Developmental and epileptic encephalopathies

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Abstract

Developmental and epileptic encephalopathies (DEEs), the most severe group of epilepsies, are characterised by seizures and frequent epileptiform activity associated with developmental slowing or regression. Onset typically occurs in infancy or childhood and includes many well-defined epilepsy syndromes. Patients have wide-ranging comorbidities including intellectual disability, psychiatric features, such as autism spectrum disorder and behavioural problems, movement and musculoskeletal disorders, gastrointestinal and sleep problems, together with an increased mortality rate. Problems change with age and patients require substantial support throughout life, placing a high psychosocial burden on parents, carers and the community. In many patients, the aetiology can be identified, and a genetic cause is found in >50% of patients using next generation sequencing technologies. More than 900 genes have been identified as monogenic causes of DEEs and many cell components and processes have been implicated in their pathophysiology, including ion channels and transporters, synaptic proteins, cell signalling and metabolism and epigenetic regulation. Polygenic risk score analyses show that common variants also contribute to phenotypic variability. Holistic management, which encompasses antiseizure therapies and care for multimorbidities, is determined both by epilepsy syndrome and aetiology. Identification of the underlying aetiology enables the development of precision medicines to improve the long-term outcome of patients with these devastating diseases.

[H1] Introduction

Developmental and epileptic encephalopathies (DEEs) are the most severe group of epilepsies, with seizure onset typically occurring in infancy or childhood. A DEE is a complex concept that incorporates two facets: a developmental encephalopathy, which usually leads to intellectual disability, coupled with an epileptic encephalopathy. The International League Against Epilepsy's (ILAE) definition of an epileptic encephalopathy is that the epileptic activity itself contributes to severe cognitive and, sometimes, behavioural impairment, beyond what might be expected from the underlying pathology alone, and that these can worsen over time[1]. Most, but not all, patients with an epileptic encephalopathy have frequent seizures, often with multiple seizure types (Figure 1). An essential feature of an epileptic encephalopathy is that there is slowing or regression in development, cognition or behaviour associated with frequent epileptiform activity on the electroencephalogram (EEG). Diagnosis of an epileptic encephalopathy is crucial because there may be therapeutic strategies that improve this epileptiform activity, thereby enabling the patient to make developmental gains.

In 2017, the ILAE expanded this concept to a 'developmental and epileptic encephalopathy', owing to a growing recognition that the aetiology, whether genetic, structural or otherwise, often causes developmental impairment in its own right[2]. Thus, the aetiology results in delayed development, either from birth or thereafter, before epileptiform activity appears on the EEG, as in the prototypic DEE, Dravet syndrome. The epileptic encephalopathy is then superimposed on the developmental encephalopathy, further adversely affecting the child's development. By contrast, it is often impossible to separate the developmental encephalopathy from the epileptic encephalopathy aspects of a neonatal-onset DEE as both components affect the same period in development (Box 1). A DEE should be distinguished from a static developmental encephalopathy (typically resulting in intellectual disability) with epilepsy, in which the developmental encephalopathy alone (that is, not the epilepsy) causes developmental impairment[3] .

The DEEs are classified according to epilepsy syndrome, defined as a distinctive cluster of clinical and EEG features, often associated with aetiological findings[4], however, not all patients can be classified with a known syndrome (Figure 2). One of the best examples is Lennox-Gastaut syndrome (LGS), defined in 1945 on the basis of tonic and atypical absence seizures, intellectual disability and slow spike-wave on EEG[5, 6]. In 2022, LGS was defined by the ILAE for the first time, with the additional EEG feature of generalized paroxysmal fast activity in sleep[7]. LGS is highly aetiologically heterogeneous, with both acquired and genetic aetiologies, with or without a structural correlate. From an aetiological perspective, LGS mirrors the heterogeneous aetiologies of the DEEs more broadly.

In this Primer, we discuss the epidemiology, pathophysiological mechanisms, diagnosis and management of the DEEs. We review the effects of these devastating diseases on patients' quality of life and the tantalising promise of precision medicine to improve outcomes.

[H1] Epidemiology

The considerable individual and societal impact of DEEs is best understood in the context of their epidemiology, which provides essential information to prioritise clinical, educational, social, financial and research resources[3, 8-10]. Studies differ in recruitment methodology, epilepsy syndrome, aetiological classification, age range, cohort size and specific population, and whether they are prospective or retrospective. Despite these differences, consensus is emerging on the incidence and prevalence of the more common syndromes. DEEs typically present in childhood, before the age of 16 years, with a study from 2023 not identifying any presentations between 9 and 16 years[3]. DEEs are distinguished from epilepsies in adults and children with static intellectual disability, and epilepsies associated with progressive intellectual and neurological deterioration in which older patients of normal intellect develop cognitive, neurological or psychiatric impairment due to the underlying aetiology, which may

be associated with an epileptic encephalopathy (for example, progressive myoclonus epilepsies such as Lafora disease)[11].

In Wellington, New Zealand, the cumulative incidence of DEEs with onset up to age 16 years has been estimated at 169 in 100,000 (95% CI 144-199) or 1 in 590 children, based on EEG ascertainment[3]. Age-specific incidence varies through childhood with ~75% of cases beginning under 3 years of age, with a cumulative incidence estimated at 122 in 100,000 children (95% CI 102-146) in a retrospective study in Wellington[3]. In comparison, the estimated incidence of all epilepsies presenting under 3 years was 239 in 100,000 (95% CI 216-263) in a prospective study in Scotland, UK, with DEEs accounting for 86.1 in 100,000 (95% CI 72.7-101.3) children[9]. These studies differed in duration and size of birth cohort, but both used EEG records in their recruitment strategy.

Incidence estimates have been reported for many DEE syndromes; however, around one-third of patients cannot be classified as having a specific syndrome[3, 9]. Table 1 lists the incidence estimates for the more common DEE syndromes; all studies were performed in high-resource settings. The global incidence of these syndromes is not known as access to the required specialised care and investigations is limited in resource-restricted settings. The most common DEE syndrome is Infantile Epileptic Spasms Syndrome (IESS) with an incidence of 30.7 in 100,000 individuals (95% CI 22.9-40.2) to 48.9 in 100,000 individuals (95% CI 37.0-64.7); ~27% of IESS have a structural aetiology[3, 9]. The most common structural aetiologies in people with DEEs can be divided into antenatal, perinatal or infantile acquired brain lesions and genetically determined malformations of cortical development (Box 2). IESS and LGS are defined by their seizure types and EEG features, and have multiple aetiologies, whereas Dravet syndrome is defined by electroclinical features, supported by a *SCN1A* pathogenic variant in 90% of cases[10, 12]. In addition to enabling precision diagnosis, identifying the aetiology of DEE syndromes informs targeted management and genetic counselling, and underpins the development of precision therapies.

The aetiologies of DEEs vary around the world, with most studies undertaken in high-resource settings. Genetic studies currently identify the aetiology in ~50% of patients, including *de novo*, recessive, and X-linked pathogenic variants. The incidence of syndromes associated with *de novo* genetic variants is likely to be similar around the world[13]; whereas, recessive causes occur more frequently in populations with high rates of consanguinity[14]. In resource-restricted regions, the incidence of acquired antenatal, perinatal and early infantile structural brain injury is increased[15, 16].

Patients with DEEs have an increased mortality risk related to their seizures and comorbidities. The primary cause of death is sudden unexpected death in epilepsy (SUDEP)[17]; other causes include cerebral oedema following status epilepticus[18], chest infections and accidental causes[19]. The established mortality rate for Dravet syndrome is that 17% of patients die by age 20 years[20]. SUDEP rates for different genetic DEE syndromes have not been well defined, with the exception of Dravet syndrome, which has a Dravet-specific SUDEP rate of 4.4 in 1000 person-years (98% CI 2.3-7.8)[19], accounting for most of the Dravet-specific mortality. Although cardiac dysfunction as evidenced by altered heart rate variability has been shown in Dravet syndrome, there is no definite evidence that the high SUDEP rate has a cardiac basis[21]. Different genetic DEEs vary considerably in their SUDEP risk, which is increased in DEEs due to sodium channelopathies[19]. Patients with DEEs with seizure onset in early infancy have an even higher mortality rate with 50% dying by age 2 years[7, 8].

[H1] Mechanisms/pathophysiology

From the first identification of epilepsy genes, *CHRNA4, KCNQ2* and *SCN1B* using family studies in the 1990s, genetic discoveries have shed light on disease mechanisms[22-25]. With >1000 genes now implicated as a monogenic cause of epilepsy in the Genes4Epilepsy database (http://github.com/bahlolab/genes4epilepsy)[26], the diverse functions of these genes highlight a vast array of biological processes that interact at cellular, organ and network levels. In this section, we discuss

common disease mechanisms (Supplementary Table 1), with attention to inheritance patterns, loss or gain of protein function and phenotypic features, all of which underpin the development of precision therapies.

[H2] Channelopathies

Genes encoding voltage-gated or ligand-gated ion channels were the first genes identified in the pathophysiology of DEEs and remain the largest class today. They include voltage-gated sodium, potassium, and calcium channels; Gamma-aminobutyric acid (GABA) receptor subunits; and ligand-gated glutamate (AMPA and NMDA) receptors. Genes encoding transporters of GABA, glutamate, glucose, and ions are also implicated in DEE causation.

The most studied epilepsy gene is *SCN1A*, which encodes $Na_v1.1$, the alpha 1 subunit of the voltage-gated sodium channel (Supplementary Table 1). Loss-of-function (LOF) missense or truncating variants cause Dravet syndrome, the prototypic DEE[13, 27], and also the non-DEE syndrome of Genetic Epilepsy with Febrile Seizures Plus (GEFS+)[28]. *SCN1A* LOF particularly affects inhibitory interneurons, leading to impaired inhibition and epileptogenesis[29, 30], with early ataxia and later crouch gait in Dravet syndrome likely due to involvement of cerebellar Purkinje neurons[31]. Recently, a new type of Early Infantile DEE (EIDEE) was identified that is caused by gain of function (GOF) *SCN1A* pathogenic variants with onset by three months[32, 33]. In this profound *SCN1A* EIDEE, epileptic spasms, tonic seizures, hyperkinetic movement disorder and arthrogryposis may occur in addition to the characteristic convulsive seizure types of Dravet syndrome, hemiclonic and tonic-clonic seizures. Understanding the functional consequences of the *SCN1A* pathogenic variant informs management, as some sodium channel blocker (SCB) antiseizure medications (ASMs) may exacerbate seizures in Dravet syndrome, whereas patients with the non-Dravet, EIDEE phenotype due to GOF variants may respond to SCB, such as carbamazepine and phenytoin (Supplementary Table 1).

Pathogenic variants in *SCN2A*, *SCN8A* and *SCN3A*, each encoding a sodium channel alpha subunit, cause DEEs with different phenotypes associated with GOF and LOF variants. Seizure onset under age 3 months in *SCN2A* DEEs and 6 months in *SCN8A* DEEs, is associated with GOF[34, 35], and SCBs are efficacious in these phenotypes[34]. Some GOF and LOF variants also cause self-limited infantile-onset seizures, which are critical to distinguish from EIDEEs. Intriguingly, 75% of patients with *SCN3A* GOF variants have a malformation of cortical development (MCD), such as polymicrogyria[36, 37]. MCD are disorders of disrupted brain development resulting in abnormal cortex formation including sulcation and gyration that can be focal or involve an entire hemisphere. MCDs may result in abnormal brain size and are due to range of aetiologies including vascular, infectious, metabolic and genetic causes[38]. The association of *SCN3A* pathogenic variants with MCD[37], therefore, reflects a key role for sodium conductance in cortical progenitors, which affects cortical gyration during early brain development[39]. Taken together, genetic DEEs may cause structural changes, such as MCDs, reinforcing that a genetic aetiology should be sought for MCDs which are often associated with a DEE[40, 41].

Voltage-gated potassium channelopathies are an important cause of DEEs. LOF *de novo KCNQ2* variants cause neonatal-onset EIDEE[42], whereas inherited variants result in self-limited seizures[10]. *KCNQ2* EIDEE typically causes severe to profound impairment, despite seizures remitting in early life in >50% of patients[10, 42]. Seizures often respond to SCBs[43]. Trials of precision therapy with KCNQ channel openers, such as retigabine or ezogabine, were complicated by aberrant skin and eye pigmentation in a small number of patients; modified compounds are in development[44,45-47]. Conversely, GOF *KCNQ2* DEEs include IESS associated with a recurrent GOF variant with severe outcome[48]. An intermediate non-DEE GOF group exists with mild to severe intellectual disability and seizures in some patients[49]. *KCNQ3* pathogenic variants are also a rare cause of DEE[50]. KCNQ3 and KCNQ2 form the heterotetrameric M-channel, which is important in regulating neuronal excitability, with loss of function, therefore, predisposing to epileptic seizures.

GOF and mixed GOF/LOF variants in *KCNA2*, which encodes the $K_v1.2$ channel subunit, are associated with DEEs[51]. The use of 4-aminopyridine, a K_v1 blocker, in patients with GOF variants improved seizures,

ataxia, cognition and speech[52]. LOF variants in *KCNA1*, encoding the $K_v1.1$ channel subunit and typically associated with episodic ataxia type 1[53], are rarely associated with DEEs[54, 55].

Heterozygous *de novo* pathogenic variants in *KCNT1*, encoding a sodium-activated potassium channel, cause a spectrum of DEEs from Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) to sleep-related hypermotor epilepsy (SHE)[56, 57]. Functional studies show a range of GOFs due to increased potassium current amplitude, correlating with phenotypic severity[56, 58]. There is cell-type specific vulnerability in inhibitory neurons, where GOF leads to decreased firing and, therefore, a loss of inhibition[59]. Initial hopes of precision therapy with quinidine, a non-specific potassium channel blocker, have not been fulfilled[60, 61].

Calcium signalling is integral to key processes in early brain development, including synapse formation, neurotransmitter release, cell signalling and mitochondrial function. Pathogenic variants in voltage-gated calcium channel subunit genes cause DEEs. *CACNA1A* encodes $Ca_v1.1$, a subunit of the voltage-activated calcium channel intrinsic to synaptic neurotransmission. GOF variants cause DEEs with status epilepticus, alternating focal seizures, paroxysmal hemiplegia, neonatal jitteriness, ataxia and movement disorder[62, 63]. LGS may occur with GOF and LOF *CACNA1A* variants[64, 65]. Thus, it is difficult to predict functional effect based on phenotype, and functional characterisation of variants or use of *in silico* tools is required[66]. GOF variants in *CACNA1E* and recessive LOF *CACNA1B* variants are associated with severe DEEs with dyskinesias[67, 68].

Dysfunction of many GABA receptor subunit genes cause DEEs, as GABA is the principal inhibitory neurotransmitter in the brain. LOF variants in *GABRA1*, *GABRA2, GABRB2* and *GABRB3,* which encode $GABA_A$ subunits, lead to decreased neuronal inhibition resulting in many DEE phenotypes[64, 69-72]. GOF and LOF *GABRB3* variants cause distinct DEE phenotypes with seizure onset under 6 months in GOF and after one year in LOF groups[73]. GOF phenotypes include hypersensitivity to vigabatrin, a GABA transaminase inhibitor that leads to increased GABA availability at the synapse, with functional testing showing increased receptor sensitivity[74]. GOF variants in *GABRB2* cause a severe DEE phenotype, with LOF variants leading to GEFS+ or later onset epilepsies[72]. GOF variants were also identified in *GABRD* which encodes an extra-synaptic GABA receptor subunit[75]. Fast inhibition in the brain is due to release of GABA onto post synaptic $GABA_A$ receptors (phasic inhibition). However, disrupted tonic inhibition, a slower form of signalling due to activation of extrasynaptic $GABA_A$ receptors by GABA in the synaptic cleft, is emerging as a key disease process in DEE. Pathogenic variants in *SLC6A1* which encodes GABA transporter 1 (hGAT-1), responsible for clearing GABA from the synaptic cleft, also lead to activation of extra-synaptic GABA receptors and increased tonic inhibition, resulting in epilepsy with myoclonic-atonic seizures[76]. "Tonic GABApathy" has been suggested as the common disease mechanism underlying extrasynaptic GABA receptor DEEs[77]. An interesting corollary is seen in Angelman syndrome which results from *UBE3A* dysfunction, in which decreased GABA uptake results in reduced tonic inhibition leading to a myoclonic DEE with ataxia[78].

Ionotropic glutamate receptors are the major conduit of fast excitatory transmission in the brain and include NMDA and AMPA receptors. LOF and GOF variants in *GRIA2,* encoding the GluA2 subunit of the AMPA receptor, cause DEEs such as IESS[79]. NMDA receptors (NMDARs) are largely post-synaptic and co-activated by glutamate/glycine and depolarisation of the post-synaptic membrane, enabling influx of calcium ions involved in regulation of processes key to encoding neuronal activity and, therefore, learning and memory[80]. Pathogenic variants in *GRIN1,* encoding GluN1, causes both dominant and recessive DEEs, highlighting the importance of considering both inheritance patterns when a variant of interest is identified. *De novo* heterozygous missense variants cause a neonatal DEE with a hyperkinetic movement disorder, stereotypies and oculogyric crises[64, 81]; whereas, truncating heterozygous variants do not cause disease. Autosomal recessive null and missense variants lead to a more severe phenotype with increased mortality[81, 82]. Both GOF and LOF variants cause a dominant negative effect on other channel subunits[81]. Extensive diffuse polymicrogyria can be seen. Variants affecting GluN2B, encoded by *GRIN2B,* cause intellectual disability and/or autism spectrum disorder (ASD) in all patients with a range of DEEs, including IESS[83, 84], and a hyperkinetic movement disorder. MCDs occur in some

individuals with *GRIN2B* and *GRIN1* pathogenic variants[85], highlighting that NMDA receptors are involved in early brain development beyond neurotransmitter signalling. Functional characterisation of *GRIN2B* variants shows complex effects[86]. Variants in *GRIN2D* cause infantile-onset DEE[87], whereas *GRIN2A* variants cause DEEs with onset from infancy to childhood, particularly Developmental and/or Epileptic Encephalopathy with spike-wave activation in sleep (D/EE-SWAS)[83, 88] and a speech disorder[88]. For GOF variants in *GRIN1*, *GRIN2A* and *GRIN2D*, there are limited reports of success using the precision medicine memantine, an NMDAR blocker[89]. For null variants in *GRIN2B* and *GRIN2A*, an n-of-1 trial (single-patient crossover study)[90] of L-serine, an essential amino acid which is a co-agonist of NMDA receptors, was effective for seizures in 4 of 9 patients, but caused behavioural deterioration in a child with a GOF variant that was inadvertently treated[91, 92]. A recent Phase 2A trial in 24 children with LOF *GRIN* variants showed substantial improvements in motor function and improved seizures in one patient[92].

Several ion or solute transporters have been implicated in DEEs. Heterozygous LOF variants in *SLC2A1* encoding GLUT1, the major glucose transporter at the blood-brain barrier, cause early onset absence epilepsy, ataxia, epilepsy with myoclonic-atonic seizures, and exercise-induced dyskinesia[93]. Others include Na^+,K^+-ATPase transporters (subunits encoded by *ATP1A2* and *ATP1A3*)[94]; stretch-activated ion channels *TMEM63B*[95] and GABA transporter hGAT-1 (*SLC6A1*), and EAAT2 glutamate transporter (*SLC1A2*)[96].

Understanding whether a variant in a gene encoding a subunit of an ion channel, receptor or transporter leads to LOF or GOF directs treatment selection, both with ASMs and emerging specific treatments, such as small molecules and antisense oligonucleotides. An overall GOF in an ion channel may, however, reflect several complex biophysical changes, such as altered voltage dependence of channel activation or inactivation, changes in rates of fast or slow inactivation, rates of recovery from inactivation and channel opening probability. Moreover, the mechanisms of channel or receptor dysfunction are likely to be even more complex due to differing temporal, age-dependent, regional and cell-type dependent isoform expression patterns, effects of other subunit genes and acute and chronic compensatory changes in other channels which may be helpful or harmful to brain function. For example, an antisense oligonucleotide which down-regulates *SCN8A* ameliorates seizures and survival in mice with *Scn1a* or *Kcnq2* LOF, or *Scn8a* GOF variants[97].

[H2] Synaptopathies

There are more than 200 proteins in the synaptome[98], comprising pre-synaptic and post-synaptic membranes, synaptic vesicle machinery and associated supporting matrix and glial cell components, with many implicated in DEEs (Figure 3). The SNARE (Soluble NSF Attachment Protein Receptor) complex is responsible for synaptic vesicle formation, fusion and recycling, and neurotransmitter release into the synaptic cleft. "SNAREopathies"[99] cause DEEs, often accompanied by movement disorders[100-104], due to pathogenic variants in genes including *STXBP1*, *SNAP2, VAMP2*, *DNM1*, and *CPLX1,* disrupting the pre-synaptic complex (Supplementary Table 1). Autosomal recessive LOF variants in *TBC1D24,* encoding a GTPase-activating protein essential for synaptic vesicle trafficking[105], lead to DEEs with myoclonic seizures and EIMFS, with dystonia[106].

Disruption of the post-synaptic density, a massive assembly of cell adhesion molecules, scaffolding proteins, signalling molecules and cytoskeletal components at excitatory glutamatergic synapses, also results in DEEs. *SYNGAP1* encodes a major downstream component of the NMDA receptor signalling complex that interacts with small GTPases and other signalling proteins. SYNGAP1 influences synaptic transmission, AMPA receptor density and the morphology and plasticity of dendritic spines[107]. Pathogenic variants in *SYNGAP1* cause a generalised DEE with myoclonic-atonic seizures, absence with eyelid myoclonia, eating-induced reflex seizures and photosensitivity[108-110].

IQSEC2, a guanine nucleotide exchange factor that interacts with ARF6 and other GTPases, regulates AMPA receptor trafficking and, therefore, synaptic plasticity[111]. *IQSEC2* is associated with DEEs; males are more severely affected than females with *de novo* pathogenic variants[64, 111, 112].

Finally, several interacting synaptic adhesion and scaffolding molecules are implicated in DEEs. *CNTNAP2* encodes CASPR2, which forms a molecular bridge at synapses in addition to mediating neuronal migration. Biallelic variants result in a Pitt-Hopkins-like syndrome with early onset epilepsy, hyperventilation, ASD, developmental delay and cortical dysplasia in some patients[113]. Disruptions of *NRXN1*, and rarely *NRXN2*, pre-synaptic neuronal adhesion proteins, cause DEEs including EIDEE[114]. The neurexins connect to synaptic organisers including gephyrin encoded by *GPHN,* the major scaffolding protein of post-synaptic glycinergic and GABAergic receptors. Heterozygous dominant negative *GPHN* variants cause DEEs[115] and biallelic LOF variants with EIMFS[116], confirming the role of gephyrin in maintaining inhibitory signalling in the brain. Collybistin is a brain-specific GDP/GTP-exchange factor encoded by *ARHGEF9*, which anchors gephyrin to the post-synaptic membrane in a tripartite interaction with neuroligin cell adhesion molecules (and binds directly to the α3 subunit of $GABA_A$), forming a lattice to scaffold glycine and $GABA_A$ receptors[117]. Other synaptic genes associated with DEEs include *TANC2*[118], *SHANK3*[119, 120] and *ADAM22*[121].

[H2] Cell signalling

Several cell signalling pathways have been implicated in epilepsies, with the most prominent being the mechanistic (formerly mammalian) target of rapamycin (mTOR) pathway[122, 123]. The mTOR signalling pathway regulates fundamental processes including cell metabolism, growth, proliferation, and survival. Both germline and somatic mosaic pathogenic variants in most genes encoding components of the canonical mTOR signalling ("mTOR-opathies") and amino acid-sensing ("GATORopathies") pathways are associated with focal epilepsies. These may occur as germline variants, somatic variants limited to dysplastic brain, or as a combination of a germline variant with a brain somatic mosaic variant within dysplastic tissue representing a "second hit"[124]. Germline variants in *TSC1* and *TSC2* cause tuberous sclerosis complex (TSC); TSC is a complex multisystem disorder affecting brain, skin, kidneys, heart, lungs and eyes. Neurodevelopmental disorders and epilepsy are common, 88% of patients have epilepsy and 40% IESS[125]. MRI reveals cortical tubers, in which a second somatic mosaic variant may be identified. Vigabatrin is the first line treatment for TSC, and mTOR inhibitors are considered after failure of two appropriate ASMs[126]. Germline variants in *PTEN* cause ASD and macrocephaly with epilepsy, whereas variants in *AKT3* and *PIK3CA* cause megalencephaly. Germline LOF variants in proteins that comprise the GATOR1 complex (*DEPDC5, NPRL2, NPRL3*), responsible for sensing amino acid levels, cause both non-lesional focal epilepsy and epilepsy associated with focal cortical dysplasia (FCD) type II[122]. *DEPDC5* pathogenic variants were first reported in familial focal epilepsies[127, 128], and later associated with DEEs[129]. Studies employing deep targeted sequencing in resected brain tissue highlight the role of brain-restricted somatic mosaic variants in nearly all of these genes in FCD type II, sometimes with hemimegalencephaly[123], with variant allele frequencies as low as 0.01%[130]. mTOR pathway inhibitors, including everolimus and sirolimus may be beneficial as a targeted treatment[131].

G-protein signalling is another ubiquitous cell signalling pathway relevant in DEEs. Heterotrimeric G-proteins transmit signal from transmembrane G-protein coupled receptors (GPCRs) at the cell surface affecting many cellular processes. GPCRs that are important in epilepsy include NMDA and AMPA receptors. *De novo* variants in *GNAO1*, *GNB1* and *GNAI1* are important causes of DEEs. *GNAO1* and *GNAI1* encode alpha subunits of the G-protein complex, and both inhibit adenylate cyclase to reduce cyclic adenosine monophosphate (cAMP) levels. Biochemical studies of *GNAO1* pathogenic variants causing DEE show loss of cAMP inhibition. By contrast, *GNAO1* GOF variants cause an early-onset movement disorder with or without epilepsy[132]. *De novo* pathogenic variants in *GNAI1* in a series of 24 individuals caused developmental delay, substantial speech impairment, and seizures in 75% of individuals[133]. Missense variants affect the GDP binding domain, but the functional effect of the variants

(LOF versus GOF) has not yet been elucidated. *GNB1* encodes a beta subunit of the G-protein complex; pathogenic variants disrupt protein-protein interactions between alpha and beta/gamma subunits[134].

[H2] Epigenetic regulation

Genes that encode parts of the epigenetic machinery, such as transcription factors, chromatin remodellers, and histone modifiers, have been implicated in DEEs[135]. Key genes include *MECP2*, a ubiquitously expressed methyl-CpG binding protein, for which LOF leads to Rett syndrome in girls and duplication typically leads to DEE with profound impairment in boys[136]. *ARX*, which encodes a homeodomain transcription factor, results in a phenotypic spectrum with LOF variants early in the gene causing MCDs, including lissencephaly, and repeat expansions lead to IESS, often associated with a severe hyperkinetic movement disorder. *CHD2*, encoding a chromodomain helicase binding protein[108], causes photosensitive myoclonic DEEs including epilepsy with eyelid myoclonia and epilepsy with myoclonic-atonic seizures[137]. *EEF1A2,* encoding a translation elongation factor[138], is associated with IESS. *PURA*, is involved in transcriptional regulation[139], and pathogenic variants cause severe myoclonic DEE with respiratory insufficiency and hypotonia[140]. *SETD1B*, a histone methyltransferase[141], causes a multisystem disorder with obesity and epilepsy with eyelid myoclonia. In each case, haploinsufficiency of the protein results from *de novo* dominant LOF variants. Genes involved in epigenetic regulation of gene expression are ubiquitously expressed; yet, phenotypes resulting from haploinsufficiency are largely restricted to the brain. Deciphering tissue-specific functions and downstream targets may shed light on disease mechanisms.

Epigenetic methylation studies are unlocking the etiology in patients with unsolved DEEs. A recent study of methylation profiles in 582 patients identified the etiology in 2% of individuals[142] (a similar yield to that observed when performing genome sequencing after exome sequencing). Episignatures can reveal abnormal patterns suggestive of specific genes[143], highlighting the need for further sequencing to identify intronic or previously-missed variants or structural anomalies.

[H2] Cell metabolism

The clinical phenotype of many classic metabolic disorders includes epilepsy. This section describes recently identified genetic causes of DEE that affect cellular metabolism or related processes. *UBA5* encodes an E1-activating enzyme, the initial enzyme that is required for a process called ufmylation, a ubiquitin-like post-translational modification of proteins. Biallelic pathogenic variants in *UBA5* cause DEEs, severe developmental impairment, hypotonia, spasticity, microcephaly, and growth failure[144]. Nearly all affected individuals have one LOF allele and one hypomorphic allele that retains some enzymatic activity, suggesting that complete loss of *UBA5* is lethal.

De novo dominant mutations in *KLHL20* were identified[145]; KLHL20 protein is part of a complex that mediates ubiquitination, a process implicated in Angelman syndrome due to variants involving *UBE3A*. *WWOX* encodes a ubiquitously expressed WW domain-containing oxidoreductase that is involved in cell growth and differentiation and was originally identified as a tumor suppressor. Recessive variants cause a spectrum of phenotypes including DEE with microcephaly and profound delay and spinocerebellar ataxia[146].

CLN2 disease causes the recessive neurodegenerative late-infantile form of neuronal ceroid lipofuscinosis, or late-infantile Batten disease[147]. Onset of focal seizures or myoclonic-atonic seizures occurs at 2-4 years of age in a child with normal development or isolated language delay. It is followed by rapid progression to a progressive myoclonus epilepsy, severe regression, visual failure and early death. Precision therapy using intracerebroventricular enzyme replacement with recombinant human tripeptidyl peptidase 1 slowed disease progression in one study[148].

As with epigenetic regulators, dissecting cell-type-specific effects or functions may shed light on how disruption of these ubiquitous processes results in largely brain-restricted disorders.

[H1] Diagnosis, screening and prevention

Diagnosis of an epileptic encephalopathy is based on the child showing developmental slowing or regression in association with frequent epileptiform activity on EEG[1]. This can be challenging to identify, especially in children with pre-existing developmental delay. Listening carefully to parental concerns is crucial, as they are the best placed to identify a subtle change in their child's abilities, particularly in those with preceding impairment, such as a reduction in eye contact or social interaction. Similarly, when a child with normal development develops an epileptic encephalopathy, slowing in development can be hard to identify. For example, children with Landau-Kleffner syndrome may present with behavioural problems due to their auditory agnosia during which they cannot comprehend common sounds in their environment[7, 149]. For specific DEE syndromes, appropriate management may facilitate a good outcome with the child ultimately being of normal intellect, as is common in the epileptic encephalopathy of Epilepsy with Myoclonic-Atonic Seizures[7, 150]. A DEE can be distinguished from an epileptic encephalopathy as a pure epileptic encephalopathy occurs in the context of normal development before either seizure onset or development of frequent epileptiform activity on EEG. Such a distinction is, however, often impossible in an infant under 3 months of age who presents with developmental impairment and an EE, such as EIDEE, including Ohtahara syndrome and Early Myoclonic Encephalopathy[10] (Box 1).

As a group, DEEs are far more complex diseases than just seizure disorders. They are multimorbidity diseases typically affecting a range of systems. They often include motor dysfunction such as cerebral palsy[42], movement disorders[151] and gait decline[31]; psychiatric features such as ASD[110], behavioural problems[152], mood disorders, psychosis[153]; speech[154], sleep[155], respiratory and gastrointestinal problems. As the child grows, many of these morbidities, such as behaviour, become the main concern for families who are already skilled at managing seizures[156]. Holistic clinical care requires consideration of the entire gamut of morbidities that a child or adult with a DEE faces.

DEEs have historically been diagnosed on the basis of their electroclinical presentation[1]. It typically takes time for the full syndromic picture to emerge, during which the child often shows developmental slowing or regression. Hence, rapid diagnosis with molecular testing in the setting of early electroclinical syndromic features promises to revolutionise clinical practice[157]. Diagnosis of a DEE can now be made far earlier with increasing recognition of the initial presentation together with prompt access to molecular diagnosis in clinical practice, often even before the EEG shows epileptiform activity and developmental slowing occurs. Indeed, a recent study of rapid genome sequencing (median time from seizure onset to sequencing result of 37 days) in infants with seizures beginning under one year of age, identified the genetic aetiology in 46% of 100 children, with clinical utility in 56%, prognostic counselling in 86% and genetic counselling implications in all those with a pathogenic variant[157]. Access to genetic testing means that infants with Dravet syndrome are diagnosed as early as their initial presentation. As one-third of patients present with febrile status epilepticus, either a hemiclonic or generalized tonic-clonic seizure, the diagnosis of Dravet syndrome may be considered from age 6 months when development and the EEG are typically normal[12, 158]. This enables early targeted treatment with the most appropriate ASMs to control life-threatening seizures to ameliorate the adverse developmental consequences of frequent seizures and status epilepticus. Observational studies suggest that appropriate therapies improve developmental outcomes, but long-term outcome is rarely normal and a multimorbidity picture remains usual[27]. Early diagnosis also helps to avoid contraindicated ASMs that exacerbate seizures in specific DEEs. A still common example is the use of SCB, carbamazepine or oxcarbazepine in infants with hemiclonic or tonic-clonic seizures who have undiagnosed Dravet

syndrome, as these specific ASMs commonly cause seizure exacerbation with adverse developmental consequences[159].

Of note, a serious diagnosis, such as a DEE, in infancy carries considerable consequences that require proactive clinical management. From diagnosis, families experience considerable grief and need intense support as the disease evolves[160, 161]. With the accessibility of the internet and social media, families are faced with far more information than ever before, which is both empowering and daunting, as the future may appear bleak with so many issues that could develop. The treating clinician should, therefore, provide holistic care, ideally supported by a multidisciplinary team, such as nurses trained specifically in managing patients with DEEs. They need to guide families to the appropriate specialist for management of new problems as they emerge and ensure that therapies and education are targeted to the child's level of function.

[H2] Epilepsy syndromes

DEEs include a wide range of epilepsy syndromes, defined by their electroclinical features and, in some cases, imaging findings (Figure 2)[4, 7, 10, 11, 162]. Epilepsy syndromes are defined by their age of onset, seizure types[163], EEG features, developmental course, and associated features. Diagnosis of a DEE syndrome informs aetiological investigations, prognostic and genetic counselling, and selection of therapeutic approaches. The aetiology of DEEs is frequently genetic, and may be associated with normal imaging, diffuse or focal structural abnormalities such as MCD[164, 165] and, less commonly, metabolic features. Acquired causes, such as ischaemic injury, infection, and hypoglycaemia, are a small but important group[166]. For some of the rarer syndromes, such as Rasmussen syndrome and Febrile Infection-Related Epilepsy Syndrome, the aetiology is currently unknown.

With the rapid advances in next generation sequencing, 50% of patients with DEEs have a pathogenic variant of major effect identified[167]. Current analyses of monogenic epilepsy genes implicates >900 genes in DEEs (Gene4Epilepsy; http://github.com/bahlolab/genes4epilepsy), out of >1000 established monogenic genes[26]. Genetic DEEs are most commonly regarded as *de novo* dominant disorders; however, more DEE genes follow autosomal recessive than dominant inheritance, with a small number following X-linked or mitochondrial inheritance patterns[26]. The percentage of patients who have a causative variant identified varies markedly across different DEE syndromes. For example, Dravet syndrome is relatively genetically homogeneous with >90% of patients having a pathogenic variant in *SCN1A*[12], whereas EIMFS is highly genetically heterogeneous with >30 genes implicated and 70% of all cases having a pathogenic variant of major effect identified. The genes that cause EIMFS may follow autosomal dominant, X-linked and autosomal recessive inheritance, so an understanding of how each gene is inherited is essential when providing accurate diagnostic and genetic counselling for families[168]. Genetic DEEs implicating a range of disease mechanisms may also be associated with structural changes in the brain, such as MCD, that likely result from changes in gene expression during early brain development. These findings reinforce the need to consider a genetic aetiology for all structural changes in the brain.

One should aim to identify both the DEE epilepsy syndrome diagnosis *and* aetiology for each patient, as they provide complementary information that critically inform patient management. Knowing the gene is not sufficient, as each gene is typically associated with a spectrum of phenotypes. For example, mutations in the sodium channel subunit genes, *SCN1A, SCN2A* and *SCN8A,* cause DEEs and self-limited epilepsies, which require very different treatment approaches[10]. Furthermore, a gene can be associated with different DEE syndromes that reflect GOF or LOF and, therefore, need therapies with the mode of action tailored to the underlying dysfunction. *SCN1A* again provides a good example with Dravet syndrome arising due to LOF pathogenic variants[169], and GOF pathogenic variants causing a profound Early Infantile DEE with an expanded phenotypic spectrum[32, 33].

Despite the epilepsy syndrome informing diagnosis, aetiology and management, many patients with a DEE or an epileptic encephalopathy do not fit neatly into a recognised epilepsy syndrome diagnosis. They do, however, share the increased risk of comorbidities and SUDEP that occur in DEE syndromes; thus, recognizing the severe nature of their disease is crucial.

[H2] Investigations

All patients with DEEs require investigations to characterize their epilepsy and identify an underlying aetiology[166]. Video-EEG studies, often beginning with a routine EEG incorporating hyperventilation and intermittent photic stimulation, are required. Both hyperventilation and intermittent photic stimulation increase the likelihood of eliciting epileptiform activity (such as generalized spike-wave) and sometimes seizures (typically absence seizures if hyperventilation is well performed, which is often not possible for these patients). Detailed characterisation with video-EEG studies of ictal episodes often adds useful information. Epileptic and non-epileptic seizures and movement disorders can be distinguished[151], providing vital information in guiding patient management. Often, an EEG during sleep provides additional findings that guide epilepsy syndrome classification (such as generalized paroxysmal fast activity in LGS and spike-wave activation in sleep in the syndromes of epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS) and DEE-SWAS), directing therapy selection[170].

All patients should have brain MRI, ideally with a 3 Tesla machine using epilepsy sequences, to exclude a congenital or acquired structural lesion, such as a MCD or an ischaemic insult. If there is evidence of a unifocal lesion that could be driving an epileptic encephalopathy network, presurgical evaluation is indicated (Figure 4). Further studies such as SPECT (ictal compared with interictal), fluorodeoxyglucose PET, and, for some individuals, more sophisticated imaging, such as functional MRI studies, may be useful, but may be challenging to perform. Overall, relatively few patients with DEEs are candidates for epilepsy surgery but, if a unifocal resectable lesion is identified, such as a FCD, successful surgery can be transformational[166, 171]. In an epidemiological study of severe epilepsies beginning before age 18 months, which excluded patients with Dravet syndrome for methodological reasons, the aetiology was determined in 67% (76/114) of patients. Specifically, a genetic or presumed genetic basis was identified in 62 (54%) patients: 14 with FCD, 17 had other brain malformations, 6 had a metabolic disorder, 9 with chromosomal disorders and 16 had a single gene disorder, and 14 with acquired brain lesions[8, 166]. MCD, including FCD, may be associated with a pathogenic germline or somatic variant, which may show a mutation gradient in resected brain tissue. In some individuals, a second genetic hit with a combination of both somatic and germline mutations in the same gene or genes in related pathways (eg. mTOR pathway) is identified[124].

Neuropsychological evaluation is invaluable in characterising a patient's cognition, together with negative or positive changes over time, and responses to specific therapies. Cognitive decline may indicate the need for sleep EEG studies to identify a, so far, unrecognised epileptic encephalopathy, such as DEE-SWAS or EE-SWAS[170].

Routine genetic testing often begins with a chromosomal microarray as causative copy number variants (CNVs) are identified in at least 4% of patients with DEEs[172]. Contributory pathogenic CNVs occur in another 4%, in whom the CNV contributes to, but is not wholly causative of, the underlying aetiology[172]. New chromosomal microarrays with increased density detect smaller CNVs not visible previously. Mosaic pathogenic CNVs are increasingly identified, with a greater yield from salivary DNA than from blood-derived DNA, as salivary epithelial cells are embryologically closer to neural cells, deriving from ectoderm, compared with lymphocytes[173].

Next generation sequencing has transformed our understanding of the aetiologies of the DEEs, enabling identification of their cause in 50% of patients[166, 167]. Testing is moving from exome sequencing, analysing the 1-2% of the genome that encode proteins (exons) and in which most pathogenic variants are found, to genome sequencing[63, 157]. Gene panels have been extensively used but only capture a

subset of all >900 DEE genes, thereby failing to identify causative variants in genes that have not been sequenced[26]. Some gene panels use exome sequencing with analysis limited to genes included in a panel; in such instances, re-interrogation for genes that have not been analysed should be requested. However, the genetic landscape constantly evolves owing to the discovery of new genes, so exome sequencing is now recommended where feasible[174]. Genome sequencing, now moving into clinical practice, enables analysis of intronic and regulatory regions. A 2023 genome analysis of infants with seizures beginning in the first year of life identified a genetic cause in 43% of 100 infants, and all had implications for disease management[157].

Mosaicism is increasingly recognised as an important cause of DEEs, including germline and somatic (tissue-limited) mosaicism. Detection of low-level germline mosaicism in blood-derived DNA requires high-depth sequencing or specialised techniques, such as droplet digital polymerase chain reaction[175]. Sometimes, lower mosaicism levels are associated with milder disease[12, 175, 176]. Somatic mosaicism can be found in brain-derived DNA at low levels on surgical specimens, cerebrospinal fluid or implanted EEG electrodes[122, 177, 178].

Epigenetic analysis is beginning to shed light on other types of pathogenic changes. Episignatures, derived from disruption in genome-wide DNA methylation profiles, are recognised for many genes resulting in neurodevelopmental disorders including ASD, with some relevant to DEEs[143]. As genomic DEE episignatures are identified, testing may clarify the pathogenicity of variants of unknown significance and identify other pathogenic variants with imprinting and repeat expansion disorders[142, 179].

Routine blood and urine tests should be performed early in the child's presentation, including specific testing tailored to the patient's presentation[166]. These include blood creatinine, ammonia, amino acids, acylcarnitines, biotinidase, uric acid, recurrent mitochondrial pathogenic variants, *POLG* common pathogenic variants, transferrin isoforms, copper, caeruloplasmin, very long chain fatty acids, white cell enzymes, glucose, lactate, pyruvate, and amino acids. Urine testing includes organic acids, amino acids, piperideine-6-carboxylate, S-sulfocysteine, guanidinoacetic acid, purines and pyrimidines. Cerebrospinal fluid tests should be considered including cell count, protein, glucose, lactate, pyruvate, amino acids, and neurotransmitters. Testing should focus on treatable conditions, such as vitamin-responsive epilepsies[180]. The full gamut of investigations is often not available in low-income and middle income settings, where access may be limited to EEG and imaging studies, and a genetic aetiology cannot be identified due to lack of availability of genetic testing.

[H2] Reproductive counselling

For any patient with a genetic DEE, reproductive counselling is essential. In patients thought to have a *de novo* pathogenic variant, high-depth sequencing of parental blood or salivary samples found that 8% of patients had a parent with low-level mosaicism[175]. Parents with mosaic levels <13% were unaffected and those with higher levels had febrile seizures or epilepsy. Parental mosaicism places parents at an increased risk of having a second child with a DEE, as a small population of their sperm or ova carry the pathogenic variant. Testing of blood or saliva would not detect mosaicism limited to gonads, so genetic counselling should always discuss this possibility and potential testing of a subsequent pregnancy should be considered (eg with IVF, chorionic villus sampling or amniocentesis). If patients with genetic DEEs wish to have children, the recurrence risk also needs to be carefully discussed.

[H1] Management

Management of the DEEs requires a focus on both seizure control and comorbidities. A holistic approach involves a multidisciplinary team to provide appropriate therapies to mitigate developmental, psychiatric, and behavioural challenges.

[H2] Reducing seizure burden

In the epilepsies, ASMs have historically been selected to treat seizure type, rather than epilepsy syndrome, beginning with empirical trials of standard ASMs appropriate to the patient's presenting seizure type, such as carbamazepine for focal, valproate for generalized, and broad spectrum ASMs, such as valproate, levetiracetam and lamotrigine, for combined focal and generalized seizure types. For DEEs, seizures are usually drug-resistant, with patients trialling many ASMs in an effort to control seizures. This approach can be particularly problematic for DEEs, in which a lack of diagnosis of the epilepsy syndrome may result in inappropriate prescription of an ASM that causes seizure exacerbation with potential adverse developmental consequences[159].

Until now, ASM treatment choices for DEEs were made largely on the same general principles of targeting the seizure types mentioned above; however, seizures in DEEs are typically drug-resistant. There are ASM protocols published for specific DEE syndromes based on expert consensus[181, 182]. Even when an aetiologic genetic diagnosis is made, meaningful change in the treatment paradigm has not yet been possible for most DEEs[183]. In a 2021 observational study in 293 patients with genetic epilepsies, treatment changes were undertaken because of the genetic findings in 32%, including rational precision medicine treatment or a treatment change prompted by the genetic diagnosis, but not directly related to known pathophysiological mechanisms[183]. By contrast, a 2023 genome sequencing study of infants presenting with seizures under age 1 year identified the causal variant in 43% with immediate treatment implications in 56%, informing additional evaluation in 65% and prognostic counselling in 86%[157].

Nonetheless, we are at an inflection point in DEE management as precision therapy should be considered from the day a genetic diagnosis is made. Traditional ASMs can be used as precision therapies when the functional effect of the pathogenic variant is understood (Supplementary Table 1). SCBs, particularly carbamazepine and phenytoin, are efficacious in GOF-DEEs due to pathogenic variants in sodium channel (*SCN1A*[33], *SCN2A*[184] and *SCN8A*[185]) and potassium channel (*KCNQ2*[43]) genes. Trials targeting specific channelopathies are being developed: potent selective potassium channel openers, retigabine and ezogabine, for *KCNQ2*-DEE; a powerful, highly selective $Na_v1.6$ inhibitor for *SCN8A*-DEE[186], and a selective GluN2B negative allosteric modulator, radiprodil, for *GRIN2B* GOF DEE[187].

With recent scientific insights into the marked genetic heterogeneity and phenotype-genotype complexity of DEEs, it is unsurprising that few evidence-based trials to guide therapy currently exist. However, several trials have focused on orphan genetic DEEs, such as Dravet syndrome and *CDKL5* deficiency disorder. Randomised placebo-controlled trials (RCTs) of cannabidiol demonstrated efficacy in Dravet syndrome, LGS and TSC, with significant median percent reductions in target seizures compared with placebo of 38.9%[188], 41.9%[189] and 48.6%[190]. However, a statistically significant reduction in seizures is not as important as complete seizure control in terms of improving a patient's quality of life. A phase 2 RCT of soticlestat in patients with Dravet syndrome showed a significant placebo-adjusted median reduction in convulsive seizure frequency of 46% over the full treatment period, whereas reduction in drop seizures in those with LGS was not significant[188, 191]. A RCT in *CDKL5* deficiency disorder found a median percentage change in 28-day major motor seizure frequency of-30.7% with ganaxolone, compared with -6·9% for placebo. Treatment-emergent adverse events occurred in 43 of 50 (86%) patients in the ganaxolone group and in 45 of 51 (88%) patients in the placebo group[192].

Other controlled trials have been designed based on clinical experience suggesting efficacy in specific DEEs. In Dravet syndrome, a RCT of stiripentol demonstrated clear efficacy[193], after initially being trialled in drug-resistant epilepsy. Stiripentol was more effective, in association with clobazam, in individuals with Dravet syndrome[194]. In a RCT on stable doses of clobazam and valproate, 71% of children with

Dravet syndrome receiving add-on stiripentol compared with only 5% receiving placebo achieved a >50% reduction in seizures[193]. Owing to the trial design, one cannot infer that this combination of ASMs is necessarily the most effective; real-world data may show other combinations to be more effective or have improved tolerability.

Identification of the efficacy of fenfluramine in Dravet syndrome followed the observation that it was particularly beneficial in children with drug-resistant, self-induced photosensitive epilepsy[195], resulting in seizure freedom in 7 of 12 patients with Dravet syndrome in one study[196]. In the first of two RCTs, fenfluramine in two different doses was added to antiseizure regimens without stiripentol[197]. The higher dose of fenfluramine was associated with a significantly greater likelihood of achieving a >50% (68% versus 12% placebo) and a >75% reduction (50% versus 2% placebo) in convulsive seizure frequency. In the second RCT, an intermediate dose of fenfluramine, owing to drug interactions, was added to stiripentol resulting in >50% (54% vs 5% placebo) and a >75% reduction (35% vs 2% placebo) in convulsive seizures[198]. Subsequent studies of fenfluramine in Dravet syndrome demonstrated dose-dependent clinically meaningful effects on regulating behaviour, emotion, cognition, and everyday executive functions in preschool age[199] and sustained efficacy and safety in children, adolescents and adults in real-world practice[200, 201].

Fenfluramine has also proven effective in reducing drop seizures in LGS in a double-blind, placebo-controlled, parallel-group RCT[202]. The most responsive seizure type was the generalized tonic-clonic seizure (GTCS) in 120 of 263 [46%] patients, with a decrease in frequency of 45.7% and 58.2% in the higher and lower dose groups, respectively. Most common treatment-emergent adverse events included decreased appetite (22%), somnolence (13%), and fatigue (13%). The open-label extension phase of this study, in which 142 patients completed their final visit after 12 months[203], confirmed GTCS to be the most responsive seizure type, with median reductions over the entire extension period of 48.8%, whereas tonic seizures reduced by 35.8%.

Of note, interest is growing in clinical trials of new or repurposed drugs that target orphan syndromes or gene-specific DEEs. These may target the altered neurobiological pathways even though the underlying epileptogenic mechanisms often remain unclear. One example is the EXIST-3 RCT in which the mTOR inhibitor everolimus was trialled in patients with drug-resistant focal seizures in the setting of tuberous sclerosis complex, due to pathogenic variants in the mTOR pathway genes, *TSC1* or *TSC2*. In this RCT, responder rates were greater with higher-dose everolimus than with placebo; however, they were perhaps less compelling than one might expect for a precision therapy (40% vs 15.1%, $p<0.0001$)[131]. Effects on cognition and other neuropsychiatric symptoms were not reported. In contrast to most RCTs, the clinical response increased over time as measured in the open-label extension study of patients on everolimus for ≥48 weeks, postulated to be due to a disease-modifying effect[204]. A post-hoc analysis of patients <18 years showed that children <6 years of age had greater benefit, suggesting that this precision therapy may be more beneficial if commenced earlier[205]. In addition to the efforts devoted to development of precision therapies targeting aetiologies, RCTs of new or repurposed agents for epilepsy syndromes also hold promise. Epilepsy syndromes remain clinically important, as consistent phenotypes may suggest pathways modifiable by more broadly beneficial ASMs and may prove to be more pharmacoeconomically viable than drugs targeting each genetic disease[4].

[H2] Avoiding factors that cause seizure exacerbation

Environmental factors exacerbate seizures in many patients with DEEs. In Dravet syndrome and *PCDH19*-epilepsies, fever or hyperthermia (even simply a hot environment or hot bath) are well-recognised seizure triggers, and may have even more serious consequences. For instance, a 10 year old girl with Dravet syndrome, who had been seizure-free for 2 years, was found deceased when walking outside on a day with extremely hot temperatures (46.5 degree Celsius)[206]. Fatigue, stress or excitement in most patients, and environmental photic or pattern stimulation in some, may trigger seizures. The precipitating role of such factors varies between patients, and should be carefully extracted from their

disease history. Instructions to avoid precipitants (or to use rescue medication when appropriate) should be provided to families.

Certain ASMs may lead to seizure exacerbation in specific genetic DEEs. For example, in Dravet syndrome, SCBs such as carbamazepine and oxcarbazepine should be avoided[207]. However, the SCB topiramate can be useful in Dravet syndrome[181], whereas others, such as lamotrigine and phenytoin, may exacerbate seizures in some patients and be helpful in others[208, 209].

[H2] Treatment of acute seizures and status epilepticus

Episodes of repetitive seizures or status epilepticus often occur in patients with DEEs. Caregivers of every individual with a DEE who has experienced repetitive seizures or status epilepticus should have a seizure action plan for first aid and out-of-hospital rescue therapy. Different genetic DEEs have different risks of convulsive and non-convulsive status epilepticus and death[19]; understanding these risks informs diagnosis, prognostic counselling and management strategies. These include recognition and treatment of precipitating factors (e.g. prompt treatment of fever). Early, appropriate treatment of seizures may reduce the likelihood of status epilepticus[210]. Guidance for in-hospital acute seizure management should also be provided, although different hospitals have their own status epilepticus protocols. This is a delicate matter, as simply adopting a protocol reduces mortality and morbidity, although there is little evidence to show that one of the numerous recommended protocols is better than another[211]. Furthermore, intensive care specialists may be reluctant to use a protocol with which they are unfamiliar.

The main options for out-of-hospital intervention include benzodiazepines such as midazolam (nasal or buccal), diazepam (nasal, rectal or buccal), lorazepam (buccal or sublingual) or clonazepam (oral)[206]. Pre-hospital benzodiazepine administration may be effective in controlling repetitive seizures or status epilepticus and avoid hospitalization[212, 213]. Overdosing should be avoided due to the increased risk of respiratory depression[214].

[H2] Targeting comorbidities

The severity of epilepsy in patients with DEEs should not reduce the focus on comorbidities as cognitive, psychiatric (such as ASD, anxiety, mood and behavioural disorders, psychosis), motor and medical disorders occur frequently[110, 152, 153, 156, 215]. The aetiologies are multifactorial, reflecting the underlying neurobiology of the DEE, exacerbated by poorly controlled seizures, frequent epileptiform activity on EEG, sedative and psychiatric adverse effects of medication, restrictions, and social stigma[216]. Patients with DEEs are at high risk of the typical medical complications associated with severe neurodevelopmental impairment, including aspiration pneumonia, feeding problems, constipation, sleep disorders and orthopaedic deformities[110, 152, 215]. A multidisciplinary team is essential to address the care of these severely disabled patients.

Severe behavioural disorders may warrant a trial of pharmacological treatment such as risperidone, aripiprazole or a selective serotonin reuptake inhibitor, with careful discussion about potential adverse effects, including sedation, weight gain and serotonin syndrome, and the risk of seizure exacerbation. Forced normalization, in which psychiatric problems emerge in the setting of seizure control, can occur in patients with longstanding drug-resistant seizures[217].

[H1] Quality of life

Health-related quality of life (HRQOL) studies measure the effect of chronic disease on an individual's physical, social and mental well-being[218]. In children with DEEs, QOL measures extend to parents, carers,

and the wider family, as there is lifelong caregiver responsibility and burden. Such measures address important personal, societal and health economic consequences of disease.

Classification of DEEs into syndromes has enabled condition-specific patient advocacy groups to form, facilitating research participation of carers[215, 219]. Caregivers emphasise the importance of sleep, communication, behaviour, daily activities, motor skills and language problems, which often eclipse seizures in importance as the individual ages[219]. Given the young age at presentation, intellectual disability and comorbidities in patients with DEEs, HRQOL assessments comprise proxy questionnaires completed by caregivers. Studies typically incorporate several validated questionnaires to assess different aspects of HRQOL, such as the Epilepsy & Learning Disability Quality of Life Questionnaire[220], the Impact of Pediatric Epilepsy Scale[221], the Pediatric Quality of Life Inventory[222], the Parental Stress Index[223] and the Strength and Difficulties Questionnaire[224]. By comparing phenotypic features, such as seizure type and frequency with HRQOL, studies identify predictors of outcome. RCTs now include parental questionnaires measuring behaviour and everyday function, which typically aid the descriptive aspects of the study rather than acting as primary or secondary end points[199]. The development of composite endpoints for DEE trials, acknowledging the importance of improving comorbidities as well as reducing seizure frequency, is a new area of trial design[225].

Cross-sectional studies in DEEs demonstrate considerably worse HRQOL than in both the general population and unselected childhood epilepsy cohorts[226]. In Dravet syndrome, increased epilepsy severity and behavioural factors were strong predictors of HRQOL at baseline and at 10-year-follow-up[227]. The use of SCBs leading to increased seizure frequency was associated with a reduced HRQOL at 10-year-follow-up (F-ratio (1,34) = 4.13, p = +0.05)[227]. Carers of children with Dravet syndrome have more depressive symptoms than carers of patients with other drug-resistant epilepsies or in seizure remission, and are more likely to resign from employment resulting in greater financial burden for the caregiver's family[228]. Most of the caregiver burden for children with DEEs falls on female carers. Parents of children with LGS, the vast majority mothers, reported constant anxiety, difficulties in accessing childcare, restriction of social life and poor mental health[229, 230].

Transition to adult care is a particularly stressful and anxiety-provoking period for caregivers. In people with TSC who developed epilepsy during childhood, 75% felt the disease led to isolation and social withdrawal, negatively affected relationships and only 15% of respondents were optimistic about their state of health over the next 5 years[231]. Although 90% of adults with TSC remained on anti-seizure medication, almost 40% did not have neurological follow-up[231], highlighting the need for a supportive medical framework into adult life, when new medical issues often emerge[232].

[H1] Outlook

Although DEEs have a vast array of mainly genetic etiologies that alter different developmental processes and aspects of neural cell functioning, a shared consequence is impairment of higher cortical functions, in addition to drug-resistant seizures. Although severity varies across and within specific epilepsy syndromes and genetic diseases, language, memory, attention, and executive functions are usually impaired in the long term, with almost all patients having cognitive impairment and many have features of ASD. There has been increasing awareness that ASMs that mitigate epileptic activity do not adequately address the widespread cortical dysfunction resulting from defective developmental processes and severe epilepsy. This has prompted efforts to repurpose drugs and develop new molecules and precision treatment approaches, embracing a broader therapeutic goal of curing not just the seizure disorder, but all the comorbidities.

The promise of gene therapy is both tantalizing and imminent; however, many limitations exist regarding implementation in children and adults with DEEs[233]. Many genes causing DEEs have a role in transcriptional regulation and control a range of downstream pathways that cannot be targeted

individually. Dosing is an important issue, which requires a delicate balance to ensure that a GOF phenotype is not turned into a LOF phenotype, as many genes demonstrate severe phenotypes with both types of dysfunction[34]. Furthermore, the optimal timing of gene therapy administration is unclear. DEEs have, by definition, developmental effects, which are unlikely to be reversed postnatally; this limitation likely applies to developmental genes, receptors and channels. Thus, even early postnatal delivery of gene therapy is probably too late to fully reverse the formation of abnormal brain networks. That said, the widespread nature of neuronal dysfunction typical of DEE requires a delivery system capable of targeting the whole brain in a critical period before mature connections are in place. Mosaicism and X-linked disorders further complicate cellular targeting.

The recent advent of many forms of gene therapy is promising. Viral vectors, such as adeno-associated virus 9 (AAV9), enable widespread gene transfer in the adult brain[234]. However, they can only carry a limited amount of DNA and some genes, such as *SCN1A*, remain too large for present vectors. New approaches include targeting regulatory elements of large genes, such as *SCN1A*, employing cell-selective specificity[235]. An alternative to DNA is to target messenger RNA (mRNA) using antisense oligonucleotides, which can be administered intrathecally to either inhibit or increase mRNA transcription, alter mRNA splicing or increase mRNA degradation[236]. Trials of antisense oligonucleotides in mouse models of DEEs have shown positive effects for several genes including *SCN1A, SCN2A, SCN8A* and *KCNT1*[237, 238]. The use of antisense oligonucleotides to increase the production of translated mRNA, termed Targeted Augmentation of Nuclear Gene Output (TANGO), has been used successfully in an animal model of Dravet syndrome to increase the production of sodium channels[239], and is currently undergoing clinical trials in Dravet syndrome[240]. Another approach, used to correct nonsense point mutations, has taken advantage of small molecules that induce translational read-through, suppressing stop codons. A clinical trial is ongoing in Dravet syndrome and *CDKL5* deficiency disorder[241].

There is growing interest in delineating the natural history of DEEs, often focused on paediatric studies[242]. The disease-modifying potential of new treatments, especially precision and gene therapies, can only be determined if natural history profiles of each genetic DEE are well described[243]. For most DEEs, it is not known, for example, whether and how the cognitive outcome would improve if seizures were controlled soon after epilepsy onset. It is also unclear whether differences in severity of cognitive impairment among family members with the same *SCN1A* pathogenic variant, where one individual has Dravet syndrome and another has GEFS+, is due to genomic background, environmental factors or more severe seizures in the individual with Dravet syndrome[244]. Answering these questions will benefit in the future from sophisticated genomics studies and increasing involvement of family associations[215, 245]. These associations focus on advocacy and fundraising for research on their specific genetic DEE, for which, because of their rarity, adequate attention and development of precision therapies would otherwise be delayed for years.

Despite these caveats, the future is far brighter for patients with DEEs than ever before. In just 23 years, the field has moved from considering that DEEs were acquired disorders to identifying the genetic aetiology underlying DEEs in at least 50% of patients. Development of new genomic methodologies will probably discover the aetiology in the remaining individuals. Already, techniques are emerging, such as polygenic risk scores, that aid in understanding the interaction of rare and common variation in determining phenotypic variability[244, 246]. In the future, exploration of environmental factors, such as viral infections, is likely to illuminate phenotypic differences further. Development of precision therapies, in their many guises, will hopefully lead to dramatic improvements in the outcome for patients with DEEs with the ultimate promise, one day, of cure.

References

1. Berg A. T. et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 51, 676-85 (2010).
2. Scheffer I. E. et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 58, 512-21 (2017).

   This is the first major revision of the International League Against Epilepsy Classification of the Epilepsies in almost three decades in which the term Developmental and Epileptic Encephalopathies was introduced and defined.
3. Poke G., Stanley J., Scheffer I. E., Sadleir L. G. Epidemiology of Developmental and Epileptic Encephalopathy and of Intellectual Disability and Epilepsy in Children. Neurology. 100, e1363-e75 (2023).

   This is the key epidemiology study of all DEEs with onset prior to 16 years of age, highlighting that DEEs have a cumulative incidence of 1 in 590 children and providing the cumulative incidence for several DEE syndromes.
4. Wirrell E. C. et al. Methodology for classification and definition of epilepsy syndromes with list of syndromes: Report of the ILAE Task Force on Nosology and Definitions. Epilepsia. 63, 1333-48 (2022).
5. Lennox W. G. The petit mal epilepsies; their treatment with tridione. J Am Med Assoc. 129, 1069-74 (1945).
6. Gastaut H. et al. Childhood epileptic encephalopathy with diffuse slow spike-waves (otherwise known as "petit mal variant") or Lennox syndrome. Epilepsia. 7, 139-79 (1966).
7. Specchio N. et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia. 63, 1398-442 (2022).

   This is one of four papers officially defining epilepsy syndromes for the International League Against Epilepsy and focuses on syndromes beginning in the childhood and includes DEEs.
8. Howell K. B. et al. The severe epilepsy syndromes of infancy: A population-based study. Epilepsia. 62, 358-70 (2021).
9. Symonds J. D. et al. Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. Brain. 144, 2879-91 (2021).
10. Zuberi S. M. et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 63, 1349-97 (2022).

    This is one of four papers officially defining epilepsy syndromes for the International League Against Epilepsy and focuses on syndromes beginning in the newborn and infantile period and includes DEEs.
11. Riney K. et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 63, 1443-74 (2022).
12. Li W., Schneider A. L., Scheffer I. E. Defining Dravet syndrome: An essential pre-requisite for precision medicine trials. Epilepsia. 62, 2205-17 (2021).
13. Symonds J. D. et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 142, 2303-18 (2019).

    This Scottish epidemiological study provides the incidence and phenotypes of seizure disorders with onset under 3 years of age.
14. Elkhateeb N. et al. The clinical and genetic landscape of developmental and epileptic encephalopathies in Egyptian children. Clin Genet. 105, 510-22 (2024).

15. Surana P. et al. Infantile spasms: Etiology, lead time and treatment response in a resource limited setting. Epilepsy Behav Rep. 14, 100397 (2020).
16. Raga S. V., Essajee F., Solomons R., Van Toorn R., Wilmshurst J. M. Epileptic spasms: A South African overview of aetiologies, interventions, and outcomes. Dev Med Child Neurol. 65, 526-33 (2023).
17. Nashef L., So E. L., Ryvlin P., Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia. 53, 227-33 (2012).
18. Myers K. A. et al. Fatal Cerebral Edema With Status Epilepticus in Children With Dravet Syndrome: Report of 5 Cases. Pediatrics. 139, e20161933 (2017).
19. Donnan A. M., Schneider A. L., Russ-Hall S., Churilov L., Scheffer I. E. Rates of Status Epilepticus and Sudden Unexplained Death in Epilepsy in People With Genetic Developmental and Epileptic Encephalopathies. Neurology. 100, e1712-e22 (2023).

This study examined the frequency of convulsive and non-convulsive status epilepticus and mortality rates in different genetic DEEs, informing counselling of families, diagnosis and clinical management.

20. Akiyama M., Kobayashi K., Yoshinaga H., Ohtsuka Y. A long-term follow-up study of Dravet syndrome up to adulthood. Epilepsia. 51, 1043-52 (2010).
21. Myers K. A. et al. Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk. Epilepsia. 59, 1372-80 (2018).
22. Steinlein O. K. et al. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 11, 201-3 (1995).
23. Biervert C. et al. A potassium channel mutation in neonatal human epilepsy. Science. 279, 403-6 (1998).
24. Singh N. A. et al. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. Nat Genet. 18, 25-9 (1998).
25. Wallace R. H. et al. Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel beta1 subunit gene SCN1B. Nat Genet. 19, 366-70 (1998).
26. Oliver K. L. et al. Genes4Epilepsy: An epilepsy gene resource. Epilepsia. 64, 1368-75 (2023).

This study identified 926 known monogenic epilepsy genes in 2023 and showed that 825 genes were associated with DEEs. Since publication, >1000 genes are listed on the publicly accessible database http://github.com/bahlolab/genes4epilepsy.

27. Dravet C., Bureau, M., Oguni, H., Cokar, O., Guerrini, R., & Wolf, P. Dravet syndrome (previously Severe Myoclonic Epilepsy in Infancy). In: M. Bureau P. G., C. Dravet, A. V. Delgado-Escueta, R. Guerrini, C. A. Tassinari, & P. Thomas, editor. Epileptic Syndromes in Infancy, Childhood and Adolescence. 6th ed: John Libbey Eurotext; 2019. p. 139–71.
28. Zhang Y. H. et al. Genetic epilepsy with febrile seizures plus: Refining the spectrum. Neurology. 89, 1210-9 (2017).
29. Sun Y. et al. A deleterious Nav1.1 mutation selectively impairs telencephalic inhibitory neurons derived from Dravet Syndrome patients. Elife. 5, e13073 (2016).
30. Kaneko K. et al. Developmentally regulated impairment of parvalbumin interneuron synaptic transmission in an experimental model of Dravet syndrome. Cell Rep. 38, 110580 (2022).
31. Rodda J. M., Scheffer I. E., McMahon J. M., Berkovic S. F., Graham H. K. Progressive gait deterioration in adolescents with Dravet syndrome. Arch Neurol. 69, 873-8 (2012).
32. Sadleir L. G. et al. Not all SCN1A epileptic encephalopathies are Dravet syndrome: Early profound Thr226Met phenotype. Neurology. 89, 1035-42 (2017).
33. Brunklaus A. et al. The gain of function SCN1A disorder spectrum: novel epilepsy phenotypes and therapeutic implications. Brain. 145, 3816-31 (2022).

This study expands the spectrum of SCN1A DEEs associated with gain of function pathogenic variants, highlighting the therapeutic implications for the gain of function SCN1A diseases.

34. Wolff M. et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain. 140, 1316-36 (2017).
35. Johannesen K. M. et al. Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications. Brain. 145, 2991-3009 (2022).
36. Zaman T. et al. Mutations in SCN3A cause early infantile epileptic encephalopathy. Ann Neurol. 83, 703-17 (2018).
37. Zaman T. et al. SCN3A-Related Neurodevelopmental Disorder: A Spectrum of Epilepsy and Brain Malformation. Ann Neurol. 88, 348-62 (2020).
38. Severino M. et al. Definitions and classification of malformations of cortical development: practical guidelines. Brain. 143, 2874-94 (2020).
39. Smith R. S. et al. Sodium Channel SCN3A (Na(V)1.3) Regulation of Human Cerebral Cortical Folding and Oral Motor Development. Neuron. 99, 905-13.e7 (2018).
40. Guerrini R., Dobyns W. B. Malformations of cortical development: clinical features and genetic causes. Lancet Neurol. 13, 710-26 (2014).
41. Akula S. K. et al. Exome Sequencing and the Identification of New Genes and Shared Mechanisms in Polymicrogyria. JAMA Neurol. 80, 980-8 (2023).
42. Weckhuysen S. et al. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. Ann Neurol. 71, 15-25 (2012).
43. Pisano T. et al. Early and effective treatment of KCNQ2 encephalopathy. Epilepsia. 56, 685-91 (2015).
44. Millichap J. J. et al. KCNQ2 encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients. Neurol Genet. 2, e96 (2016).
45. Weckhuysen S. et al. Extending the KCNQ2 encephalopathy spectrum: clinical and neuroimaging findings in 17 patients. Neurology. 81, 1697-703 (2013).
46. Knight D., Mahida S., Kelly M., Poduri A., Olson H. E. Ezogabine impacts seizures and development in patients with KCNQ2 developmental and epileptic encephalopathy. Epilepsia. 64, e143-e7 (2023).
47. Olson H. E. et al. Genetics and genotype-phenotype correlations in early onset epileptic encephalopathy with burst suppression. Ann Neurol. 81, 419-29 (2017).
48. Millichap J. J. et al. Infantile spasms and encephalopathy without preceding neonatal seizures caused by KCNQ2 R198Q, a gain-of-function variant. Epilepsia. 58, e10-e5 (2017).
49. Malerba F. et al. Genotype-phenotype correlations in patients with de novo KCNQ2 pathogenic variants. Neurol Genet. 6, e528 (2020).
50. Sands T. T. et al. Autism and developmental disability caused by KCNQ3 gain-of-function variants. Ann Neurol. 86, 181-92 (2019).
51. Masnada S. et al. Clinical spectrum and genotype-phenotype associations of KCNA2-related encephalopathies. Brain. 140, 2337-54 (2017).
52. Hedrich U. B. S. et al. 4-Aminopyridine is a promising treatment option for patients with gain-of-function KCNA2-encephalopathy. Sci Transl Med. 13, eaaz4957 (2021).
53. Eunson L. H. et al. Clinical, genetic, and expression studies of mutations in the potassium channel gene KCNA1 reveal new phenotypic variability. Ann Neurol. 48, 647-56 (2000).
54. Verdura E. et al. Complete loss of KCNA1 activity causes neonatal epileptic encephalopathy and dyskinesia. J Med Genet. 57, 132-7 (2020).
55. Miceli F. et al. Distinct epilepsy phenotypes and response to drugs in KCNA1 gain- and loss-of function variants. Epilepsia. 63, e7-e14 (2022).
56. Barcia G. et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet. 44, 1255-9 (2012).
57. Heron S. E. et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 44, 1188-90 (2012).
58. Quraishi I. H. et al. An Epilepsy-Associated KCNT1 Mutation Enhances Excitability of Human iPSC-Derived Neurons by Increasing Slack K(Na) Currents. J Neurosci. 39, 7438-49 (2019).

59. Gertler T. S., Cherian S., DeKeyser J. M., Kearney J. A., George A. L., Jr. K(Na)1.1 gain-of-function preferentially dampens excitability of murine parvalbumin-positive interneurons. Neurobiol Dis. 168, 105713 (2022).
60. Mullen S. A. et al. Precision therapy for epilepsy due to KCNT1 mutations: A randomized trial of oral quinidine. Neurology. 90, e67-e72 (2018).
61. Xu D. et al. Precision therapy with quinidine of KCNT1-related epileptic disorders: A systematic review. Br J Clin Pharmacol. 88, 5096-112 (2022).
62. Le Roux M. et al. CACNA1A-associated epilepsy: Electroclinical findings and treatment response on seizures in 18 patients. Eur J Paediatr Neurol. 33, 75-85 (2021).
63. Hamdan F. F. et al. High Rate of Recurrent De Novo Mutations in Developmental and Epileptic Encephalopathies. Am J Hum Genet. 101, 664-85 (2017).
64. Epi4K Consortium et al. De novo mutations in epileptic encephalopathies. Nature. 501, 217-21 (2013).
65. Jiang X. et al. Both gain-of-function and loss-of-function de novo CACNA1A mutations cause severe developmental epileptic encephalopathies in the spectrum of Lennox-Gastaut syndrome. Epilepsia. 60, 1881-94 (2019).
66. Heyne H. O. et al. Predicting functional effects of missense variants in voltage-gated sodium and calcium channels. Sci Transl Med. 12, eaay6848 (2020).
67. Helbig K. L. et al. De Novo Pathogenic Variants in CACNA1E Cause Developmental and Epileptic Encephalopathy with Contractures, Macrocephaly, and Dyskinesias. Am J Hum Genet. 103, 666-78 (2018).
68. Gorman K. M. et al. Bi-allelic Loss-of-Function CACNA1B Mutations in Progressive Epilepsy-Dyskinesia. Am J Hum Genet. 104, 948-56 (2019).
69. Orenstein N. et al. A de novo GABRA2 missense mutation in severe early-onset epileptic encephalopathy with a choreiform movement disorder. Eur J Paediatr Neurol. 22, 516-24 (2018).
70. Hernandez C. C. et al. Dravet syndrome-associated mutations in GABRA1, GABRB2 and GABRG2 define the genetic landscape of defects of GABA(A) receptors. Brain Commun. 3, fcab033 (2021).
71. Papandreou A. et al. GABRB3 mutations: a new and emerging cause of early infantile epileptic encephalopathy. Dev Med Child Neurol. 58, 416-20 (2016).
72. Mohammadi N. A. et al. Distinct neurodevelopmental and epileptic phenotypes associated with gain- and loss-of-function GABRB2 variants. EBioMedicine. 106, 105236 (2024).
73. Absalom N. L. et al. Gain-of-function and loss-of-function GABRB3 variants lead to distinct clinical phenotypes in patients with developmental and epileptic encephalopathies. Nat Commun. 13, 1822 (2022).
74. Absalom N. L. et al. Gain-of-function GABRB3 variants identified in vigabatrin-hypersensitive epileptic encephalopathies. Brain Commun. 2, fcaa162 (2020).
75. Ahring P. K. et al. Gain-of-function variants in GABRD reveal a novel pathway for neurodevelopmental disorders and epilepsy. Brain. 145, 1299-309 (2022).
76. Carvill G. L. et al. Mutations in the GABA Transporter SLC6A1 Cause Epilepsy with Myoclonic-Atonic Seizures. Am J Hum Genet. 96, 808-15 (2015).
77. Gataullina S., Bienvenu T., Nabbout R., Huberfeld G., Dulac O. Gene mutations in paediatric epilepsies cause NMDA-pathy, and phasic and tonic GABA-pathy. Dev Med Child Neurol. 61, 891-8 (2019).
78. Guerrini R. et al. Cortical myoclonus in Angelman syndrome. Ann Neurol. 40, 39-48 (1996).
79. Coombs I. D. et al. A gain-of-function GRIA2 variant associated with neurodevelopmental delay and seizures: Functional characterization and targeted treatment. Epilepsia. 63, e156-e63 (2022).
80. Hansen K. B. et al. Structure, function, and allosteric modulation of NMDA receptors. J Gen Physiol. 150, 1081-105 (2018).

81. Lemke J. R. et al. Delineating the GRIN1 phenotypic spectrum: A distinct genetic NMDA receptor encephalopathy. Neurology. 86, 2171-8 (2016).
82. Blakes A. J. M., English J., Banka S., Basu H. A homozygous GRIN1 null variant causes a more severe phenotype of early infantile epileptic encephalopathy. Am J Med Genet A. 188, 595-9 (2022).
83. Endele S. et al. Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes. Nat Genet. 42, 1021-6 (2010).
84. Platzer K., Lemke J. R. GRIN2B-Related Neurodevelopmental Disorder. In: Adam M. P., Everman D. B., Mirzaa G. M. et al, editors. GeneReviews®. Seattle (WA): University of Washington, Seattle. Copyright © 1993-2022, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
85. Brock S. et al. Overlapping cortical malformations in patients with pathogenic variants in GRIN1 and GRIN2B. J Med Genet. 60, 183-92 (2023).
86. Swanger S. A. et al. Mechanistic Insight into NMDA Receptor Dysregulation by Rare Variants in the GluN2A and GluN2B Agonist Binding Domains. Am J Hum Genet. 99, 1261-80 (2016).
87. Platzer K., Krey I., Lemke J. R. GRIN2D-Related Developmental and Epileptic Encephalopathy. In: Adam M. P., Everman D. B., Mirzaa G. M. et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2018 [updated 2021 Mar 25].
88. Strehlow V. et al. GRIN2A-related disorders: genotype and functional consequence predict phenotype. Brain. 142, 80-92 (2019).
89. Xu Y. et al. Recurrent seizure-related GRIN1 variant: Molecular mechanism and targeted therapy. Ann Clin Transl Neurol. 8, 1480-94 (2021).
90. Defelippe V. M. et al. Toward responsible clinical n-of-1 strategies for rare diseases. Drug Discov Today. 28, 103688 (2023).
91. Krey I. et al. L-Serine Treatment is Associated with Improvements in Behavior, EEG, and Seizure Frequency in Individuals with GRIN-Related Disorders Due to Null Variants. Neurotherapeutics. 19, 334-41 (2022).
92. Julia-Palacios N. et al. L-serine treatment in patients with GRIN-related encephalopathy: a phase 2A, non-randomized study. Brain. 147, 1653-66 (2024).
93. Mullen S. A. et al. Glucose transporter 1 deficiency as a treatable cause of myoclonic astatic epilepsy. Arch Neurol. 68, 1152-5 (2011).
94. Vetro A. et al. ATP1A2- and ATP1A3-associated early profound epileptic encephalopathy and polymicrogyria. Brain. 144, 1435-50 (2021).
95. Vetro A. et al. Stretch-activated ion channel TMEM63B associates with developmental and epileptic encephalopathies and progressive neurodegeneration. Am J Hum Genet. 110, 1356-76 (2023).
96. Epi4K Consortium. De Novo Mutations in SLC1A2 and CACNA1A Are Important Causes of Epileptic Encephalopathies. Am J Hum Genet. 99, 287-98 (2016).
97. Hill S. F., Ziobro J., Jafar-Nejad P., Rigo F., Meisler M. H. Genetic interaction between Scn8a and potassium channel genes Kcna1 and Kcnq2. Epilepsia. 63, e125-e31 (2022).
98. Grant S. G. Synaptopathies: diseases of the synaptome. Curr Opin Neurobiol. 22, 522-9 (2012).
99. Verhage M., Sorensen J. B. SNAREopathies: Diversity in Mechanisms and Symptoms. Neuron. 107, 22-37 (2020).
100. Xian J. et al. Assessing the landscape of STXBP1-related disorders in 534 individuals. Brain. 145, 1668-83 (2021).
101. Klöckner C. et al. De novo variants in SNAP25 cause an early-onset developmental and epileptic encephalopathy. Genet Med. 23, 653-60 (2021).
102. Salpietro V. et al. Mutations in the Neuronal Vesicular SNARE VAMP2 Affect Synaptic Membrane Fusion and Impair Human Neurodevelopment. Am J Hum Genet. 104, 721-30 (2019).
103. Appenzeller S. et al. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. American Journal of Human Genetics. 95, 360-70 (2014).

104. Redler S. et al. Variants in CPLX1 in two families with autosomal-recessive severe infantile myoclonic epilepsy and ID. Eur J Hum Genet. 25, 889-93 (2017).
105. Finelli M. J. et al. The epilepsy-associated protein TBC1D24 is required for normal development, survival and vesicle trafficking in mammalian neurons. Hum Mol Genet. 28, 584-97 (2019).
106. Balestrini S. et al. TBC1D24 genotype-phenotype correlation: Epilepsies and other neurologic features. Neurology. 87, 77-85 (2016).
107. Llamosas N. et al. SYNGAP1 Controls the Maturation of Dendrites, Synaptic Function, and Network Activity in Developing Human Neurons. J Neurosci. 40, 7980-94 (2020).
108. Carvill G. L. et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet. 45, 825-30 (2013).
109. Hamdan F. F. et al. De novo SYNGAP1 mutations in nonsyndromic intellectual disability and autism. Biol Psychiatry. 69, 898-901 (2011).
110. Vlaskamp D. R. M. et al. SYNGAP1 encephalopathy: A distinctive generalized developmental and epileptic encephalopathy. Neurology. 92, E96-E107 (2019).
111. Zerem A. et al. The molecular and phenotypic spectrum of IQSEC2-related epilepsy. Epilepsia. 57, 1858-69 (2016).
112. Shoubridge C., Harvey R. J., Dudding-Byth T. IQSEC2 mutation update and review of the female-specific phenotype spectrum including intellectual disability and epilepsy. Hum Mutat. 40, 5-24 (2019).
113. Smogavec M. et al. Eight further individuals with intellectual disability and epilepsy carrying bi-allelic CNTNAP2 aberrations allow delineation of the mutational and phenotypic spectrum. J Med Genet. 53, 820-7 (2016).
114. Castronovo P. et al. Phenotypic spectrum of NRXN1 mono- and bi-allelic deficiency: A systematic review. Clin Genet. 97, 125-37 (2020).
115. Dejanovic B. et al. Simultaneous impairment of neuronal and metabolic function of mutated gephyrin in a patient with epileptic encephalopathy. EMBO Mol Med. 7, 1580-94 (2015).
116. Macha A. et al. Biallelic gephyrin variants lead to impaired GABAergic inhibition in a patient with developmental and epileptic encephalopathy. Hum Mol Genet. 31, 901-13 (2022).
117. Shimojima K. et al. Loss-of-function mutation of collybistin is responsible for X-linked mental retardation associated with epilepsy. Journal of human genetics. 56, 561-5 (2011).
118. Tian Y. et al. Truncating mutation in TANC2 in a Chinese boy associated with Lennox-Gastaut syndrome: a case report. BMC Pediatr. 21, 546 (2021).
119. Holder J. L., Jr., Quach M. M. The spectrum of epilepsy and electroencephalographic abnormalities due to SHANK3 loss-of-function mutations. Epilepsia. 57, 1651-9 (2016).
120. Phelan K., Rogers R. C., Boccuto L. Phelan-McDermid Syndrome. In: Adam M. P., Mirzaa G. M., Pagon R. A. et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2005 [updated 2018 Jun 7].
121. van der Knoop M. M. et al. Biallelic ADAM22 pathogenic variants cause progressive encephalopathy and infantile-onset refractory epilepsy. Brain. 145, 2301-12 (2022).
122. Lee W. S. et al. Cortical Dysplasia and the mTOR Pathway: How the Study of Human Brain Tissue Has Led to Insights into Epileptogenesis. Int J Mol Sci. 23, 1344 (2022).
123. Iffland P. H., 2nd, Carson V., Bordey A., Crino P. B. GATORopathies: The role of amino acid regulatory gene mutations in epilepsy and cortical malformations. Epilepsia. 60, 2163-73 (2019).
124. Ribierre T. et al. Second-hit mosaic mutation in mTORC1 repressor DEPDC5 causes focal cortical dysplasia-associated epilepsy. J Clin Invest. 128, 2452-8 (2018).
125. Gupta A. et al. Epilepsy and Neurodevelopmental Comorbidities in Tuberous Sclerosis Complex: A Natural History Study. Pediatr Neurol. 106, 10-6 (2020).
126. Specchio N. et al. Updated clinical recommendations for the management of tuberous sclerosis complex associated epilepsy. Eur J Paediatr Neurol. 47, 25-34 (2023).
127. Dibbens L. M. et al. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. Nat Genet. 45, 546-51 (2013).

128. Ishida S. et al. Mutations of DEPDC5 cause autosomal dominant focal epilepsies. Nat Genet. 45, 552-5 (2013).
129. Carvill G. L. et al. Epileptic spasms are a feature of DEPDC5 mTORopathy. Neurol Genet. 1, e17 (2015).
130. Pirozzi F. et al. Profiling PI3K-AKT-MTOR variants in focal brain malformations reveals new insights for diagnostic care. Brain. 145, 925-38 (2022).
131. French J. A. et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet. 388, 2153-63 (2016).

This randomised controlled trial analysed the efficacy of an mTOR inhibitor for drug-resistant focal epilepsy in tuberous sclerosis, showing that a precision therapy approach is efficacious for this disease.

132. Feng H. et al. Movement disorder in GNAO1 encephalopathy associated with gain-of-function mutations. Neurology. 89, 762-70 (2017).
133. Muir A. M. et al. Variants in GNAI1 cause a syndrome associated with variable features including developmental delay, seizures, and hypotonia. Genet Med. 23, 881-7 (2021).
134. Petrovski S. et al. Germline De Novo Mutations in GNB1 Cause Severe Neurodevelopmental Disability, Hypotonia, and Seizures. Am J Hum Genet. 98, 1001-10 (2016).
135. Van Loo K. M. J. et al. Epigenetic genes and epilepsy- emerging mechanisms and clinical applications. Nat Rev Neurol. 18, 530-43 (2022).

This review focuses on the increasing recognition of the role of various epigenetic processes in the epilepsies, highlighting mechanistic, diagnostic and therapeutic implications.

136. Cutri-French C. et al. Comparison of Core Features in Four Developmental Encephalopathies in the Rett Natural History Study. Ann Neurol. 88, 396-406 (2020).
137. Thomas R. H. et al. CHD2 myoclonic encephalopathy is frequently associated with self-induced seizures. Neurology. 84, 951-8 (2015).
138. Nakajima J. et al. De novo EEF1A2 mutations in patients with characteristic facial features, intellectual disability, autistic behaviors and epilepsy. Clin Genet. 87, 356-61 (2015).
139. Hunt D. et al. Whole exome sequencing in family trios reveals de novo mutations in PURA as a cause of severe neurodevelopmental delay and learning disability. J Med Genet. 51, 806-13 (2014).
140. Johannesen K. M. et al. PURA-Related Developmental and Epileptic Encephalopathy: Phenotypic and Genotypic Spectrum. Neurol Genet. 7, e613 (2021).
141. Hiraide T. et al. De novo variants in SETD1B are associated with intellectual disability, epilepsy and autism. Hum Genet. 137, 95-104 (2018).
142. LaFlamme C. W. et al. Diagnostic Utility of Genome-wide DNA Methylation Analysis in Genetically Unsolved Developmental and Epileptic Encephalopathies and Refinement of a CHD2 Episignature. Preprint at https://wwwmedrxivorg/content/101101/2023101123296741v1. (2023).
143. Aref-Eshghi E. et al. Diagnostic Utility of Genome-wide DNA Methylation Testing in Genetically Unsolved Individuals with Suspected Hereditary Conditions. Am J Hum Genet. 104, 685-700 (2019).
144. Muona M. et al. Biallelic Variants in UBA5 Link Dysfunctional UFM1 Ubiquitin-like Modifier Pathway to Severe Infantile-Onset Encephalopathy. Am J Hum Genet. 99, 683-94 (2016).
145. Sleyp Y. et al. De novo missense variants in the E3 ubiquitin ligase adaptor KLHL20 cause a developmental disorder with intellectual disability, epilepsy, and autism spectrum disorder. Genet Med. 24, 2464-74 (2022).
146. Oliver K. L. et al. WWOX developmental and epileptic encephalopathy: Understanding the epileptology and the mortality risk. Epilepsia. 64, 1351-67 (2023).

147. Nickel M. et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. Lancet Child Adolesc Health. 2, 582-90 (2018).
148. Schulz A. et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. N Engl J Med. 378, 1898-907 (2018).
149. Tassinari C. A. et al. Encephalopathy Related to Status Epilepticus During Slow Sleep (ESES) Including Landau-Kleffner Syndrome. In: Bureau M., Genton P., Dravet C. et al, editors. Epileptic Syndromes in Infancy, Childhood and Adolesence. 6th ed. United Kingdom: John Libbey Eurotext Ltd; 2019. p. 261-84.
150. Guerrini R., Mari F., Auvin S., Dravet C. Myoclonic Epilepsies in Infancy and Early Childhood. In: Bureau M., Genton P., Dravet C. et al, editors. Epileptic Syndromes in Infancy, Childhood and Adolesence. 6th ed. United Kingdom: John Libbey Eurotext Ltd; 2019. p. 173-88.
151. van der Veen S. et al. Movement Disorders in Patients With Genetic Developmental and Epileptic Encephalopathies. Neurology. 101, e1884-e92 (2023).
152. Stamberger H. et al. NEXMIF encephalopathy: an X-linked disorder with male and female phenotypic patterns. Genet Med. 23, 363-73 (2021).
153. Vlaskamp D. R. M. et al. Schizophrenia is a later-onset feature of PCDH19 Girls Clustering Epilepsy. Epilepsia. 60, 429-40 (2019).
154. Turner S. J. et al. Dysarthria and broader motor speech deficits in Dravet syndrome. Neurology. 88, 743-9 (2017).
155. Licheni S. H., McMahon J. M., Schneider A. L., Davey M. J., Scheffer I. E. Sleep problems in Dravet syndrome: a modifiable comorbidity. Dev Med Child Neurol. 60, 192-8 (2018).
156. Skluzacek J. V., Watts K. P., Parsy O., Wical B., Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia. 52 Suppl 2, 95-101 (2011).
157. D'Gama A. M. et al. Evaluation of the feasibility, diagnostic yield, and clinical utility of rapid genome sequencing in infantile epilepsy (Gene-STEPS): an international, multicentre, pilot cohort study. Lancet Neurol. 22, 812-25 (2023).

    This international collaborative study analysed the yield of rapid genome sequencing in infants presenting with seizures in the first year of life and highlighted the utility in determining management, prognostic and reproductive counselling.

158. Claes L. et al. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet. 68, 1327-32 (2001).
159. Scheffer I. E., Liao J. Deciphering the concepts behind "Epileptic encephalopathy" and "Developmental and epileptic encephalopathy". Eur J Paediatr Neurol. 24, 11-4 (2020).
160. Brett G. R. et al. Parental experiences of ultrarapid genomic testing for their critically unwell infants and children. Genet Med. 22, 1976-85 (2020).
161. Australian Genomics Health Alliance Acute Care F. et al. Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System. JAMA. 323, 2503-11 (2020).
162. Hirsch E. et al. ILAE definition of the Idiopathic Generalized Epilepsy Syndromes: Position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 63, 1475-99 (2022).
163. Fisher R. S. et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 58, 522-30 (2017).
164. Uddin M. et al. Germline and somatic mutations in STXBP1 with diverse neurodevelopmental phenotypes. Neurol Genet. 3, e199 (2017).
165. Nagarajan L. et al. Epilepsy surgery in PCDH19 related developmental and epileptic encephalopathy: A case report. Epilepsy Behav Rep. 19, 100560 (2022).
166. Howell K. B. et al. A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy. Epilepsia. 59, 1177-87 (2018).

167. Palmer E. E. et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: Evidence of clinical utility and cost effectiveness. Mol Genet Genomic Med. 6, 186-99 (2018).
168. Burgess R. et al. The Genetic Landscape of Epilepsy of Infancy with Migrating Focal Seizures. Ann Neurol. 86, 821-31 (2019).
169. Scheffer I. E., Nabbout R. SCN1A-related phenotypes: Epilepsy and beyond. Epilepsia. 60 Suppl 3, S17-S24 (2019).
170. Viswanathan S. et al. Solving the etiology of Developmental and Epileptic Encephalopathy with Spike-Wave activation in Sleep (D/EE-SWAS). Ann Neurol. In press, (2024).
171. Kolosky T. et al. Epilepsy surgery for children with epileptic spasms: A systematic review and meta-analysis with focus on predictors and outcomes. Epilepsia Open. (2024).
172. Mefford H. C. et al. Rare copy number variants are an important cause of epileptic encephalopathies. Ann Neurol. 70, 974-85 (2011).
173. Francis D. I. et al. Comparing saliva and blood for the detection of mosaic genomic abnormalities that cause syndromic intellectual disability. Eur J Hum Genet. 31, 521-5 (2022).
174. Smith L. et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 32, 266-80 (2023).
175. Myers C. T. et al. Parental Mosaicism in "De Novo" Epileptic Encephalopathies. N Engl J Med. 378, 1646-8 (2018).

    This study found that 8% of patients with a DEE thought to have a de novo pathogenic variant had a parent who was mosaic for their pathogenic variant, carrying significant reproductive counselling implications.

176. de Lange I. M. et al. Mosaicism of de novo pathogenic SCN1A variants in epilepsy is a frequent phenomenon that correlates with variable phenotypes. Epilepsia. 59, 690-703 (2018).
177. Ye Z. et al. Somatic Mosaic Mutation Gradient Detected in Trace Brain Tissue From Stereo-EEG Depth Electrodes. Neurology. (2022).
178. Ye Z. et al. Cerebrospinal fluid liquid biopsy for detecting somatic mosaicism in brain. Brain Commun. 3, fcaa235 (2021).
179. Levy M. A. et al. Functional correlation of genome-wide DNA methylation profiles in genetic neurodevelopmental disorders. Hum Mutat. 43, 1609-28 (2022).
180. Plecko B. On pathways and blind alleys-The importance of biomarkers in vitamin B(6)-dependent epilepsies. J Inherit Metab Dis. 46, 839-47 (2023).
181. Wirrell E. C. et al. International consensus on diagnosis and management of Dravet syndrome. Epilepsia. 63, 1761-77 (2022).
182. Wilmshurst J. M. et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia. 56, 1185-97 (2015).
183. Balestrini S. et al. Real-life survey of pitfalls and successes of precision medicine in genetic epilepsies. J Neurol Neurosurg Psychiatry. 92, 1044-52 (2021).
184. Wolff M., Brunklaus A., Zuberi S. M. Phenotypic spectrum and genetics of SCN2A-related disorders, treatment options, and outcomes in epilepsy and beyond. Epilepsia. 60 Suppl 3, S59-s67 (2019).
185. Gardella E., Møller R. S. Phenotypic and genetic spectrum of SCN8A-related disorders, treatment options, and outcomes. Epilepsia. 60 Suppl 3, S77-S85 (2019).
186. Bialer M. et al. Progress report on new antiepileptic drugs: A summary of the Sixteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVI): I. Drugs in preclinical and early clinical development. Epilepsia. 63, 2865-82 (2022).
187. Mullier B. et al. GRIN2B gain of function mutations are sensitive to radiprodil, a negative allosteric modulator of GluN2B-containing NMDA receptors. Neuropharmacology. 123, 322-31 (2017).

188. Devinsky O. et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 376, 2011-20 (2017).

This is a key randomised controlled trial of cannabidiol in epilepsy showing that it is effective in Dravet syndrome, moving from anecdotal reports of the efficacy of cannabidiol to class I evidence for its use in a DEE.

189. Devinsky O. et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 378, 1888-97 (2018).
190. Thiele E. A. et al. Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex: A Placebo-Controlled Randomized Clinical Trial. JAMA Neurol. 78, 285-92 (2021).
191. Hahn C. D. et al. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox-Gastaut syndrome (ELEKTRA). Epilepsia. 63, 2671-83 (2022).
192. Knight E. M. P. et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 21, 417-27 (2022).
193. Chiron C. et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet. 356, 1638-42 (2000).
194. Perez J. et al. Stiripentol: efficacy and tolerability in children with epilepsy. Epilepsia. 40, 1618-26 (1999).
195. Casaer P., Boel M. Fenfluramine as a potential antiepileptic drug. Epilepsia. 43, 205-6 (2002).
196. Ceulemans B. et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia. 53, 1131-9 (2012).
197. Lagae L. et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 394, 2243-54 (2019).

This randomised controlled trial showed that fenfluramine is highly efficacious in Dravet syndrome, highlighting that trials targeting a repurposed drug in specific epilepsy syndrome can offer major improvements to clinical care.

198. Nabbout R. et al. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 77, 300-8 (2020).
199. Bishop K. I. et al. Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (<5 years) with Dravet syndrome: A critical period for early neurodevelopment. Epilepsy Behav. 138, 108994 (2023).
200. Specchio N. et al. Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: A real-world study. Epilepsia. 61, 2405-14 (2020).
201. Guerrini R. et al. An examination of the efficacy and safety of fenfluramine in adults, children, and adolescents with Dravet syndrome in a real-world practice setting: A report from the Fenfluramine European Early Access Program. Epilepsia Open. 7, 578-87 (2022).
202. Knupp K. G. et al. Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial. JAMA Neurol. 79, 554-64 (2022).
203. Knupp K. G. et al. Fenfluramine provides clinically meaningful reduction in frequency of drop seizures in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. Epilepsia. 64, 139-51 (2023).
204. Franz D. N. et al. Everolimus for treatment-refractory seizures in TSC: Extension of a randomized controlled trial. Neurol Clin Pract. 8, 412-20 (2018).
205. Curatolo P. et al. Management of epilepsy associated with tuberous sclerosis complex: Updated clinical recommendations. Eur J Paediatr Neurol. 22, 738-48 (2018).
206. Sisodiya S. M., Scheffer I. E., Lowenstein D. H., Free S. L. Why should a neurologist worry about climate change? Lancet Neurol. 18, 335-6 (2019).

207. Guerrini R., Balestrini S., Wirrell E. C., Walker M. C. Monogenic Epilepsies: Disease Mechanisms, Clinical Phenotypes, and Targeted Therapies. Neurology. 97, 817-31 (2021).
208. Dalic L., Mullen S. A., Roulet Perez E., Scheffer I. Lamotrigine can be beneficial in patients with Dravet syndrome. Dev Med Child Neurol. 57, 200-2 (2015).
209. Zographos G. A., Russ-Hall S. J., Scheffer I. E. Does long-term phenytoin have a place in Dravet syndrome? Ann Clin Transl Neurol. 9, 2036-40 (2022).
210. Guerrini R., Parrini E., Marini C., Mei D. What is the role of next generation sequencing in status epilepticus? Epilepsy Behav. 101, 106373 (2019).
211. Guerrini R. Epilepsy in children. Lancet. 367, 499-524 (2006).
212. Kienitz R. et al. Benzodiazepines in the Management of Seizures and Status Epilepticus: A Review of Routes of Delivery, Pharmacokinetics, Efficacy, and Tolerability. CNS Drugs. 36, 951-75 (2022).
213. Penovich P. E., Rao V. R., Long L., Carrazana E., Rabinowicz A. L. Benzodiazepines for the Treatment of Seizure Clusters. CNS Drugs. 38, 125-40 (2024).
214. Spatola M., Alvarez V., Rossetti A. O. Benzodiazepine overtreatment in status epilepticus is related to higher need of intubation and longer hospitalization. Epilepsia. 54, e99-e102 (2013).
215. Villas N., Meskis M. A., Goodliffe S. Dravet syndrome: Characteristics, comorbidities, and caregiver concerns. Epilepsy Behav. 74, 81-6 (2017).
216. Guerrini R. et al. Developmental and epileptic encephalopathies: from genetic heterogeneity to phenotypic continuum. Physiol Rev. 103, 433-513 (2023).
217. Calle-Lopez Y. et al. Forced normalization: A systematic review. Epilepsia. 60, 1610-8 (2019).
218. Sabaz M. et al. Validation of a new quality of life measure for children with epilepsy. Epilepsia. 41, 765-74 (2000).
219. Chemaly N. et al. A European pilot study in Dravet Syndrome to delineate what really matters for the patients and families. Epilepsia Open. 9, 388-96 (2021).
220. Buck D., Smith M., Appleton R., Baker G. A., Jacoby A. The development and validation of the Epilepsy and Learning Disabilities Quality of Life (ELDQOL) scale. Epilepsy Behav. 10, 38-43 (2007).
221. Camfield C., Breau L., Camfield P. Impact of pediatric epilepsy on the family: a new scale for clinical and research use. Epilepsia. 42, 104-12 (2001).
222. Varni J. W., Seid M., Rode C. A. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 37, 126-39 (1999).
223. Abidin R. R. Parenting stress index–fourth edition (PSI-4) Lutz. FL: Psychological Assessment Resources. (2012).
224. Goodman R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry. 38, 581-6 (1997).
225. Nabbout R. et al. Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet Syndrome. Epilepsy Behav. 78, 232-42 (2018).
226. Brunklaus A., Dorris L., Zuberi S. M. Comorbidities and predictors of health-related quality of life in Dravet syndrome. Epilepsia. 52, 1476-82 (2011).
227. Makiello P. et al. Comorbidities and predictors of health-related quality of life in Dravet syndrome: A 10-year, prospective follow-up study. Epilepsia. 64, 1012-20 (2023).
228. Strzelczyk A. et al. A multicenter, matched case-control analysis comparing burden-of-illness in Dravet syndrome to refractory epilepsy and seizure remission in patients and caregivers in Germany. Epilepsia. 60, 1697-710 (2019).
229. Gallop K. et al. Lennox-Gastaut syndrome (LGS): development of conceptual models of health-related quality of life (HRQL) for caregivers and children. Seizure. 19, 23-30 (2010).
230. Strzelczyk A., Zuberi S. M., Striano P., Rosenow F., Schubert-Bast S. The burden of illness in Lennox-Gastaut syndrome: a systematic literature review. Orphanet J Rare Dis. 18, 42 (2023).

231. Bar C. et al. Experience of follow-up, quality of life, and transition from pediatric to adult healthcare of patients with tuberous sclerosis complex. Epilepsy Behav. 96, 23-7 (2019).
232. Catarino C. B. et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. Brain. 134, 2982-3010 (2011).
233. Turner T. J., Zourray C., Schorge S., Lignani G. Recent advances in gene therapy for neurodevelopmental disorders with epilepsy. J Neurochem. 157, 229-62 (2021).
234. Deverman B. E. et al. Cre-dependent selection yields AAV variants for widespread gene transfer to the adult brain. Nat Biotechnol. 34, 204-9 (2016).
235. Tanenhaus A. et al. Cell-Selective Adeno-Associated Virus-Mediated SCN1A Gene Regulation Therapy Rescues Mortality and Seizure Phenotypes in a Dravet Syndrome Mouse Model and Is Well Tolerated in Nonhuman Primates. Hum Gene Ther. 33, 579-97 (2022).
236. Ersoz E., Demir-Dora D. Unveiling the potential of antisense oligonucleotides: Mechanisms, therapies, and safety insights. Drug Dev Res. 85, e22187 (2024).
237. Burbano L. E. et al. Antisense oligonucleotide therapy for KCNT1 encephalopathy. JCI Insight. 7, e146090 (2022).
238. Li M. et al. Antisense oligonucleotide therapy reduces seizures and extends life span in an SCN2A gain-of-function epilepsy model. J Clin Invest. 131, e152079 (2021).
239. Han Z. et al. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. Sci Transl Med. 12, eaaz6100 (2020).
240. US National Library of Medicine. An Open-Label Study to Investigate the Safety of Single and Multiple Ascending Doses in Children and Adolescents With Dravet Syndrome. https://ClinicalTrials.gov/show/NCT04442295.
241. US National Library of Medicine. Ataluren for Nonsense Mutation in CDKL5 and Dravet Syndrome. https://ClinicalTrials.gov/show/NCT02758626.
242. US National Library of Medicine. Natural History Study of Infants and Children With Developmental and Epileptic Encephalopathies. https://ClinicalTrials.gov/show/NCT04537832.
243. Palmer E. E., Howell K., Scheffer I. E. Natural History Studies and Clinical Trial Readiness for Genetic Developmental and Epileptic Encephalopathies. Neurotherapeutics. 18, 1432-44 (2021).
244. Martins Custodio H. et al. Widespread genomic influences on phenotype in Dravet syndrome, a 'monogenic' condition. Brain. 146, 3885-97 (2023).

This study employs polygenic risk scores for longevity and intellect in a relatively small cohort of adults with Dravet syndrome, providing the first insights into the role of common variation in explaining these phenotypic features.

245. Balestrini S. et al. A registry for Dravet syndrome: The Italian experience. Epilepsia Open. 8, 517-34 (2023).
246. Campbell C. et al. The role of common genetic variation in presumed monogenic epilepsies. EBioMedicine. 81, 104098 (2022).
247. McTague A. et al. Migrating partial seizures of infancy: expansion of the electroclinical, radiological and pathological disease spectrum. Brain. 136, 1578-91 (2013).
248. Stodberg T. et al. Epilepsy syndromes, etiologies, and the use of next-generation sequencing in epilepsy presenting in the first 2 years of life: A population-based study. Epilepsia. 61, 2486-99 (2020).
249. Wu Y. W. et al. Incidence of Dravet Syndrome in a US Population. Pediatrics. 136, e1310-5 (2015).
250. Kloc M. L. et al. Spatial learning impairments and discoordination of entorhinal-hippocampal circuit coding following prolonged febrile seizures. Hippocampus. 33, 970-92 (2023).
251. O'Callaghan F. J. K. et al. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. Lancet Child Adolesc Health. 2, 715-25 (2018).

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Author contributions

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Competing Interests

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Supplementary information

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Tables

Table 1. Incidence estimates of developmental and epileptic encephalopathy (DEE) syndromes

Epilepsy syndrome	Cumulative Incidence per 100,000 live births (95% CI)	Methodology	Region and population size	Reference
Early Infantile Developmental and Epileptic Encephalopathy (including Ohtahara syndrome and Early myoclonic encephalopathy)	10 (5.8-16)	Prospective population-based, 3 years	Scotland; 169,500 live births	[9]
	Ohtahara syndrome 2.0 (0.5-7.9)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108, 861 live births	[3]
	Early myoclonic encephalopathy 2.0 (0.5-7.9)			
	Ohtahara syndrome 3.6 (1.8-7.2)	Retrospective population-based EEG and case record review period of 3 years	State of Victoria, Australia; 222,818 live births	[8]
	Early myoclonic encephalopathy 0.9 (0.23-3.6)			
KCNQ2 DEE	1.2 (0.14-4.3)	Prospective population-based, 3 years	Scotland; 169,500 live births	[9]
Epilepsy of Infancy with Migrating Focal Seizures	0.40 (CI not reported)	Surveillance study, 27 months	UK; members of British Paediatric Neurology Association	[247]
Infantile Epileptic Spasms Syndrome	30.7 (22.9-40.2)	Prospective population-based, 3 years	Scotland; 169,500 live births	[9]
	48.9 (37.0-64.7)	Retrospective population-based EEG and case record review period of 16 years.	Wellington region, New Zealand; 108,861 births	[3]
	32.6 (26-41)	Retrospective population-based EEG and case record review period of 3 years	State of Victoria, Australia; 222,818 births	[8]

	47.6 (34-69)	Retrospective epilepsy registry, EEG and medical record review period of 64 months	Northern Stockholm, Sweden; 69,333 births	[248]
Dravet Syndrome	6.5 (3.2-10)	Prospective population-based, 3 years	Scotland; 169,500 live births	[9]
	5.1 (2.1-12.2)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	[3]
	6.4 (3.2-12.5)	Retrospective population-based EEG and case record review period of 42 months	Northern California, USA; 125,547 births	[249]
PCDH19 Clustering Epilepsy	4.85 (1.97-9.15); female births	Prospective population-based, 3 years	Scotland; 169,500 live births	[9]
	3.1 (1-9.5)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	[3]
CDKL5 DEE	2.36 (0.80-5.59)	Prospective population-based, 3 years	Scotland; 169,500 live births	[9]
SLC2A1 DEE	4.13 (1.07-7.19)	Prospective population-based, 3 years; epilepsy onset <3 years	Scotland; 169,500 live births	[9]
Gelastic seizures with hypothalamic hamartoma	2.0 (0.5-7.9)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	[3]
Lennox-Gastaut Syndrome	13.2 (4.1-41.9)	Retrospective population-based EEG and case record review period of 16 years	Wellington region, New Zealand; 108,861 births	[3]

Myoclonic-atonic epilepsy	5.3 (2.4-10.1)	Prospective population-based, 3 years; epilepsy onset <3 years	Scotland; 169,500 live births	[9]
	16.64 (9.69-27.7)	Retrospective population-based EEG and case record review period of 16 years; epilepsy onset ≤16 years	Wellington region, New Zealand; 108,861 births	[3]
DEE-Spike Wave Activation in Sleep and Epileptic Encephalopathy-Spike Wave Activation in Sleep	12.8 (6.6-24.7)	Retrospective population-based EEG and case record review period of 16 years.	Wellington region, New Zealand; 108,861 births	[3]

EEG, electroencephalogram.

Figure Legends

Figure 1. ILAE Classification of Seizure Types.

Seizures are classified according to the 2017 International League Against Epilepsy (ILAE) Classification of Seizure Types. This formal revision of the international classification of seizure types in 2017 introduced updated terminology that has been adopted in clinical practice. [a]Degree of awareness is typically not specified. [b]Due to inadequate information or inability to place in another category.

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Figure 2: DEE Epilepsy syndromes and their aetiologies

Multiple DEE epilepsy syndromes have been delineated but many individuals have DEEs that cannot be classified into a specific epilepsy syndrome. DEEs with onset by 3 months of age are classified as Early Infantile DEE. The range of ages of seizure onset and median (maximal height of diamond shape) differ between DEE epilepsy syndromes. The predominant aetiology of each syndrome also varies according to syndrome. D/EE-SWAS, Developmental and/or Epileptic Encephalopathy with Spike-Wave Activation in Sleep; EIMFS, Epilepsy of Infancy with Migrating Focal Seizures; EMAtS, Epilepsy with myoclonic-atonic seizures; FIRES, Febrile infection-related epilepsy syndrome; LGS, Lennox-Gastaut syndrome.

Figure 3: Biological mechanisms implicated in DEEs

A wide range of biological processes are perturbed in DEEs. Synaptopathies include disruption of the SNARE machinery responsible for synaptic vesicle formation and release, synaptic scaffold proteins, post-synaptic receptors and signalling cascades. Dysfunction of sodium, potassium and calcium channels and ion and solute transporters also result in DEEs. A number of genes in key cellular processes including the MTOR pathway and G protein receptor signalling lead to DEEs. Epigenetic regulation including chromatin modification and transcription modification are also major causes of DEEs. Excitatory neurons are represented in blue, inhibitory neurons in green and glial cells in purple. Ca, calcium; cAMP, cyclic AMP; GTP, Guanosine-5'-triphosphate; MTOR, mammalian/mechanistic target of rapamycin; SNARE, Soluble N-ethylmaleimide-sensitive factor activating protein receptor; Ub, ubiquitin; UFM, Ubiquitin-fold modifier 1.

Figure 4: Examples of structural aetiologies of DEEs.

A. 7 Tesla MRI scan of a young patient with focal epilepsy. Extensive subcortical heterotopia in right anterior quadrant.
B. 7 Tesla MRI scan of a young patient with focal epilepsy. Polymicrogyria involving left posterior quadrant.
C. 7 Tesla MRI scan of patient with focal cortical dysplasia and focal epilepsy. There is thickening of the cortex surrounding the depth of a sulcus and high signal intensity of the underlying white matter. This anatomic location of the dysplasia is called 'bottom of the sulcus dysplasia' and the white matter abnormality is called a 'transmantle sign'.
D. Left hemispheric porencephaly in a patient with focal epilepsy.

Text Boxes

Box 1. The relationship between seizures and developmental impairment in DEEs

The relationship between seizures and developmental impairment in developmental and epileptic encephalopathies (DEEs) is complex. The prominent role of genes implicated in DEEs in early brain development indicates a considerable contribution of aetiology to cognitive outcome, so developmental impairment (compounded by slowing or regression) is inherent to DEEs. However, several lines of evidence suggest that ongoing seizures and/or epileptiform activity worsen outcomes. In animal models, induced (non-genetic) seizures affect early brain development and network formation resulting in cognitive impairment[250]. In humans, lack of a period of normal development in neonatal and infantile DEE make it difficult to determine any additive effect of seizures on cognitive outcome, but there are clear examples where improvement of seizure control or resolution of interictal EEG abnormalities ameliorate cognitive outcome. For example, cessation of specific sodium channel blockers, which are contraindicated in Dravet syndrome, leads to improved seizure control and developmental gains in children and adults with Dravet syndrome[232]. In Landau-Kleffner syndrome, the onset of EEG abnormalities is associated with an acquired epileptic aphasia, and cognitive gains are often linked to improvement in the EEG abnormalities with appropriate treatment, although this is not always the case. Finally, in Infantile Epileptic Spasms Syndrome, a shorter time to spasm cessation is associated with improved developmental outcome in the group of children without a clear aetiology[251].

Box 2. Most frequent structural aetiologies in individuals with DEEs

[bH1] Acquired structural aetiologies include
- [b1] Infection
- [b1] Perinatal hypoxic-ischaemic encephalopathy
- [b1] Perinatal stroke
- [b1] Neonatal hypoglycaemia
- [b1] Traumatic brain injury

[bH1] Genetic malformations of cortical development include
- [b1] Lissencephaly and pachygyria spectrum
- [b1] Focal cortical dysplasia
- [b1] Polymicrogyria
- [b1] Sturge-Weber Syndrome

ToC blurb

Developmental and epileptic encephalopathies are a severe group of epilepsies that usually first occur in infancy or childhood. In this Primer, Scheffer and colleagues review the epidemiology, pathophysiology, diagnosis, management and quality of life of patients with this condition, and highlights areas for future research.