makes the application of targeted treatments challenging. However, there is evidence that tailored treatment could significantly improve epilepsy treatment and prognosis.

Introduction

Severe epilepsies starting in infancy and childhood represent a significant proportion of intractable epilepsies characterised by frequent epileptic seizures and developmental delay, arrest, or regression. Co-morbidities are common, and include autism spectrum disorder, and behavioural and movement disorders. The overall outcome, including epilepsy, co-morbidities and quality of life, is often poor. These conditions, in which the epileptiform abnormalities are thought to significantly contribute to the overall functional brain disturbance, are referred to as epileptic encephalopathies [1,2]. However, in most patients with severe epilepsy and in most genetic epilepsies, distinguishing between the contributions of the epilepsy activity (including seizures and interictal epileptiform activity) and of the underlying disease is difficult [3]. Nevertheless the term 'epileptic encephalopathies' is widely accepted by the epilepsy community and encompasses a broad range of clinical syndromes characterized by severe phenotypes. Whilst these conditions start in infancy and childhood, it is important to note that many affected individuals live on into adulthood, in which age group the concept of 'epileptic encephalopathy' is generally less well recognised. The longer term outcomes for seizure control are not well documented, and most available data come from studies in children, upon which we largely rely.

A prospective population-based study estimated an ascertainment-adjusted incidence of epilepsy of 70.1 (95% CI [56.3, 88.5])/100,000 children less than two years of age/year (with 76% completeness of ascertainment). Epileptic encephalopathy was the electroclinical syndrome in 22 of 57 infants (39%), but the overall incidence of epileptic encephalopathies was probably underestimated because many disorders in children were not classifiable despite poor seizure outcomes and developmental impairment [4]. There are no data available in adults.

Epileptic encephalopathies comprise many age-related epilepsy syndromes characterised by specific seizure types, EEG, and neurological features, sometimes with additional extra-neurological aspects. The era of genome-wide screening technologies has allowed the identification of more and more genes which when mutated cause epileptic encephalopathies, leading to delineation of more or less distinctive electroclinical features and comorbidities for specific genetic encephalopathies. However, there remains a significant degree of genetic and phenotypic pleiotropy. Furthermore, although a number of recent studies have identified additional epileptic encephalopathy genes in large cohorts through whole exome or targeted sequencing [5-10], currently a genetic diagnosis in the clinic can be made in ~10-15% of tested patients [11].

The treatment of epileptic encephalopathies is often challenging as epilepsy is severe and drug-resistant in most cases. Various combinations of antiepileptic drugs and vitamin supplements are often used. Alternative methods of treatment, such as vagal nerve stimulator therapy and the ketogenic diet, offer relief in a number of patients. Surgical treatments, including corpus callosotomy, multiple sub-pial transections, hemispherectomy, or focal epilepsy surgery, could be considered in selected patients. Balancing effectiveness and tolerability is not always easy [12].

'Precision medicine' is an approach for disease treatment and prevention for each person based on individual variability in genes, environment, and lifestyle [13]. This approach, incorporating the identification of an underlying genetic aetiology to promote personalised therapeutic choice, or to drive re-purposing of drugs, builds upon thoughtful clinical practice that has been applied for years. The 'precision medicine' paradigm has been implemented with discovery of a genetic aetiology in more and more epilepsy cases, and with the wider availability of the necessary genetic technologies [14-16]. In epilepsy, if a specific gene mutation causes a functional alteration of physiological systems involved in the control of brain excitability, a rational treatment strategy might ideally aim to reverse or circumvent the dysfunction. The current targeted treatment approach in precision medicine requires the identification of the underlying causative genetic alteration, determination of the functional alteration of the physiological system caused by the genetic mutation, and evaluation of the effect of treatment putatively intended and able to reverse or inhibit the functional alteration. The aim of targeted treatment is to improve not only seizure control, but also developmental outcome and associated co-morbidities, by directly addressing the mechanisms that produce the widespread effects of the disorder, which might be more extensive than epilepsy and cognitive dysfunction alone. However, genetic and phenotypic heterogeneity often limit or complicate the targeted approach, which may in fact not always prove successful. This might be due to a number of reasons, including the fact that no causal variant acts in isolation, but does so in the context of the rest of the genome and its variation; the fact that finding the genetic aetiology does not necessarily imply that appropriate targeted treatment is available; and because of compensatory and adaptive changes that may become difficult to reverse with treatment of the perceived original defect. Currently, drug therapies targeted to the underlying genetic cause are available for only a minority of genetic epilepsies[17,18]. For the remaining patients, treatment options are based on symptomatic strategies (e.g., antiepileptic drugs), which in general are not believed to address the underlying systemic functional alteration caused by the genetic mutation. Appropriate treatment strategies are required for children but also adults, as epileptic encephalopathies are increasingly recognised in adulthood, and many children with epileptic encephalopathies survive to adulthood.

Here we present an overview of the treatment of epileptic encephalopathies with known genetic determinants, including established treatment, anecdotal reports of specific treatment, and potential tailored precision medicine strategies. Genes were selected through a systematic review of those reported in the recent review by McTague et al. [2]; present in the 104 Epilepsy Gene Panel of the Glasgow Epilepsy service (http://www.nhsggc.org.uk/media/239338/epilepsy-service-proforma-pre-18-revision-2-june-2016.pdf); or other genes known to be associated to epileptic encephalopathy. Genes where the association was uncertain, or with no report of details on treatment, were not included. We searched the PubMed database using a combination of terms, including each selected gene and "epilepsy" or "epileptic encephalopathy". We limited search to papers written in English. We imposed no limitations on publication date. In many papers, response to treatment was described in qualitative terms, which we report without any interpolation. Although some of the genes included in this review are associated with multiple epilepsy phenotypes or other organ involvement, we have mainly focused on the epileptic encephalopathies and the related antiepileptic treatment. It must be appreciated that almost all reports are anecdotal: formal treatment trials for most epileptic encephalopathies will need novel design.

AARS-related epileptic encephalopathy

The *AARS* gene encodes alanyl-tRNA synthetase which catalyzes the amino-acylation of tRNA$^{\text{Ala}}$ with alanine in a reaction dependent on ATP. Two siblings and an unrelated child were recently reported, with a similar severe neurologic disorder characterized by congenital microcephaly and vertical talus, failure to thrive in infancy, spasticity, and refractory myoclonic epilepsy with onset between 3 and 6 months. Additional clinical features included blepharospasm, orobuccal dyskinesia, dystonia, chorea, and loss of peripheral deep tendon reflexes, consistent with a peripheral neuropathy. Their brain MRI showed progressive diffuse cerebral atrophy and hypomyelination. This form of early infantile epileptic encephalopathy was associated with compound heterozygous (in the two siblings) or homozygous (in the unrelated child) missense mutations in the *AARS* gene. In vitro studies showed that the two identified mutations resulted in a significant reduction of AARS function. All three cases had ongoing myoclonic and tonic-clonic seizures, despite multiple antiepileptic drugs, including levetiracetam, lamotrigine, topiramate, oxcarbazepine, phenobarbital, lacosamide, clonazepam, and zonisamide [19].

ADSL-related epileptic encephalopathy

Adenylosuccinase (ADSL) is an enzyme involved in two pathways of purine nucleotide metabolism [20]. ADSL deficiency is an autosomal recessive inborn error of metabolism caused by an enzymatic defect in de novo purine synthesis pathway, leading to the accumulation of toxic intermediates, including succinyladenosine (S-Ado) and succinylaminoimidazole carboxamide riboside (SAICAr) in body fluids. There are three major phenotypic forms of the disorder that correlate with different values of the S-Ado/SAICAr concentration ratios in the cerebrospinal fluid [21]. Clinical features include refractory seizures with variable degrees of hypotonia, global developmental delay, autistic traits and progressive brain atrophy [22]. The severity of the clinical symptoms tends to correlate inversely with residual enzyme activity. The wide diversity of clinical presentations of ADSL deficiency renders systematic screening for the defect mandatory in all patients presenting with unexplained intractable neonatal convulsions, severe infantile epilepsy, marked or mild psychomotor retardation, hypotonia, microcephaly, autistic features, and neurological disease without clear etiology. Diagnosis is based on the presence in urine and cerebrospinal fluid of the succinyl purines, S-Ado and SAICA-riboside, both normally nearly undetectable. Treatment with oral supplements of adenine and allopurinol or D-ribose and uridine have not been associated with significant clinical or biochemical improvement, except for some acceleration of growth [23,24]. The prognosis is variable, depending on the severity of the phenotype [24].

ALDH7A1-related epileptic encephalopathy

The *ALDH7A1* gene encodes antiquitin, an aldehyde dehydrogenase in the pipecolic acid pathway of lysine catabolism [25]. Pyridoxine (vitamin B6)-dependent epilepsy is caused by bi-allelic mutations in the *ALDH7A1* gene. Deficiency of antiquitin causes seizures because

accumulating Δ1-piperideine-6-carboxylate (P6C) condenses with pyridoxal 5'-phosphate (PLP) and inactivates this enzyme cofactor, which is essential for normal metabolism of neurotransmitters. Pyridoxine-dependent epilepsy is characterized by a combination of various seizure types, usually occurs in the first hours of life and is resistant to standard anticonvulsants, responding only to administration of pyridoxine hydrochloride. The dependence is permanent, and the interruption of daily pyridoxine supplementation leads to the recurrence of seizures. *ALDH7A1* mutation analysis could also be used for prenatal diagnosis of pyridoxine-dependent epilepsy. Seizures are often fully controlled by treatment with pyridoxine [25].

ALG13-related epileptic encephalopathy

ALG13 is located on the X-chromosome and encodes the protein ALG13 which forms the UDP-GlcNAc transferase with ALG14 and catalyzes a key step in endoplasmic reticulum N-linked glycosylation [26]. Seven cases of early infantile epileptic encephalopathy with intractable epilepsy, including West syndrome and Lennox-Gastaut syndrome, due to *ALG13* mutations, are reported in the literature [5,27-31]. Some evidence of control of infantile spasms is reported with adrenocorticotropic hormone (ACTH) and/or topiramate treatment [5,28,31] and ketogenic diet improved seizure control in one case [29].

ARHGEF9-related epileptic encephalopathy

The *ARHGEF9* gene encodes collybistin, a brain-specific guanine nucleotide exchange factor (GEF), belonging to a family of Rho-like GTPases that act as molecular switches by cycling from the active GTP-bound state to the inactive GDP-bound state. Collybistin has a pivotal role in the formation of postsynaptic glycine and inhibitory gamma-aminobutyric acid receptor clusters [32]. A patient with hyperekplexia and early infantile epileptic encephalopathy was found to have an *ARHGEF9* missense mutation [33]. Lesca et al.[34] described a *de novo* Xq11.11 microdeletion including *ARHGEF9* in a patient with severe mental retardation, focal epilepsy, tall stature, macrocephaly, and dysmorphism; treatment with oxcarbazepine and levetiracetam led to a complete cessation of seizures. Shimojima et al. [32] identified a loss-of-function mutation in the *ARHGEF9* gene in a patient with early-onset epileptic encephalopathy and right frontal polymicrogyria; epilepsy was reported as drug-resistant.

ARX-related epileptic encephalopathy

The aristaless-related homeobox gene *ARX* is a developmentally-regulated homeobox transcription factor, located in the human chromosome Xp22 region. It is expressed in the developing hypothalamus, thalamus, basal ganglia and cerebral cortex, modulates development of interneurons in the fetal brain, and regulates ventricular zone proliferation [35]. *ARX* comprises five exons encoding a protein of 562 aminoacids, including a paired-class homeodomain and four repeats of 7–16 alanine residues called "polyalanine tracts" [36]. In healthy individuals, the maximum length of alanine repeats is twenty [37]. Mutation of the second polyalanine tract with expansion by eight more alanine residues, which is the

most common mutation in *ARX,* results in different phenotypes, including West syndrome or infantile spasms in males [38,39]. An expansion of seven alanine residues in the first polyalanine tract causes West syndrome that is more severe than that caused by the second polyalanine tract expansion mutation [38,40,41]: for example, Guerrini et al.[41] described an infantile epileptic-dyskinetic encephalopathy, with recurrent life-threatening status dystonicus associated with mutation in the first polyalanine tract. An expansion of eleven alanine residues in the first polyalanine tract was associated with Early Infantile Epileptic Encephalopathy with Suppression-Burst Pattern (Ohtahara Syndrome) [42]. Correlation between the length of the repeat and the severity of the clinical phenotype has emerged. Other *ARX* variants have been more recently reported with severe forms of early-onset epileptic encephalopathies in males [43-45]. The same phenotype has been also described in females, probably due to skewing of X-chromosome inactivation leading to *ARX* haploinsufficiency [46,47]. There is no evidence for specific treatment, with severe drug-resistant epilepsy reported in all cases with epilepsy encephalopathy.

BRAT1-related epileptic encephalopathy

The *BRAT1* gene encodes a protein that interacts with the tumor suppressor gene *BRCA1* at its C terminus and binds to *ATM1*, considered a master controller of the cell-cycle signaling pathways required for cellular responses to DNA damage. *BRAT1* may also be involved in cell growth and apoptosis [48]. *BRAT1* mutations have been associated with particularly severe, rapidly progressive, intractable epileptic encephalopathy (including Ohtahara syndrome) with age of presentation at birth or shortly thereafter; this phenotype is known as rigidity and multifocal seizure syndrome, lethal-neonatal (RMFSL), and has autosomal recessive inheritance [48-52]. More recently, milder phenotypes have emerged, with later-onset epilepsy and survival past infancy [53-55]. In most reported cases, epilepsy was refractory to antiepileptic drug treatment or high-dose pyridoxine. In two cases with Ohtahara syndrome, zonisamide was effective for tonic-clonic seizures and apneic episodes, but did not help control myoclonic seizures; in one of these cases, phenytoin seemed to worsen seizure control [51]. In cases with the milder phenotype, clinical and EEG improvement is described with levetiracetam [55] or valproate treatment [53]; however, in one case seizures worsened with levetiracetam treatment [53].

CACNA1A-related epileptic encephalopathy

The *CACNA1A* gene encodes the transmembrane pore-forming alpha-1A subunit of the P/Q-type or CaV2.1 voltage-gated calcium channel, acting as an ion pore and a voltage sensor [56]. *CACNA1A*-related epileptic encephalopathies include epilepsy of infancy with migrating focal seizures, Lennox-Gastaut syndrome and infantile spasms [5,57-60]. Auvin et al. [57] reported a case with a *de novo* 0.7Mb deletion in 19p13.13 including *CACNA1A* associated with mental retardation and epilepsy with infantile spasms: seizure were initially controlled with vigabatrin and the patient remained seizure-free even after vigabatrin withdrawal. Damaj et al.[58] reported three unrelated families with epileptic encephalopathy and mild cerebellar symptoms: full seizure control was achieved on a combination of valproate, topiramate and levetiracetam, in one case; in another, seizures were partially

responsive to a combination of valproate and levetiracetam; intermittent acute cerebellar symptoms responded to continuous treatment with acetazolamide.

CACNA2D2-related epileptic encephalopathy

The *CACNA2D2* gene encodes the alpha-2-delta-2 auxiliary subunit of high voltage-gated calcium channels. High voltage-gated calcium channels are heteromultimeric protein complexes composed of the main channel forming alpha1 subunit, which carries calcium influx across the plasma membrane, and the auxiliary subunits beta, gamma, and alpha-2-delta-2. Auxiliary subunits modulate calcium current and channel activation and inactivation kinetics, and may be involved in proper assembly and membrane localization of the channels [61]. Only four cases with early-onset epileptic encephalopathy and *CACNA2D2* mutations have been reported so far: three siblings with early infantile epileptic encephalopathies [61], and one patient, offspring to consanguineous parents, with early infantile epileptic encephalopathy, dyskinesia, cerebellar atrophy and dysmorphic features [62]. Seizures are described as refractory to treatment in the siblings [61], whilst improvement of absence seizures with ethosuximide is reported in the case described by Pippucci et al. [62].

CASK-related epileptic encephalopathy

The *CASK* gene at Xp11.4 encodes a calcium/calmodulin-dependent serine protein kinase that is a member of the membrane-associated guanylate kinase (MAGUK) protein family [63]. *CASK* is involved in synapse formation at both presynaptic and postsynaptic junctions; in addition, CASK enters the nucleus and regulates expression of genes involved in cortical development [64]. Heterozygous loss of function mutations of *CASK* in females cause epilepsy, severe intellectual disability, and microcephaly with pontine and cerebellar hypoplasia. Associated syndromes include epileptic encephalopathies (e.g., West syndrome and Lennox-Gastaut syndrome), with drug-resistant epilepsy [65,66]. Male patients present a broad phenotypic spectrum ranging from mild (X-linked intellectual disability with or without nystagmus) to severe (with early-infantile epileptic encephalopathy and intractable seizures; Ohtahara syndrome, West syndrome, or early myoclonic epilepsy), cerebellar hypoplasia, and multiple congenital anomalies [65,67-71].

CDKL5-related epileptic encephalopathy

The *CDKL5* gene encodes cyclin-dependent kinase-like 5 and its mutations can cause early-onset epileptic encephalopathy, including West syndrome, Lennox-Gastaut syndrome or the 'early-onset seizure variant of Rett syndrome' [72-75]. *CDKL5* is located on the X chromosome (Xp22.13), and therefore genetic traits of *CDKL5* alterations have been considered to be X-linked dominant [76]. *CDKL5* mutations have mainly been reported in female patients with an early infantile epileptic encephalopathy phenotype including infantile spasms, severe intellectual disability, and 'Rett-like' features with absent or limited speech, stereotypic hand movements, and deceleration of head growth [77,78]. A distinctive electroclinical seizure type with hypermotor-tonic-spasms sequence has been described in females with *CDKL5*-related encephalopathy [79]. The condition seems to be less common,

but with a more severe phenotype, in male patients [76,78,80]. The milder clinical spectrum of *CDKL5* mutations in female patients is hypothesized to be due to variable X-chromosome inactivation [81]. In most cases the epilepsy is described as refractory to conventional antiepileptic and corticosteroid treatment [73]. Three cases with *CDKL5*-related epileptic encephalopathy had improvement of seizure control following implantation of a vagus nerve stimulator [74,82].

CHD2-related epileptic encephalopathy

The gene *CHD2* encodes chromodomain helicase DNA-binding protein 2, involved in transcriptional regulation and chromatin remodelling. *CHD2* mutations cause childhood-onset epileptic encephalopathies, including epilepsy with myoclonic-atonic seizures, fever-sensitive myoclonic encephalopathy, Lennox-Gastaut syndrome and myoclonic encephalopathy with clinical photosensitivity [5,7,83-86]. Most cases had drug-resistant epilepsy [86]. However one case with fever-sensitive myoclonic epileptic encephalopathy became seizure-free after the introduction of clobazam [84]; and one case with myoclonic-atonic seizures was initially treated with valproate with a slight reduction in seizure frequency; lamotrigine and clobazam were subsequently added, and he remained seizure-free for four years, therefore antiepileptic drugs were gradually withdrawn and six months later he had seizure recurrence and valproate was restarted with only two further seizures, both photoinduced [87].

CLCN4-related epileptic encephalopathy

The X-chromosomal gene *CLCN4* encodes the voltage-dependent $2Cl^-/H^+$-exchanger ClC-4 [88]. In a 14-month-old boy with epileptic encephalopathy and intractable seizures, Veeramah et al. [9] identified a de novo hemizygous missense mutation in the *CLCN4* gene by whole-exome sequencing. In vitro functional expression studies in Xenopus oocytes showed that the mutation almost abolished the outwardly rectifying currents, consistent with a loss of function. Fifty-two individuals from 16 families with *CLCN4*-related disorder were recently reported: 5 affected females and 2 affected males with a de novo variant in *CLCN4* and 27 affected males, 3 affected females and 15 asymptomatic female carriers from 9 families with inherited *CLCN4* variants. A seizure disorder was reported in 15 males (52%) from seven families varying from infrequent seizures, well controlled with monotherapy (47%), to severe infantile-onset intractable epilepsy (53%), even within a family. Three seizure-related deaths were reported in one family, which may have resulted from limited antiepileptic treatment options. No particular antiepileptic medication was found to be consistently more effective in the eight families with seizure disorder [89].

DNM1-related epileptic encephalopathy

The dynamin 1 gene (*DNM1*) encodes a large guanosine triphosphatase (GTPase), which plays a key role in clathrin-mediated synaptic vesicle endocytosis, particularly during post-natal development [90]. A few cases with early-onset epileptic encephalopathy, including West syndrome and Lennox-Gastaut syndrome, have been described [6,91,92]. Not all

patients were reported as drug-resistant; one patient was seizure-free on vigabatrin and valproate from 3 to 8 years, one on ketogenic diet since age 3.5 years until last follow-up at age 6 years, one on clobazam and valproate from 3 to 5 years of age [6,92]. Dhindsa et al. [93]performed in vitro functional expression assays of three missense mutations in the *DNM1* gene; all caused impaired endocytosis of transferrin in a dominant-negative manner, although the mechanisms differed slightly. The findings were consistent with a defect in synaptic vesicle cycling and endocytosis, which none of the effective treatments probably target directly.

DOCK7-related epileptic encephalopathy

DOCK7 is a member of the DOCK180-related protein superfamily, which functions as a guanine nucleotide exchange factor (GEF) for Rac and/or Cdc42 GTPases. It plays a role in neurogenesis [94]. In three female patients (two affected female siblings born to nonconsanguineous healthy French Canadians parents and one affected female case born to nonconsanguineous healthy French parents) from two unrelated families with early infantile epileptic encephalopathy, Perrault et al. [95] identified four different (compound) heterozygous truncating mutations in the *DOCK7* gene, predicted to result in a loss of protein function. The clinical syndrome included dysmorphism and cortical blindness, with intractable seizures with hypsarrhythmia despite the administration of multiple antiepileptic drugs in various combinations and the ketogenic diet [95].

EEF1A2-related epileptic encephalopathy

The *EEF1A2* gene encodes eukaryotic translation elongation factor-1, alpha-2, a protein that plays an essential role in protein synthesis by transporting aminoacyl-tRNA to the A-site of the ribosome [96]. Few cases with *EEF1A2*-related epileptic encephalopathy have been reported [9,27,96-98]. Sodium valproate was effective in three cases, in monotherapy or associated with zonisamide or lamotrigine [96,98]. Most cases had drug-resistant epilepsy.

FOXG1-related epileptic encephalopathy

The *FOXG1* gene encodes a developmental transcription factor with repressor activities, and is involved in the transcription regulatory network that controls proliferation, differentiation, neurogenesis, and neurite outgrowth [99]. Duplications of *FOXG1* have been associated with West syndrome [100,101]. There is evidence that infantile spasms in children with *FOXG1* duplications respond to hormonal therapy with ACTH [102,103], with cessation of clinical spasms and resolution of hypsarrhythmia on EEG. Deletions or intragenic mutations manifest with a more severe phenotype, with developmental delay, prominent dyskinetic movements, and drug-resistant epilepsy [103,104].

GABRA1/GABRB1/GABRB3/GABRG2-related epileptic encephalopathy

Mutations affecting the receptor gene family of heteromeric pentameric ligand-gated ion channels through which gamma-aminobutyric acid (GABA) acts have been associated with epileptic encephalopathies. The Epi4K Consortium and Epilepsy Phenome/Genome Project [5] found six mutations in subjects with infantile spasms or Lennox-Gastaut syndrome affecting subunits of the GABA ionotropic receptor (four in *GABRB3*, and one each in *GABRA1* and *GABRB1*). Some *de novo* missense variants in *GABRB1* and *GABRB3* have been functionally characterized and shown to affect GABAA ligand-gated chloride channel function, either by reducing channel opening (Lennaux–Gastaut syndrome-related mutations in *GABRB3*), or by affecting opening/closing kinetics (infantile spasm-related mutations, one in *GABRB1* and one in *GABRB3*)[105]. A further case with *GABRB1*-related epileptic encephalopathy has been recently reported and has shown a positive response (no further details on response available) to ketogenic diet [106]. Mutations in *GABRB3* have been associated with various epileptic encephalopathies, including a 'Dravet-like' phenotype, myoclonic atonic epilepsy, West syndrome and Lennox-Gastaut syndrome [107]. Mutations in *GABRA1* have also been associated with various epileptic encephalopathies, including a 'Dravet-like' phenotype, 'myoclonic atonic epilepsy-like' phenotype, or other milder undefined epilepsy encephalopathy phenotypes [108,109]. One patient with a 'Dravet-like' phenotype was reported as seizure-free on levetiracetam monotherapy, and one patient with 'mild epileptic encephalopathy' was seizure-free on valproate and levetiracetam combination therapy [109]. Similarly, mutations in *GABRG2* have been associated with Dravet syndrome, epilepsy with myoclonic-atonic, Lennox-Gastaut syndrome or other unclassified epileptic encephalopathies [110,111]. Shen et al.[111] reported two out of seven cases seizure-free on levetiracetam or on a combination of valproate and topiramate, respectively. Huang et al. [112] studied the *GABRG2* nonsense mutation, Q40X, associated with Dravet syndrome. They found that the mutant subunit mRNA was degraded by nonsense-mediated mRNA decay, and the undegraded mutant mRNA was translated to a truncated peptide. They used an aminoglycoside, gentamicin, to rescue translation of intact mutant subunits by inducing mRNA read-through. In the presence of gentamicin, the cellular phenotype was partly rescued. These findings might direct future treatment strategies.

GAMT/GATM-related epileptic encephalopathy

Amidinotransferase converts glycine to guanidinoacetate; guanidinoacetate methyltransferase (GAMT) converts the latter to creatine with S-adenosylmethionine as the methyl donor. GAMT deficiency, also known as cerebral creatine deficiency syndrome-2, is an autosomal recessive inborn error of creatine synthesis. Its clinical features are developmental delay/regression, mental retardation, severe disturbance of expressive and cognitive speech, intractable seizures and movement disturbances, severe depletion of creatine/phosphocreatine in the brain, and accumulation of guanidinoacetic acid (GAA) in brain and body fluids [113]. Mikati et al. [114] found that epilepsy was present in 81% of patients with GAMT deficiency, with age at onset usually between 10 months and 3 years. Drug resistance was observed in approximately 45%. Epilepsy syndromes associated with GAMT deficiency include Lennox-Gastaut and West syndrome. Current treatment options include oral high-dose creatine which significantly increases brain creatine concentrations [115], and dietary manipulation combining suuplementation of ornithine with restriction of arginine, to reduce guanidinoacetate toxicity [116]. Establishment of early treatment may prevent some features

of the condition from developing, i.e. intellectual disability [117]. There is evidence that also treatment in adults with GAMT deficiency can dramatically reduce seizure frequency [116].

The enzyme L-arginine: glycine amidinotransferase (GATM) catalyzes the transfer of a guanido group from arginine to glycine, forming guanidinoacetic acid, the immediate precursor of creatine [118]. GATM (or AGAT) deficiency, also known as cerebral creatine deficiency syndrome-3, is caused by homozygous mutation in the *GATM* gene. Its clinical phenotype is similar to the one caused by GAMT deficiency [113], but here most patients develop a myopathy characterized by muscle weakness and atrophy later in life. As for GAMT deficiency, early diagnosis and treatment with oral creatine supplementation can significantly improve the outcome [119,120].

GNAO1-related epileptic encephalopathy

The *GNAO1* gene encodes an alpha subunit of the heterotrimeric guanine nucleotide-binding proteins (G proteins), a large family of signal-transducing molecules. The phenotypic spectrum can vary from movement disorder with no or controlled seizures to early infantile epileptic encephalopathy, and Ohtahara syndrome, with drug-resistant epilepsy [6,121-123]. Nakamura et al.[121] reported four female cases with *GNAO1* mutations, three with Ohtahara syndrome and one with unclassified epileptic encephalopathy: seizures and EEG findings were temporarily improved by treatment with ACTH and valproate in two cases with Ohtahara syndrome; however all four individuals had intractable epileptic seizures in spite of combinatory therapy of antiepileptic drugs. The EuroEPINOMICS-RES Consortium [6] reported two cases with *GNAO1*-related epileptic encephalopathy**:** one case with onset of infantile spasms at 3 months, seizure-free off treatment until the last follow-up at the age of 3 years; another one with drug-resistant epilepsy with multiple seizure types. Saitsu et al.[123] reported two additional cases with *GNAO1* mutations and early-onset epileptic encephalopathy, both with drug-resistant epilepsy. No further details on treatment are available.

GRIN1/GRIN2A/GRIN2B-related epileptic encephalopathy

The ionotropic glutamate N-methyl-D-aspartate (NMDA) receptors are tetrameric ligand-gated ion channels permeable to sodium, potassium, and calcium, composed of two glycine binding GluN1 subunits and two glutamate-binding GluN2/3 subunits. *GRIN2A* encodes the GluN2A subunit, *GRIN2B* the GluN2B subunit, and *GRIN1* the GluN1 subunit [124]. NMDA receptors have important roles in synaptogenesis and synaptic plasticity [125]. The epilepsy phenotype associated with *GRIN1* mutation is highly variable. Treatment responsiveness also seems to vary: some patients were drug-resistant, two patients became seizure-free or had long periods of seizure freedom on valproate, one patient responded well to a combination of topiramate, levetiracetam, and clobazam and one other patient had good response following the introduction of vigabatrin and clonazepam in addition to valproate [126].

The most common *GRIN2A*-related disorders are epilepsy-aphasia syndromes (EAS), a spectrum that includes: Landau-Kleffner syndrome (LKS); epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS); childhood epilepsy with centrotemporal

spikes (CECTS); atypical childhood epilepsy with centrotemporal spikes (ACECTS); and autosomal dominant rolandic epilepsy with speech dyspraxia (ADRESD) [127]. Other epilepsy phenotypes are: infantile-onset epileptic encephalopathy and unclassified childhood epilepsy [128-132]. Under physiological conditions, very few ions pass through the NMDA receptors because magnesium blocks the pore. When the NMDA receptor is activated, magnesium is displaced, and this allows calcium and other cations to move into the cell. In case of dysfunction of NMDA receptors, calcium influx into the cell increases. In vitro experiments showed that a specific GRIN2A mutant (L812M) receptor showed increased activity in response to agonists and decreased response to negative modulators [131]. Memantine, an NMDA receptor antagonist, was shown to inhibit the increased activity of the NMDA receptor caused by the L812M mutation, in vitro. A child with an early-onset epileptic encephalopathy due to the same GRIN2A missense mutation was treated with memantine added on to his antiepileptic medication, with subsequent significant improvement of seizure control and interictal EEG recordings [133]. A different GRIN2A missense mutation (N615K) causing a different channel dysfunction, with no effect on receptor activity, but acting through the relief of magnesium blockade, was found in another child with epileptic encephalopathy [128]. Due to the lack of effect of the mutation on the NMDA receptor activity, treatment with memantine was not tried in this case. In another case with early-onset epileptic encephalopathy due GRIN2A mutation, addition of topiramate to levetiracetam and clonazepam, at 6 mg/kg/day, led to significant reduction of seizure duration and frequency within one month from more than a dozen seizures a day to one–two seizures per day, each lasting a few seconds, with good tolerability and improved alertness; this effect was sustained for ten months. The authors postulate that the benefit of topiramate could be explained through its action by enhancing the GABA-evoked currents [130].

GRIN2B mutations have been associated with West and Lennox–Gastaut syndromes [5,134]. The epilepsy is reported as generally drug-resistant, with some evidence in West syndrome of response to a combination of vigabatrin and pyridoxine, and later valproate, or steroid pulse therapy in two patients [134].

HCN1-related epileptic encephalopathy

The gene HCN1 encodes one of the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels, expressed in both heart and brain [135]. In six unrelated patients with early infantile epileptic encephalopathy-24, Nava et al.[136] identified six different heterozygous missense mutations in the HCN1 gene. The patients had seizure onset between 4 and 13 months of age. Seizure type at onset tended to be tonic-clonic or hemiclonic but evolved into predominantly atypical absences with or without myoclonic jerks, and focal seizures, later in childhood. Epilepsy was described as drug-resistant in all cases. Four patients had status epilepticus. All patients had intellectual disability of varying degrees, and most had behavioral disturbances including autistic features.

HNRNPU-related epileptic encephalopathy

NRNPU has 14 exons, which are highly conserved during evolution. The gene encodes the heterogeneous nuclear ribonucleoprotein (hnRNP) U, that binds RNAs and mediates different aspects of their metabolism and transport [137,138]. More than 40 patients have been reported with deletions of the subtelomeric region of the long arm of chromosome 1 (1q43q44 microdeletion syndrome) identified by chromosome microarray[139-142]. This

syndrome is associated with a complex neurological phenotype, including intellectual disability, microcephaly, epilepsy and anomalies of the corpus callosum *HNRNPU* is the main candidate for the epilepsy phenotype [139,142]. *De novo* and/or truncating mutations in *HNRNPU* causing epileptic encephalopathy have been reported [5,7,11,137,143], but details on the epilepsy phenotype are sparse. More recently, six patients with constitutive *de novo,* and one with mosaic frameshift, *HNRNPU* mutations and early-onset epilepsy were reported [142]. Seizure onset ranged from age 2.5 months to 4 years, and was within or at the first year of life in 5/6 patients. Fever was a factor triggering seizures in five patients. Seizures types included tonic–clonic, tonic, unilateral clonic or atypical absences occurring one to 20 times a day. Two patients experienced status epilepticus. Three of them were diagnosed with 'non-specific epileptic encephalopathy'. Lacosamide and valproate were described as 'effective in two cases.

IQSEC2-related epileptic encephalopathy

The *IQSEC2* gene is located on chromosome Xp11.22 and encodes a guanine nucleotide exchange factor for the ARF family of GTP-binding proteins [144]. *IQSEC2*is expressed in neurons and is involved in cytoskeletal organization, dendritic spine morphology, and excitatory synaptic organization [145]. All reported *IQSEC2* variants are missense, nonsense or lead to splicing defects, resulting in reduced enzymatic activity [144,146]. Complete abolition of enzymatic activity causes a more severe phenotype in both males and females, with epileptic encephalopathy and nonsyndromic X-linked intellectual disability and epilepsy included in the phenotypic spectrum [147]. The first report of an *IQSEC2*-related epileptic encephalopathy, due to a *de novo* chromosomal translocation t(X; 20) (p11.2;q11.2) disrupting the *IQSEC2* gene, was by Morleo et al.[148]: they reported a female case of West syndrome with spasms refractory to medical treatment. X-inactivation studies revealed an extremely skewed X-inactivation pattern with dominant use of the translocated X-chromosome. Most cases of *IQSEC2*-related disorders were found by whole-exome or targeted capture sequencing in cohorts of patients with intellectual disability and/or epileptic encephalopathy [5,59,83,144,149-155]. Zerem et al. [147] described the phenotypic spectrum of 18 patients with *IQSEC2*-related epilepsy. Of these, 9 (50%) were diagnosed with epilepsy encephalopathies, including 'late-onset epileptic spasms' and 'Lennox-Gastaut' or 'Lennox-Gastaut-like syndrome', all reported to have 'intractable' epilepsy except one case with Lennox-Gastaut syndrome where 'response' to lamotrigine and rufinamide is described. More recently, a family with four girls affected by probable *IQSEC2*-related epilepsy encephalopathy has been described, with two of them deceased due to probable SUDEP [146].

KCNA2-related epileptic encephalopathy

The *KCNA2* gene encodes the Kv1.2 channel, one of the voltage-gated potassium channels that are expressed in the central nervous system. The Kv1.2 channel belongs to the delayed rectifier class of potassium channels that enable efficient neuronal repolarization after an action potential [156]. *De novo* mutations in *KCNA2* were identified as the cause of mild to severe epileptic encephalopathy [156-158]. Two patients with *KCNA2* mutations associated

with early-onset epileptic encephalopathy had significant improvement of seizure control following introduction of acetazolamide [157,158], in keeping with observations in a mouse model [159]. Four patients with dominant-negative loss-of-function mutations had a phenotype overlapping with Dravet syndrome and epilepsy with myoclonic-atonic seizures. All four patients became seizure-free between four and 15 years old with no apparent association to a preceding change of medication. The phenotypes of two patients carrying mutations with dominant gain-of-function were more severe in terms of epilepsy with ongoing generalized tonic-clonic seizures despite treatment, ataxia and intellectual disability, and also differed electrographically, with generalized epileptic discharges [156].

KCNB1-related epileptic encephalopathy

The *KCNB1* gene encodes the Kv2.1 channel, the main contributor to delayed rectifier potassium currents in pyramidal neurons of the hippocampus and cortex. All patients with *KCNB1*-related epileptic encephalopathy were reported to have refractory epilepsy [132,160-163]. One patient had 6-month period of seizure freedom after implementation of the ketogenic diet, followed then by seizure recurrence [163]. A correlation between mutations that result in loss of Kv2.1 ion selectivity and development of epileptic encephalopathy has emerged [163].

KCNQ2/KCNQ3-related epileptic encephalopathy

The *KCNQ2* and *KCNQ3* genes encode subunits of the voltage-gated potassium M channel underlying the neuronal M-current [164]. *KCNQ2* mutations cause neonatal-onset epileptic encephalopathy of widely varying severity [165,166]. Affected individuals usually have multiple daily (mostly tonic) seizures beginning in the first week of life, with associated focal motor and autonomic features. Most cases have drug-resistant epilepsy; seizures then tend to generally cease by age nine months to four years [165]. Encephalopathy is present from birth and persists during and after the period when seizures are uncontrolled, with moderate to severe developmental impairment [5,7,165,167-172]. The most severe form of encephalopathy associated with *KCNQ2* variants is Ohtahara syndrome, with typical suppression-burst EEG pattern within the first months of life and poor outcome in terms of psychomotor development and seizure control [10,173,174]. *KCNQ3* variants also cause neonatal-onset epileptic encephalopathy [175,176].

In *KCNQ2/KCNQ3*-related epilepsy there is a potential tailored precision medicine strategy with the use of retigabine (ezogabine), a drug primarily acting as a positive allosteric modulator of KCNQ2-5 (Kv7.2-7.5) ion channels, and the first neuronal potassium (K+) channel opener licensed for the treatment of epilepsy [177]. In vitro studies identified the probable binding site of retigabine in KCNQ2 and KCNQ3 channels, explaining its voltage-dependent activating effect through a hyperpolarizing shift of the activation curve [178,179]. Orhan et al.[180] defined the disease mechanism of seven de novo missense *KCNQ2* mutations associated with severe epileptic encephalopathy and found a clear loss of function for all the mutations studied in vitro. Most mutations showed a dominant-negative effect on wild-type KCNQ2 or KCNQ3 subunits. The use of retigabine partially reversed the loss of function, in vitro, for the majority of analyzed mutations. Preliminary data from humans with

KCNQ2-related disease suggest retigabine may be a useful treatment option [167,181]. However, mainly due to the discovery of additional side effects in the early post-marketing phase (blue discoloration of skin and retina), the production of retigabine will be soon discontinued, and it will be no longer commercially available. Sodium channel blockers also seem effective in *KCNQ2*-related epilepsy [166,167,172,174], possibly because voltage-gated sodium channels and KCNQ potassium channels co-localize and are bound at critical locations of the neuronal membrane [182]; the efficacy of sodium-channel blockers could be explained by the hypothesis that modulation of one channel may significantly affect the function of the channel complex [166]. Sodium channel blockers including carbamazepine and phenytoin should also be considered as first-line treatment in patients with *KCNQ2*-related epilepsy, as there is a suggestion that early effective treatment reduces cognitive disability [17,172]. Treatment with vigabatrin or ACTH has been used for infantile spasms that can occur during the course of the disease [183-185]. A recent report described a positive effect of vitamin B6 on seizures in a few patients with *KCNQ2*-neonatal epileptic encephalopathy [186]; however, the underlying mechanism is unclear and needs further investigation. Some cases with *KCNQ3*-neonatal epileptic encephalopathy became seizure-free on valproate monotherapy or on a combination of valproate and carbamazepine [176].

KCNT1-related epileptic encephalopathy

The *KCNT1* gene encodes a sodium-dependent potassium channel that is widely expressed in the nervous system. *KCNT1* gain-of-function mutations are reported to cause early-onset epileptic encephalopathies (EOEE) including epilepsy of infancy with migrating seizures (approximately 50% of individuals with this syndrome have a *KCNT1* pathogenic variant) [187-189]. Quinidine, an antiarrhythmic drug, is a partial blocker of KCNT1. It was previously used to reverse the hyperactivity of the mutant KCNT1 in Xenopus oocytes [190]. In two case reports of epilepsy of infancy with migrating seizures due to *KCNT1* mutations, quinidine resulted in decreased seizure frequency or freedom from seizures and improved psychomotor development [187,189]. Another two cases with *KCNT1*-related epilepsy, one showing a novel phenotype with developmental regression and severe nocturnal focal and secondarily generalised seizures starting in early childhood, and the other with early-onset epileptic encephalopathy [189,191], did not respond to treatment with quinidine. More recently, a case of West syndrome caused by *KCNT1* mutation was reported to show good response to quinidine, with reduction of epileptic spasm frequency, improvement of EEG activity and progress in development [192]. Currently the therapeutic effects of quinidine in *KCNT1*-related epilepsy remain largely unknown and more work is required, although it seems a promising treatment option for epilepsy due to gain-of-function mutations in *KCNT1*.

KIAA2022-related epileptic encephalopathy

The *KIAA2022* gene maps to Xq13.3 and, when mutated, is known to cause severe intellectual disability in males [193]. *KIAA2022 i*s highly expressed in fetal and adult brain; its expression in adult brain is predominantly in the cerebral cortex and the cerebellum [193]. *KIAA2022* encodes two protein products: the primary 1516 amino acid protein X-linked Intellectual Disability Protein Related to Neurite Extension (XPN), and an unnamed 118

amino acid protein [194]. XPN regulates cell-cell and cell-matrix adhesion and cellular migration by modulating the expression of adhesion molecules in neural signaling pathways, and therefore has a crucial role in neuronal development. [195,196]. Five male patients from four families with *KIAA2022*-related syndrome including epilepsy have been reported. The described epilepsy syndromes were 'generalised epilepsy' in two unrelated cases (with remission after age 2.5 years in one case and 'response' to valproate in another), West syndrome in two siblings (in one responsive to treatment, no further details given), and Lennox-Gastaut in one case (with absences and atonic seizures 'responding' to lamotrigine and valproate) [193,197].

More recently, 18 females have been reported with *de novo* loss of function mutations in *KIAA2022* associated with intellectual disabilities and intractable epilepsy. Farach and Northrup [198] reported a 17-year-old female with short stature, microcephaly, severe intellectual disability, poor speech, epilepsy, and autistic behaviour. Her seizures did not respond to multiple antiepileptic medications and vagal nerve stimulation. At age 17 years, she had corpus callosotomy with 'vast improvement in seizure frequency'; however, at the time of the publication, she was still experiencing daily seizures. de Lange et al. [199] reported 12 female cases with heterozygous *de novo KIAA2022* mutations and epilepsy; these cases included 11 with generalized epilepsy (mostly absences and myoclonic seizures) and one with focal epilepsy, all drug-resistant. Webster et al. [200] described five further female cases with heterozygous *de novo KIAA2022* mutations and drug-resistant epilepsy, four with generalised epilepsies, and one with myoclonic-astatic epilepsy.

MEF2C-related epileptic encephalopathy

MEF2C belongs to the myocyte enhancer factor-2 (MEF2) family of transcription factors. It plays a pivotal role in myogenesis, development of the anterior heart field, neural crest and craniofacial development, and neurogenesis, among other functions [201]. *MEF2C* haploinsufficiency is a genetic syndrome known to occur in cases of microdeletion of the 5q14.3 region and *MEF2C* mutations [202,203]. The syndrome is characterized by severe intellectual disability, absence of speech and limited walking abilities, hypotonia, epilepsy, stereotypic movements, minor brain malformations, and minor dysmorphic features [203,204]. There are forty-four cases of 5q14.3 microdeletion and nine patients with *MEF2C* mutations reported thus far [205]. In two cases with epileptic encephalopathy due to *MEF2C* mutations, epilepsy was well controlled: one case on monotherapy with valproate [203], one case on a combination of lamotrigine and clobazam [205].

MOCS1/MOCS2-related epileptic encephalopathy

MOCS1, *MOCS2, MOCS3* and *GPRN* genes contribute to the synthesis of molybdenum cofactor, and the *SUOX* gene encodes sulfite oxidase. Molybdenum cofactor deficiency (MoCD) and Sulfite Oxidase Deficiency (SOD) are rare autosomal recessive disorders of sulfur-containing amino acid metabolism. The clinical phenotype is characterized by onset in infancy of poor feeding, intractable seizures, and severe psychomotor retardation. Characteristic biochemical abnormalities include decreased serum uric acid and increased urine sulfite levels due to the combined enzymatic deficiency of xanthine dehydrogenase

(XDH) and sulfite oxidase (SUOX), both of which use molybdenum as a cofactor. Most affected individuals die in early childhood [206,207]. A recent study showed that intractable neonatal seizures, spasticity, and feeding difficulties can be important early signs for these disorders [208]. Most patients have early-onset intractable seizures (generalized tonic clonic and multifocal myoclonic), not responding to antiepileptic medications. There is evidence of successful replacement therapy with cyclic pyranopterin monophosphate (cPMP), a biosynthetic precursor of the molybdenum cofactor, in patients with *MOCS1* mutations (type A deficiency), in patients either diagnosed prenatally or very early in life, which showed favorable clinical and biochemical response [209,210].

NDP-related epileptic encephalopathy

The *NDP* gene encodes norrin, a secreted cysteine-rich protein that belongs to the cystine knot growth factor family [211]. *NDP* mutations cause Norrie disease, an X-linked recessive disorder that is characterized by congenital blindness, which is often accompanied by greyish yellow fibrovascular masses (pseudogliomas) secondary to retinal vascular dysgenesis and detachment [212]. The extraocular clinical manifestations of Norrie disease include epilepsy, which is reported in ~10% of patients [213]. There are only a few reports with details of the epilepsy phenotype in Norrie disease [214,215]. One case with Norrie disease and severe neurological involvement including infantile spasms was reported by Lev et al.[214]; they describe a significant improvement of the spasms, but not of the EEG, on a combination of topiramate and clonazepam.

PCDH19-related epileptic encephalopathy

PCDH19 encodes protocadherin-19, a calcium-dependent cell adhesion molecule expressed throughout the central nervous system and involved in brain development, intracellular signaling, and synaptogenesis [216]. Mutations cause early infantile epileptic encephalopathy-9, or epilepsy and mental retardation limited to females (EFMR) [216]. The most typical phenotype seen in EFMR females comprises a normally-developing infant whose seizures begin under 3 years (mean age of 14 months), sometimes with developmental regression at seizure onset. Two thirds of affected females have borderline intellect or intellectual disability, which varies from mild to profound; autistic features may be prominent [217]. *PCDH19* mutations can also cause a 'Dravet-like' phenotype, although with later age of onset, less frequent status epilepticus, myoclonic and absence seizures, and a lesser degree of intellectual disability, than cases with *SCN1A*-related Dravet syndrome [218]. Hemizygous "carrier" males are usually asymptomatic or exhibit only psychiatric or behavioural symptoms [217]. However, two male cases with somatic mosaicism for *PCDH19* deficiency have been reported so far; both had epileptic encephalopathy with uncontrolled seizures, although improvement of motor development was reported on levetiracetam [218,219]. Data on epilepsy course and treatment are sparse. Seizures appear to be highly resistant to antiepileptic drug treatment during the first years of life, while their frequency and their pharmacoresistance tend to decrease during the course of the disease [220]. Depienne et al.[218] reported 3 out of 13 cases with a 'Dravet-like' phenotype that had seizure control on a combination of valproate and lamotrigine; valproate, clobazam and topiramate; or

valproate, clobazam and stiripentol. Hynes et al. [221] report two affected sisters and one sporadic female with EFMR: one of the siblings became seizure-free on a combination of valproate and clobazam, and she was weaned off antiepileptic treatment at 13.5 years; the other siblings achieved seizure control on a combination of levetiracetam, carbamazepine and lamotrigine; the sporadic case had episodes of convulsive status epilepticus which responded to phenytoin in combination with lamotrigine and clobazam. Also in a single case report, a combination of valproate, clobazam and stiripentol, was reported to be effective [222]. Higurashi et al. [223] reported effectiveness of phenytoin, bromide and clobazam, in monotherapy or combination. A recent retrospective multicenter study in 58 females with EFMR found that clobazam and bromide were the most effective drugs, with 74% of the cases who became seizure-free for at least for three months and 47% for at least one year. The typical loss of effectiveness of clobazam after several months of treatment was not observed [224]. Tan et al.[225] showed that defective neurosteroid metabolism is associated with EFMR, as they found dysregulation of the *AKR1C* genes, which code for crucial neurosteroid-metabolizing enzymes, causing subsequent allopregnanolone deficiency. This finding may represent a promising precision medicine approach with a novel therapeutic target in EFMR.

PIGA/PIGQ-related epileptic encephalopathy

PIGA and *PIGQ* encode proteins involved in the biosynthesis of the glycosylphosphatidylinositol (GPI) anchor, a glycolipid structure embedded in the plasma membrane that attaches dozens of different proteins to the cell surface [226,227]. Four cases with early myoclonic encephalopathy, West syndrome, or unclassified early-onset epileptic encephalopathies, all with intractable seizures, were found to have *PIGA* mutations [228]. One case with Ohtahara syndrome was found to have *PIGQ* mutation [10].

PLCB1-related epileptic encephalopathy

The *PLCB1* gene encodes a mammalian isoform of the phospholipase C-beta which catalyzes the generation of inositol 1,4,5-trisphosphate and diacylglycerol from phosphatidylinositol 4,5-bisphosphate, a key step in the intracellular transduction of many extracellular signals [229]. Homozygous or compound heterozygous loss-of-function *PLCB1* mutations have been described in four children with early-onset epileptic encephalopathies, including one with epilepsy of infancy with migrating focal seizures [230-233]. Epilepsy was drug-resistant in all cases, with some evidence of non-sustained improvement in seizure control on phenobarbitone and prednisolone [230], ketogenic diet [232], or valproate [233].

PNKP-related epileptic encephalopathy

The *PNKP* gene encodes a polynucleotide kinase 3-prime phosphatase, which is involved in the DNA repair pathway [234]. Biallelic mutations in this gene cause autosomal recessive microcephaly with early-onset intractable seizures and developmental delay [235]. This condition has a range of phenotypic severity: some patients have a disease course consistent with early infantile epileptic encephalopathy, whereas others have more well-controlled

seizures and a protracted course associated with cerebellar atrophy and peripheral neuropathy [235,236]. Among cases with epileptic encephalopathy, one had seizures well controlled on phenobarbital and levetiracetam [237]; epilepsy surgery was underataken in two cases, one with undefined outcome, one with recurrent seizures after surgery [235]; the other cases had drug-resistant epilepsy [235].

PNPO-related epileptic encephalopathy

Pyridox(am)ine-5-phosphate oxidase (encoded by the *PNPO* gene) deficiency is an autosomal recessive disorder of pyridoxine metabolism. *PNPO* deficiency is a treatable cause of neonatal epileptic encephalopathy [238]. The pyridox(am)ine-5-phosphate oxidase enzyme converts pyridoxine-5-phosphate and pyridoxamine-5-phosphate to pyridoxal 5′-phosphate (PLP; the only active form of vitamin B6), and is necessary for the recycling of PLP [239], seizures in *PNPO* deficiency are usually resistant to pyridoxine but respond to pyridoxal 5′-phosphate [240], although several pyridoxine-responsive patients have been reported [241,242]. Mills et al. [238] showed that mutations in *PNPO* led to reduced enzyme activity when expressed in Chinese hamster ovary cells.

POLG-related epileptic encephalopathy

The *POLG* gene encodes the mitochondrial DNA polymerase. *POLG* mutations were first identified in a family segregating autosomal dominant progressive external ophthalmoplegia [243]. Since then, the phenotypic spectrum has considerably broadened, including dominant or, more often, recessive diseases. The most severe presentation is Alpers-Huttenlocher syndrome characterized by childhood-onset progressive and ultimately severe encephalopathy with intractable epilepsy and hepatic failure [244]. Most syndromes associated with *POLG* mutations have usually later onset, ranging from adolescence to adulthood, including spinocerebellar ataxia with epilepsy (SCAE), mitochondrial recessive ataxia syndrome (MIRAS), sensory ataxic neuropathy with dysarthria and ophthalmoplegia (SANDO), myoclonus, epilepsy, myopathy, sensory ataxia (MEMSA), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), chronic intestinal pseudo-obstruction, occipital lobe epilepsy with status epilepticus, non-syndromic childhood-onset intractable epilepsy, Charcot-Marie Tooth-like disease, and autosomal dominant distal myopathy [245]. Alpers-Huttenlocher syndrome is a progressive disorder and often leads to death from hepatic failure or status epilepticus before the age of three years [246]. Liver dysfunction can be present at the onset of the neurologic symptoms, or it can begin following treatment with valproate for seizure control [247]. Children with *POLG1* mutations can also present with isolated encephalopathy, which can be progressive or fluctuating, and liver dysfunction can be absent. Seizures and cortical blindness are common clinical manifestations. Epilepsy is a factor influencing mortality in patients with *POLG1* mutations [248]. The combination of early encephalopathy, epilepsy, hepatopathy, and sensory axonal neuropathy was found in patients with recessive mutations in the mtDNA helicase Twinkle (*PEO1*), underlining the similarity of clinical phenotypes caused by either *PEO1* or *POLG1* mutations [249]. Similarly to the *POLG1*-associated Alpers syndrome, also these patients display mtDNA depletion. Severe elevation of the liver enzymes followed initiation of

valproate treatment in some of these patients. Therefore valproate should be avoided in all patients with *POLG1*- related disorders and Twinkle-associated epileptic encephalopathy due to the risk of fatal valproate hepatotoxicity [250]. Epilepsy, including epilepsia partialis continua, is usually drug-resistant and there are no antiepileptic drugs demonstrated with clear effectiveness for seizure control in *POLG*-associated epileptic disorders.

QARS-related epileptic encephalopathy

The gene *QARS* encodes glutaminyl-tRNA synthetase, an enzyme that charges tRNAs with their cognate amino acids [251]. Compound heterozygous mutations in the *QARS* gene have been identified in a few cases with early-onset epileptic encephalopathies [252-255]. Most cases had drug-resistant epilepsy. However, in one case, valproate was able to control generalized tonic seizures; in another case combination therapy with phenobarbital, potassium bromide, valproate, and clobazam controlled seizures [253]. More recently in a further case, the ketogenic diet was reported to significantly improve seizure control with reduced duration and clustering of seizures, and improved cognition [255].

SCN1A-related epileptic encephalopathy

SCN1A encodes the voltage-gated sodium channel type I alpha subunit. *SCN1A*-related seizure disorders encompass a spectrum that ranges from simple febrile seizures and generalized epilepsy with febrile seizures plus (GEFS+) at the mild end to Dravet syndrome and other epileptic encephalopathies at the severe end. Phenotypes with intractable seizures include Dravet syndrome, epilepsy with myoclonic-atonic seizures, Lennox-Gastaut syndrome, infantile spasms, and epilepsy of infancy with migrating focal seizures [256-260]. Dravet syndrome is a severe genetic epileptic encephalopathy with onset in infancy, often associated with drug-resistant epilepsy, developmental slowing, cognitive impairment, occurrence of status epilepticus, and elevated risk of early mortality[261]. It is caused by mutations in the *SCN1A* gene in approximately 80-90% of cases (of these >90% occur de novo, and 5 to10% are inherited)[260,262]. Adjustment of treatment in Dravet syndrome may be associated with improved seizure control, cognition and quality of life, even into later adult life[263]. Sodium channel blockers, e.g. carbamazepine, oxcarbazepine and phenytoin, should usually be avoided as they can aggravate both seizures and interictal EEG [264]. Lamotrigine can also cause seizure exacerbation [265], though has been reported to be beneficial in some cases [266]. Treatment strategies with some evidence of positive effect include valproate, clobazam, topiramate, levetiracetam, fenfluramine and bromides [267-271] or dietary therapies (ketogenic or modified Atkins diet) [272]. There are ongoing studies on the use of cannabidiol in children with Dravet syndrome. A recent open-label interventional trial of the use of cannabidiol in drug-resistant epilepsy included mostly patients with Dravet and Lennox-Gastaut syndromes: a post-hoc analysis revealed significant reduction in monthly frequency of all seizure types in patients with Dravet syndrome [273]. Randomised, double-blind, multicenter clinical trials are needed to clearly establish the effectiveness and safety profile of cannabidiol in patients with Dravet syndrome [274]. Stiripentol is the only treatment for which a randomised, placebo-controlled, trial has been performed in children with Dravet syndrome [275] showing that significantly more children with Dravet syndrome on stiripentol (in add-on to valproate and clobazam) therapy were seizure-free, or experienced at least a 50% reduction in seizure frequency, compared to placebo. However, the use of stiripentol, valproate and clobazam does not always yield complete seizure

freedom and may cause adverse side effects [276,277]. Thalamic deep brain stimulation (DBS) was reported by Andrade et al.[278] in two children with Dravet syndrome with ten-year follow up; one showed "marked improvement" after implantation, whereas the other received no benefit. The "interneurone hypothesis" is currently the best-supported pathophysiological explanation of Dravet Syndrome. According to this hypothesis, *SCN1A* mutation results in reduced function of GABAergic inhibitory interneurons, leading to an overall excessive neuronal excitation[279]. However, other studies using Dravet Syndrome patient-derived induced pluripotent stem cells (iPSC) found increased excitability of both GABAergic and glutamatergic isolated neurons [280]. A recent study identified a depolarizing GABA phenomenon, and explored the mechanism of action of benzodiazepines and stiripentol, by using a physiology-based computational model [281]. Heterologous expression systems, in which cloned sodium channel α-subunits are expressed in an intrinsically non-excitable cell, were the first models used to investigate the cellular consequences of *SCN1A* mutations associated with epilepsy, and were the first to demonstrate that *SCN1A* mutations can cause both gain and loss of function at the channel level [282]. There is increasing evidence that epileptogenic *SCN1A* mutations cause mainly loss of function, whereas familial hemiplegic migraine is caused by gain of function mutations [283]. Heterologous expression systems have been used for testing compounds that modulate voltage-gated sodium channels. For example, ranolazine, a U.S. Food and Drug Administration (FDA)-approved drug for chronic angina treatment, was first identified as a selective blocker of persistent currents in mutant NaV1.1 channels expressed in one of these models [284]. In follow-up studies in cultured rat hippocampal neurons, ranolazine was found to reduce neuronal excitability and suppress epileptiform activity evoked by NMDA receptor activation [285]. A more recent study showed that ranolazine does not inhibit the persistent Na+ current more strongly than phenytoin in central neurons, but is a better use-dependent blocker of transient Na+ current than phenytoin [286]. Furthermore, identifying compounds that can differentially modulate different subtypes/isoforms of sodium channels may contribute to identifying new treatment strategies for *SCN1A*-related epilepsy [287]. Baraban et al.[288] characterised zebrafish Nav1.1 (scn1Lab) mutants originally identified in a chemical mutagenesis screen using the optokinetic response as an assay [289]. The zebrafish scn1Lab gene shares a 77% identity with human *SCN1A* and is expressed in the central nervous system. Baraban et al. [288] demonstrated that mutants exhibit hyperactivity, including convulsive behaviour, spontaneous electrographic seizures, shortened lifespan and a pharmacological profile similar to the human condition. They then used the validated model in a novel high-throughput screening program to identify compounds that ameliorated the epilepsy phenotype. The strategy identified clemizole, a US Food and Drug Administration (FDA)-approved compound but not a licensed antiepileptic drug, as an effective inhibitor of spontaneous convulsive behaviour and electrographic seizures in these mutants. A recent study demonstrated that clemizole binds to serotonin receptors and its antiepileptic activity can be mimicked by drugs acting on serotonin signalling pathways; based on these findings, five patients with Dravet syndrome and drug-resistant epilepsy were treated with lorcaserin, a clinically-approved serotonin receptor agonist, with subsequent reductions in seizure frequency and/or severity [290].

Another example of serotonergic receptors modulation as a promising therapeutic target in Dravet Syndrome is fenfluramine [270,291]. This drug was initially developed as an appetite suppressant, but withdrawn from the market due to serious adverse effects, including valvular heart disease and pulmonary hypertension [292,293]. Fenfluramine has serotoninergic effects [294] but the exact anti-seizure mechanism has not been elucidated yet. Fenfluramine significantly reduced epileptiform dischardes in scn1Lab morphants in recent studies

[295,296]. Currently there are four ongoing clinical trials to evaluate the effectiveness and tolerability of this drug in Dravet Syndrome.

SCN1B-related epileptic encephalopathy

The *SCN1B* gene encodes the sodium channel beta1 subunit, which is an immunoglobulin-like protein that is non-covalently linked to a voltage-gated sodium channel alpha subunit [297]. Two cases with Dravet syndrome have been found to have homozygous *SCN1B* mutations so far, both with drug-resistant epilepy [298,299].

SCN2A-related epileptic encephalopathy

The *SCN2A* gene encodes the alpha2 subunit of the neuronal sodium channel, which is predominantly expressed in principal neurons of the hippocampus and cerebral cortex during early development [300]. *SCN2A* variants have been associated with epilepsy of infancy with migrating focal seizures or other severe epileptic encephalopathies, including Ohtahara syndrome (approximately 10% of individuals with Ohtahara syndrome have a *SCN2A* pathogenic variant) [301-304]. All *SCN2A*-associated disorders are known to be autosomal dominant in inheritance, and mutations associated with severe disease are often found to be *de novo* [304]. Sodium channel blockers have shown significant effectiveness in *SCN2A*-epileptic encephalopathies [303-306]. This represents a potential precision medicine treatment: the mechanism of the effect has not been elucidated yet, but, as might be expected, the effect seems mostly present in patients with gain-of-function mutations. Another hypothetical precision medicine treatment was recently reported in an anecdotal case with a *de novo SCN2A* splice site mutation associated with epileptic encephalopathy, early-onset global developmental delay, intermittent ataxia, autism, hypotonia, and cerebral/cerebellar atrophy. In the cerebrospinal fluid, both homovanillic acid and 5-hydroxyindoleacetic acid were significantly decreased; extensive biochemical and genetic investigations ruled out primary neurotransmitter deficiencies and other known inborn errors of metabolism. Treatment with oral 5-hydroxytryptophan, l-Dopa/Carbidopa, and a dopa agonist resulted in reduced seizure frequency and "some EEG improvement" (on a stable dose of valproate and ethosuximide), most likely via dopamine and serotonin receptor-activated signal transduction and modulation of glutamatergic, GABA-ergic and glycinergic neurotransmission [307]. Two other anectodal cases, with *SCN2A*-related early infantile epileptic encephalopathy and drug-resistant epilepsy, were treated with intravenous lidocaine and then transitioned to enteral mexiletine. This treatment led to improvement in seizure control in both cases: in one case seizure frequency decreased from more than 100 daily clinical events to two on average, with evidence of correlation of seizure control with mexiletine levels; in the other case seizures fell from daily to weekly frequency. Both lidocaine and mexiletine are classified as 1b antiarrhythmic drugs that block the fast activation of sodium channels in cardiac muscle; as they drugs cross the blood-brain barrier, a similar mechanism in neuronal circuits, may explain their potential effect on seizure control [308].

SCN8A-related epileptic encephalopathy

SCN8A encodes the voltage-dependent sodium channel Nav1.6, located in both inhibitory and excitatory neurons [309]. *SCN8A*-related epileptic encephalopathy is characterized by developmental delay, seizure onset in the first 18 months of life, and intractable epilepsy with multiple seizure types. Associated epilepsy syndromes can include Lennox-Gastaut, West, Dravet and Ohtahara. To date epileptic encephalopathy associated with a de novo *SCN8A* pathogenic variant has been reported in the literature in about 50 individuals (0.6-2.4% of cases with early infantile epileptic encephalopathy) [5,7,83,91,154,309-323]. In most tested cases, *SCN8A* mutations showed a gain-of-function effect [309,324]. Sudden unexpected death in epilepsy (SUDEP) has been reported in approximately 10% of published cases [310,312,318,319]. To reduce the risk of SUDEP, it is critical to improve seizure control. There is clinical evidence of a possible effective precision medicine approach in using sodium channel blockers to treat patients with *SCN8A*-related epilepsy; these drugs include phenytoin, carbamazepine, lacosamide, lamotrigine, rufinamide, and oxcarbazepine [319,322,325]. The effectiveness of sodium channel blockers is consistent with the activating effects of most *SCN8A* pathogenic variants [309,326,327]. Also valproate has been reported to be effective, possibly through modulation of sodium channel activity [309,319,326]. Most patients are maintained on multiple medications with incomplete seizure control. One study of four patients reported a positive response to high doses of phenytoin: all of them had been drug-resistant; three became seizure-free and one had dramatic reduction of seizure frequency and severity after the initiation of phenytoin treatment[322].

SETBP1-related epileptic encephalopathy

De novo dominant mutations of the SET binding protein 1 (*SETBP1*) gene are known to cause Schinzel-Giedion syndrome, a highly recognizable syndrome characterized by severe mental retardation, distinctive facial features, and multiple congenital malformations including skeletal abnormalities, genitourinary and renal malformations, and cardiac defects, as well as a higher-than-normal prevalence of tumours [328]. West syndrome has been reported in association with Schinzel-Giedion syndrome, with seizures being extremely resistant to treatment with antiepileptic drugs and ketogenic diet [329-331]. Only one patient was reported to be responsive (to phenobarbital), but no long-term follow-up is available [332], and one had hypsarrhythmia at the age of 7 months of age, which was temporarily controlled by ACTH treatment for five weeks [333].

SIK1-related epileptic encephalopathy

The *SIK1* gene encodes a member of the AMP kinase subfamily with several roles in the central nervous system including regulation of the circadian clock [334] and transcription of corticotropin-releasing hormone in the hypothalamus [335]. Six different de novo heterozygous *SIK1* mutations were found in six unrelated children with early myoclonic encephalopathy, infantile spasms or Ohtahara syndrome. All subjects had intractable seizures. None of the subjects with infantile spasms responded to ACTH [336].

SLC12A5-related epileptic encephalopathy

The *SLC12A5* gene encodes the neuronal potassium-chloride cotransporter 2 (KCC2) that is the major extruder of intracellular chloride in mature neurons, and is exclusively expressed in the central nervous system [337]. Compound heterozygous or homozygous missense mutations in the *SLC12A5* gene have been found in eight children from five unrelated families with epilepsy of infancy with migrating focal seizures. One of these patients had marked reduction in seizure frequency and no evidence of epileptiform activity on EEG following treatment with steroids (intravenous methylprednisolone for three consecutive days followed by oral prednisolone); further improvement of seizure control was achieved with the introduction of ketogenic diet and prednisolone was withdrawn, then tapering of the ketogenic diet was associated with a moderate rise in seizure frequency and the patient was on valproate and clobazam at the latest follow-up with ongoing seizures; the affected sibling did not respond to steroid treatment but had unspecified response to ketogenic diet; ketogenic diet was effective in one further unrelated case; one case had improvement of seizure control on a combination of phenobarbitone and topiramate; the combination of potassium bromide and high-dose phenobarbital was effective for two other cases; two patients had intractable seizures despite multiple antiepileptic drugs [337,338].

SLC13A5-related epileptic encephalopathy

The *SLC13A5* gene encodes a plasma membrane sodium-dependent citrate transporter [339]. In the brain, the transporter is expressed mostly in neurons. As astrocytes secrete citrate into extracellular medium, the potential function of SLC13A5 in neurons is to mediate the uptake of circulating citrate and astrocyte-released citrate for subsequent metabolism [340]. The phenotype of *SLC13A5*-related epileptic encephalopathy is characterised by seizure onset within the first weeks after birth, developmental delay, slow progression of motor function, significant impairment in language and speech development, fever sensitivity, early occurrence of status epilepticus (hemiconvulsive, convulsive and non-convulsive), defects in tooth development, and punctate white matter lesions on neonatal MRI (no longer visible at the age of 6 months, but lead to gliotic scarring visible on MRI at the age of 18 months) [341-344]. Three patients reportedly 'responded well' to ketogenic diet, although they had to stop the diet due to side effects or compliance issues, whilst four had seizure worsening or no benefit from the diet [342-344]. Epilepsy surgery was undertaken in one patient, without success [343]. Some improvement in response to drugs that affect GABA signaling, including including diazepam, lorazepam, phenobarbital, clonazepam, clobazam and midazolam, and sodium channel blockers, including phenytoin, lamotrigine and lidocaine, has been reported. However, phenytoin worsened myoclonus in one patient [343,344]. Acetazolamide decreases urinary citrate excretion by inducing metabolic acidosis [345], and this should increase citrate reabsorption by the renal NaDC1 transporter (SLC13A2) [346]: it was reported to improve seizure control without evidence of acidosis [343]. Recently biallelic *SLC13A5* mutations have been found to cause Kohlschütter–Tönz syndrome, a rare autosomal-recessive disease characterised by epileptic encephalopathy, developmental delay or regression and yellowish discolouration of the teeth due to amelogenesis imperfect [347].

SLC2A1-related epileptic encephalopathy

Glucose transport 1 (GLUT-1) deficiency is a genetic metabolic encephalopathy caused by a decrease in the transfer of glucose to the brain due to mutations in the glucose transporter 1 (*SLC2A1*) gene. GLUT-1 deficiency shows wide phenotypic pleiotropy, including delayed neurologic development, dysarthria, acquired microcephaly, complex movement disorder including ataxia, dystonia and chorea, and drug-resistant epilepsy, as antiepileptic drugs usually fail to control seizures [348]. Epilepsy syndromes include epilepsy with myoclonic-atonic seizures, caused by *SLC2A1* mutations in 5% cases [349], early-onset absence epilepsy [350], genetic generalized epilepsy [351], and more rarely West syndrome [352]. GLUT-1 deficiency syndrome represents an established example of the application of the precision medicine concept. The gold standard treatment is the ketogenic diet, which provides ketones as an alternative fuel for cerebral metabolism, thereby treating the symptoms of neuroglycopenia [353]. Early diagnosis and initiation of the ketogenic diet are crucial to improve brain metabolism and seizure control [354], although the benefit on neurodevelopment seems controversial [348]. Certain antiepileptic drugs may be relatively contraindicated as adjunctive treatment in children on the ketogenic diet, for example valproate may inhibit Glut1 transport and beta-oxidation of fatty acids [355].

SLC25A22-related epileptic encephalopathy

SLC25A22 encodes a mitochondrial glutamate/H+ symporter [356]. Mutations in this gene have been associated with early neonatal or infantile epileptic encephalopathy, including early myoclonic encephalopathy and Ohtahara syndrome [357-359], and epilepsy of infancy with migrating seizures [360]. Seizures were refractory to multiple antiepileptic drugs in all reported cases.

SLC35A2-related epileptic encephalopathy

The gene *SLC35A2* at Xp11.23 encodes the Golgi-localized Uridine diphosphate (UDP)-galactose transporter at Xp11.23. Mutation of this gene causes congenital disorders of glycosylation due to UDP-galactose deficiency in the endoplasmic reticulum-Golgi network, resulting in reduced galactosylation of glycoproteins, glycosphingolipids and proteoglycans [361]. Five females with an *SLC35A2* mutation, and two males with somatic mutation causing early-onset epileptic encephalopathy, have been reported so far [362-365]. The epilepsy is characterised by tonic partial seizures or epileptic spasms, initially. EEGs of all female patients showed hypsarrhythmia. Five patients were treated with ACTH: two had almost complete seizure remission; the other three patients had transient remission for several months or years, although seizures recurred thereafter. One patient achieved complete seizure remission after a second course of ACTH therapy, with subsequent improvement of development [362,364,365].

SLC6A1-related epileptic encephalopathy

The *SLC6A1* gene encodes one of the major GABA transporters in the brain, GAT-1, which removes GABA from the synaptic cleft [366]. Epilepsy with myoclonic-atonic seizures is caused by *SLC6A1* mutation in 4% of cases [367]. Evidence of some response is reported to a combination of clonazepam and valproate, or of levetiracetam, clonazepam, and

ethosuximide, for control of atonic seizures [367]. One patient was seizure free for 3.5 years on clobazam [367]. The ketogenic diet was effective in two cases [367,368].

SLC9A6-related epileptic encephalopathy

The *SLC9A6* gene, (also known as *NHE6*) on chromosome Xq26, encodes a monovalent sodium-selective sodium/hydrogen exchanger (NHE) that participates in a wide array of essential cellular processes, including control of intracellular pH, maintenance of cellular volume, and reabsorption of sodium across renal, intestinal, and other epithelia [369]. Mutations in *SLC9A6* cause Christianson syndrome, an X-linked neurodevelopmental and progressive mental retardation syndrome, characterized by microcephaly, impaired ocular movements, severe global developmental delay, developmental regression, hypotonia, abnormal movements, and early-onset seizures of variable types. Female carriers may be mildly affected [370,371]. Epilepsy phenotypes in Christianson syndrome include Lennox-Gastaut Syndrome and infantile spasms. No effective antiepileptic treatment has been described so far [371,372]. A spontaneous mutation in *Nhe1* was found in the slow-wave epilepsy mouse with a neurological syndrome including ataxia and a unique epilepsy phenotype consisting of 3/sec absence and tonic-clonic seizures; mutants showed selective neuronal death in the cerebellum and brainstem [373]. There are indicators from several experimental studies that NHE inhibitors could be of significant value as potential anticonvulsants [374].

SPTAN1-related epileptic encephalopathy

The *SPTAN1* gene encodes nonerythrocytic alpha-spectrin-1, which has been shown to be essential for proper axon myelination of both peripheral and central nervous systems, in zebrafish [375]. *SPTAN1* mutations have been report to cause epileptic encephalopathies, including West syndrome. Seizures were reported as refractory to various antiepileptic and hormonal therapies. In two patients, ACTH therapy was partially effective, and another patient partially responded to a ketogenic diet [376-379].

STX1B-related epileptic encephalopathy

The gene *STX1B* encodes one of the syntaxins (syntaxin 1B) that are cellular receptors for transport vesicles. STX1B is directly implicated in the process of calcium-dependent synaptic transmission in rat brain [380]. Mutations in *STX1B* cause fever-associated epilepsy syndromes with a remarkably wide phenotypic spectrum, ranging from simple febrile seizures to severe epileptic encephalopathies [381]. In particular, Schubert et al.[381] described two cases with STX1B mutation end epileptic encephalopathies: one with epilepsy with myoclonic-atonic seizures shifting to Lennox-Gastaut syndrome, with initially intractable seizures and then seizure-free at the age of 7 years on levetiracetam, stiripentol and a vagus nerve simulator; one with myoclonic-astatic epilepsy on monotherapy with valproate, with unknown seizure response. A further case with myoclonic-astatic epilepsy, showing good response to treatment with valproate, has been recently reported [382].

STXBP1-related epileptic encephalopathy

Heterozygous mutations in the syntaxin-binding protein 1, *STXBP1*, gene which encodes Munc18-1, a core component of the presynaptic membrane-fusion machinery, have been observed in patients with severe forms of early-onset epileptic encephalopathy [383-387].

STXBP1-related encephalopathy is characterized by early-onset refractory epilepsy with median age of onset of seizures of six weeks (range 1 day to 13 years) and moderate to severe intellectual disability. Epilepsy syndromes reported to be associated with *STXBP1* variants include: Ohtahara (approximately 30% of individuals with Ohtahara syndrome have a *STXBP1* pathogenic variant) [8,132,384,388-392], West (approximately 2% of individuals with West syndrome have a *STXBP1* pathogenic variant) [5,383,388,389,391,393-395], Lennox-Gastaut [5], Dravet syndrome without *SCN1A* mutation [108], and Rett (3 cases reported so far), either classic, not *MECP2*-related, or atypical Rett, not *CDKL5*-related syndromes[154,395,396].

The most commonly used antiepileptic drugs reported to have been used are phenobarbital, valproate, and vigabatrin [397]. Clobazam, zonisamide, lamotrigine, and oxcarbamazepine have also been used. In more than 20% of affected individuals, two or more antiepileptic drugs were used in combination. About 25% of affected individuals were reported to have drug-resistant epilepsy, whilst approximately 20% of affected individuals had seizures well controlled with one or more antiepileptic drugs [397]. In individuals who became seizure-free, antiepileptic drugs were discontinued between one month and 5.5 years after treatment began [393,396,398]. The longest seizure-free period documented following discontinuation of antiepileptic drugs was approximately 11 years [393]. In single cases, a response to vigabatrin, carbamazepine, phenobarbital, or valproate and levetiracetam, has been reported [387,389,393,394,396,399-404]. The ketogenic diet was used in about 1% of affected individuals, with slight or no response [389,405]. Two cases were reported to have had surgical treatment of the epilepsy: one became seizure-free following corpus callosotomy (Otsuka et al 2010); the other had a significant reduction in seizure frequency following resection of focal cortical dysplasia [389].

ST3GAL3-related epileptic encephalopathy

The *ST3GAL3* gene encodes encodes a sialyltransferase involved in the biosynthesis of sialyl-Lewis epitopes on cell surface–expressed glycoproteins. These glycoproteins form the glycocalyx, composed of sialic acids that act as key determinants of a variety of cellular recognition and communication processes [406]. In four members of a consanguineous Palestinian family with early infantile epileptic encephalopathy, a homozygous mutation in the *ST3GAL3* gene was identified. The patients had West syndrome that evolved to Lennox-Gastaut syndrome with severe intellectual disability. The authors report that only vigabatrin was effective (with "rare seizures") in three of the four cases [407].

SYNGAP1-related epileptic encephalopathy

The *SYNGAP1* gene encodes a brain-specific synaptic Ras GTP-ase activating protein that is largely localized to dendritic spines in neocortical pyramidal neurons and is critical for cognition and synapse function [408]. *Syngap1* haploinsufficiency disrupts the excitatory/inhibitory balance in the developing hippocampus and cortex and results in accelerated glutamatergic synapse maturation [409]. *SYNGAP-1* mutations are associated with a broad phenotypic spectrum, including epileptic encephalopathies, autism and intellectual disability [5,7,408,410-412]. A literature overview by von Stülpnagel et al.[411] showed that good seizure control was achieved with valproate and topiramate in previously reported patients with epilepsy associated with *SYNGAP1* mutations, although not all the patients had epileptic encephalopathies. A more recent study described 16 unrelated individuals with loss-of-function *SYNGAP1* mutations and epileptic encephalopathy; the epilepsy responded to a single antiepileptic drug, mostly valproate, in seven patients and was pharmacoresistant in nine [412].

TBC1D24-related epileptic encephalopathy

The *TBC1D24* gene encodes a member of the Tre2-Bub2-Cdc16 (TBC) domain-containing RAB-specific GTPase-activating proteins, and is involved in regulation of synaptic vesicle trafficking and in brain and somatic development [413]. *TBC1D24*-related epilepsy comprises a wide phenotypic spectrum that includes early-infantile epileptic encephalopathy [414]. Early-onset progressive myoclonic epilepsy with dystonia and epilepsy of infancy with migrating focal seizures have also been reported [415-417]. All cases with early-infantile epileptic encephalopathy due to mutations in *TBC1D24* described so far were drug-resistant, and no specific antiepileptic drugs have emerged as being effective [414].

TCF4-related epileptic encephalopathy

TCF4 is a broadly expressed basic helix-loop-helix (bHLH) protein that functions as a homodimer or as a heterodimer with other bHLH proteins. Mutations in the *TCF4* gene are known to cause Pitt-Hopkins syndrome, characterized by an intellectual disability, epilepsy, abnormal breathing patterns, short stature, microcephaly, and a specific facial gestalt, including deep-set eyes, a broad nasal base and a wide mouth with a tented upper lip [418]. It has been suggested that missense mutations are associated with higher seizure frequency [419], but a definite genotype-phenotype correlation has not been defined [420]. A recent cross-sectional study of 101 individuals with a molecularly-confirmed diagnosis of Pitt-Hopkins syndrome included 38 cases with epilepsy. Of these, 24 participants were on antiepileptic drugs, mostly valproate, levetiracetam, lamitrigine and carbamazepine, or combinations of these. There was no specific medication that was more successful in decreasing seizures than other medications. Seizures remained drug-resistant in some participants, but in most cases antiepileptic treatment was successful, with 23.7% of patients who were seizure-free. Lennox-Gastaut syndrome has been mentioned once as the epilepsy phenotype [421].

WWOX-related epileptic encephalopathy

The *WWOX* gene is a putative tumor suppressor, located at the second most fragile site of the human genome, known as FRA16D. Mutations of the *WWOX* gene have been associated with tumorigenesis [422]. The expression of WWOX protein in the developing brain and spinal cord in the embryo and newborn mice together with histological findings (many vacuoles in the hippocampus and amygdala) show a convincing evidence of its role in neural development [423]. Early-onset epileptic encephalopathies, including West syndrome, have been associated with *WWOX* mutations [424,425]. Seizures were partially controlled on a combination of valproate and lamotrigine in the siblings reported by Abdel-Salam et al.[424]. Five patients were reported by Mignot et al.[425]: all had pharmacoresistant focal or multifocal seizures, with some of them having also experienced generalised seizures. One patient had West syndrome. Seizures 'partially responded' to valproate, vigabatrin, high doses of hydrocortisone and clobazam in a case diagnosed retrospectively after death [426]. Another case with *WWOX*-related epileptic encephalopathy has been reported to show 'partial response' to antiepileptic medications including phenobarbitone, clobazam and topiramate [427].

Cases with single reports or less clear evidence

The *COL4A1* gene encodes the alpha-1 subunit of collagen type IV. Type IV collagen does not form ordered fibrillar structures; rather, a meshwork is formed by four molecules held together at the ends. Disorders related to *COL4A1* mutations are considered a systemic disease, including a broad spectrum of cerebrovascular lesions (porencephaly and transmantle lesions, causing hydranencephaly or schizencephaly), and also lesions of the kidneys, eyes, heart, and skeletal muscles [428]. Seizures are often reported as part of the clinical spectrum of *COL4A1* mutation and may not be only secondary to cerebravacular lesions [429]. Recently, Hino-Fukuyo et al.[430] reported a child with an epileptic encephalopathy (without cerebrovascular lesions on neuroimaging) and carrying a de novo *COL4A1* mutation, who became seizure-free after a functional hemispherectomy.

The *ERBB4* gene is a member of the epidermal growth factor receptor (EGFR) family of tyrosine kinase receptors and plays a crucial role in numerous neurobiological processes in the developing and adult brain [431]. A *de novo* reciprocal translocation, disrupting the *ERBB4* gene, was found in a case with early myoclonic encephalopathy, with seizures refractory to antiepileptic treatment [432]. Neuregulin 1 (NRG1) is a member of a family of neurotrophic factors that acts by activating the tyrosine kinase of ErbB receptors, including ErbB4 [433]. Li et al. [434] identified the Kv1.1 subfamily of voltage-gated potassium channels as a new molecular target of NRG1-ErbB4 signaling in the regulation of interneuronal excitability and revealed that NRG1-ErbB4-Kv1.1 signaling may be involved in the pathophysiology of epilepsy, suggesting that ErbB4 might be targeted to attain antiseizure effects in the epilepsies broadly.

The *FLNA* gene encodes filamin A, a widely expressed actin-binding protein that regulates reorganization of the actin cytoskeleton by interacting with integrins, transmembrane receptor complexes, and second messengers. Filamins crosslink actin filaments into orthogonal networks in the cytoplasm and participate in the anchoring of membrane proteins to the actin cytoskeleton. *FLNA* mutations can cause X-linked dominant periventricular heterotopia, a disorder in which many neurons fail to migrate to the cerebral cortex and persist as nodules

lining the ventricular surface. Heterozygous females with the disorder present with epilepsy and other signs, including patent ductus arteriosus and coagulopathy, whereas hemizygous affected males usually die embryonically [435]. Cases with *FLNA* mutations and epileptic encephalopathies have been reported [5,436]; of these one did not have evidence of cortical malformations on neuroimaging [5].

The *GPHN* gene encodes gephyrin, an organizational protein that clusters and localizes the inhibitory glycine and GABA receptors to the microtubular matrix of the neuronal postsynaptic membrane [437]. A *GPHN* de novo missense mutation has been reported in a patient with epileptic encephalopathy resembling Dravet syndrome. Phenobarbital was ineffective, but seizures were eventually controlled by carbamazepine. Every attempt to stop or reduce the medication led to seizure recurrence. The missense mutation was shown to abolish both postsynaptic clustering with subsequent impairment of GABAergic synapse function, and synthesis of the molybdenum cofactor, which is vital for the function of molybdo-enzymes, without affecting the structure and folding of the protein [438].

The *MAGI2* encodes a synaptic scaffolding protein which is essential for development and maintenance of synapses, including receptor endocytosis and postendocytotic trafficking. MAGI2-dependent endocytosis is also essential for ciliogenesis [439]. Marshall et al.[440] described a deletion of the *MAGI2* gene in 15 of 16 patients with infantile spasms. However more recent studies suggest that *MAGI2* mutations are not common causes of infantile spasms [5,441,442].

Hemimegalencephaly is a rare congenital malformation of the brain characterized by overgrowth of one hemisphere [443]. It has variable presentation ranging from focal seizures to epileptic encephalopathy, hemideficits, and mental retardation. The mechanistic target of rapamycin (MTOR) is a highly conserved protein kinase that is found in two structurally and functionally distinct protein complexes: TOR complex-1 (TORC1) and TORC2. The mTOR signaling cascade regulates processes involved in cell growth and homeostasis in response to many metabolic cues. Mutations of *MTOR* have been associated with a spectrum of brain overgrowth phenotypes including hemimegalencephaly [444]. Surgery is usually the treatment of choice in hemimegalencephaly [445], however targeted treatment with inhibitors of the MTOR pathway may become an alternative option in the future.

The *NECAP1* gene encodes an accessory protein involved in clathrin-mediated endocytosis in synapses. To date, only one consanguineous Saudi Arabian family, with six members who had early infantile epileptic encephalopathy (Ohtahara syndrome), has been reported. All affected subjects developed intractable seizures in early infancy [446].

NEDD4L encodes an E3 ubiquitin ligase that regulates channel internalization and turnover. It appears to have roles in regulating various respiratory, cardiovascular, renal, and neuronal functions [447]. Only one case of early-onset epileptic encephalopathy due to *NEDD4L* mutation has been reported so far, with onset of infantile spasms at the age of five months. The spasms settled by 25 months, but focal seizures continued despite multiple trials of treatment [5].

The gene *NRXN1* encodes neurexin 1, one of the cell-surface receptors that bind neuroligins to form a calcium-dependent neurexin/neuroligin complex at synapses in the central nervous system. This trans-synaptic complex is required for efficient neurotransmission and is involved in the formation of synaptic contacts [448]. Cases of epileptic encephalopathy

associated with *NRXN1* mutations have been reported, although the epilepsy phenotype is not well characterised yet [449,450].

Conclusions

Growth in gene discovery has radically changed our understanding of epileptic encephalopathies. As more and more genes have been associated with various electroclinical syndromes, such as West syndrome, Dravet syndrome, Ohtahara syndrome, and others, it will hopefully become possible to move towards treatment focused on the underlying genetic aetiology and resultant pathophysiology. The picture is certainly complex, with genotypic and phenotypic heterogeneity, and is compounded by a degree of lack of detail, often inevitable in retrospective case reports, in specification of the drug response in many published reports. Also, we note that classification of the epilepsy syndromes was variable, and not always specified in the original references. Aspects of phenotypic classification are beyond the scope of this review, and we specifically did not attempt to re-interpret or interpolate phenotypes. We therefore described epilepsy and seizure types as reported in the original articles, without attempting to re-classify epilepsy syndromes. Treatment remains challenging in most cases, but the available evidence may provide some guidance for treatment: for example, ACTH seems to be effective in controlling infantile spasms in a number of genetic epileptic encephalopathies, irrespective of the actual genetic cause, raising some questions about the precision medicine concept. This may be a biased view as ACTH is one of the few agents employed in the treatment of infantile spasms – more research is needed.

Understanding the effect of the mutation is probably crucial for targeted treatment. In epileptic encephalopathies, there is a broad range of disease mechanisms including channelopathies, synaptic dysfunction, transporter defects, transcriptional dysregulation, impaired DNA repair and chromatin remodeling and metabolic defects. Moreover, in many cases the underlying neurobiological complexity cannot be entirely defined [2]. For this reason, we are still far from systematic application of targeted treatments in epilepsy. Furthermore, it is important to note that in many epileptic encephalopathies non-pharmacological interventions may also prove helpful; these may include physical management, monitoring, and prevention of secondary complications (e.g. for Dravet Syndrome; [263,451]). Co-morbidities are often present and need to be taken in account when pharmacological treatment is chosen. Dysfunctional genetic pathways can indeed affect multiple organs and treatment should therefore be considered for the entire phenotype.

A systems-level approach based on gene co-expression network analysis has suggested functional disruption of a co-expression network of 320 genes, via gene mutation or altered expression, as a convergent mechanism regulating susceptibility to epilepsy broadly. Valproate was predicted to preferentially restore the downregulation of the network in epilepsy toward health [452]. As showed in this review, valproate is not effective in many epileptic encephalopathies. However, systems biology may expand the application of targeted treatments in epilepsy.

Gene therapy represents a further potentially promising treatment for drug-resistant epilepsy, but there are still several challenges to face, including the validation of experimental models

of human pharmacoresistant epilepsy, establishment of sensitive and specific measures of therapeutic efficacy, and evaluation of the long-term safety [453]. There is, however, accumulating evidence that treating severe epilepsies based on the genetic aetiology could dramatically transform clinical care and prognosis.

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