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Epilepsia®

CRITICAL REVIEW

The epilepsy–autism phenotype associated with developmental and epileptic encephalopathies: New mechanism-based therapeutic options

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Abstract

Epilepsy and autism often co-occur in genetic developmental and epileptic encephalopathies (DEEs), but their underlying neurobiological processes remain poorly understood, complicating treatment. Advances in molecular genetics and understanding the neurodevelopmental pathogenesis of the epilepsy–autism phenotype may lead to mechanism-based treatments for children with DEEs and autism. Several genes, including the newly reported *PPFIA3*, *MYCBP2*, *DHX9*, *TMEM63B*, and *RELN*, are linked to various neurodevelopmental and epileptic disorders, intellectual disabilities, and autistic features. These

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findings underscore the clinical heterogeneity of genetic DEEs and suggest diverse neurobiological mechanisms influenced by genetic, epigenetic, and environmental factors. Mechanisms linking epilepsy and autism include γ-aminobutyric acidergic (GABAergic) signaling dysregulation, synaptic plasticity, disrupted functional connectivity, and neuroinflammatory responses. GABA system abnormalities, critical for inhibitory neurotransmission, contribute to both conditions. Dysregulation of the mechanistic target of rapamycin (mTOR) pathway and neuroinflammation are also pivotal, affecting seizure generation, drug resistance, and neuropsychiatric comorbidities. Abnormal synaptic function and connectivity further underscore the epilepsy–autism phenotype. New treatment options targeting specific mechanisms linked to the epilepsy–autism phenotype are emerging. Genetic variants in potassium channel genes like *KCNQ2* and *KCNT1* are frequent causes of early onset DEEs. Personalized treatments like retigabine and quinidine have been explored with heterogeneous responses. Efforts are ongoing to develop more effective *KCNQ* activators and *KCNT1* blockers. *SCN1A* genetic variants, particularly in Dravet syndrome, show potential for treatment of autistic symptoms with low-dose clonazepam, fenfluramine, and cannabidiol, although human trials have yet to consistently replicate animal model successes. Early intervention before the age of 3 years, particularly in *SCN1A*- and tuberous sclerosis complex-related DEEs, is crucial. Additionally, targeting the mTOR pathway shows promise for seizure control and managing epilepsy-associated comorbidities. Understanding the distinct autism spectrum disorder phenotype in DEEs and implementing early behavioral interventions are essential for improving outcomes. Despite genetic advances, significant challenges persist in diagnosing and treating DEE-associated epilepsy–autism phenotypes. Future clinical trials should adopt precision health approaches to improve neurodevelopmental outcomes.

KEYWORDS

autism spectrum disorder, developmental and epileptic encephalopathies, epilepsy, newly reported DEE-associated genes, personalized treatment

1 | INTRODUCTION

Epilepsy and autism spectrum disorder (ASD) frequently co-occur during early childhood. The prevalence of epilepsy in individuals with autism, and vice versa, significantly exceeds reported estimates in the general population.[1] In a systematic review of 74 studies, the overall period prevalence is 11% of epilepsy in autism and 8% of autism in epilepsy,[2] compared with a prevalence of 1%–2% in the general population.[3]

Genetic developmental and epileptic encephalopathies (DEEs) constitute a group of conditions that often combine early onset, drug-resistant seizures with a range of complex neurological and neuropsychiatric symptoms, including ASD.[4] Seizure onset typically precedes the clinical detection of ASD, although delays in developmental trajectories may sometimes be observed earlier.[5]

Because the autism phenotype may not follow the usual developmental trajectories in DEEs, the diagnosis can be challenging. However, prompt recognition of ASD in children with DEEs is important, and timely diagnosis is crucial to allow appropriate early intervention.

The clinical presentation differs between patients with ASD who also have epilepsy and patients with DEEs who meet the criteria for ASD. In the former group, ASD is the primary diagnosis with co-occurring epilepsy, whereas in the latter group, DEE is the primary condition, and ASD symptoms are part of the broader neurodevelopmental impact of the underlying encephalopathy. These differences reflect variations in the severity and progression of

Key points

- Early onset genetic DEEs offer a valuable model to explore the neurobiological process underlying the epilepsy–autism phenotype.
- Common pathogenetic mechanisms linking these two disorders include function in synaptic plasticity, dysregulation of the GABA system, abnormal functional connectivity, and dysregulation of the mTOR signaling cascade and neuroinflammation.
- Mechanism-based treatment options for children with early onset genetic DEE-associated autism phenotype have the potential to improve overall quality of life.

neurodevelopmental impairments, with DEEs typically involving more profound cognitive and functional deficits. Early onset genetic DEEs offer a valuable model for exploring the potential genetic connection between epilepsy and ASD.

It is well accepted that the co-occurrence of these two brain disorders is related to the disruption of shared neurodevelopmental pathways, possibly as a consequence of a monogenic disorder.[6] Specific changes in fundamental neurobiological processes are known to be involved in both disorders, such as ion channel behavior, synaptic function, and transcription regulation.[4] Furthermore, epilepsy-specific susceptibility mechanisms can lead to neurobiological abnormalities related to ASD susceptibility.[7]

Recent advances in molecular genetics have revealed that single-gene variants can impact early brain development, resulting in structural and functional changes that lead to an epilepsy–autism phenotype. Early molecular genetic diagnosis is crucial for enabling timely pharmacological intervention and reducing the global clinical burden of DEEs. Whole-exome sequencing has become the primary molecular genetic testing method for children with DEEs.

Despite some recent advances, treating DEEs remains challenging. However, recent improvements in the understanding of the pathogenic mechanisms contributing to the epilepsy–autism phenotype associated with DEEs has raised hopes that targeted molecular therapies may enhance neurological outcomes for affected children. The aim of this article is to describe the epilepsy–autism phenotype in early onset genetic DEEs, to discuss the common pathogenic mechanisms linking these two disorders, to provide a brief overview of the current status of mechanism-based treatment options for children with DEE-related epilepsy autism phenotype, and to discuss future perspectives of research.

2 | SEARCH STRATEGY

This article is based on peer-reviewed publications from January 2017 to March 2024. Searching PubMed for the words "epilepsy" and "autism" using the combining term "AND" returned 2246 possible articles (accessed March 31, 2024). Our more refined search terms were "genetic developmental and epileptic encephalopathy" AND (as individual combinatory terms) "autism spectrum disorder", "phenotype", "treatment", "gene therapy", "targeted therapies", "genes", "gene function", "loss of function", "gain of function", "diagnostic criteria", "mechanisms", and "neurobiology". Selection criteria from full-text outputs were the novelty of study findings and their relevance to neurologists, with inclusion decided collectively by all authors. For clarity, relevant historical references outside the search timeframe were also included.

3 | EPILEPSY–AUTISM PHENOTYPE IN DEEs

DEEs, including those with syndromic presentations, exhibit significant clinical variability that can include the presence of ASD features along with epilepsy and cognitive impairment. The prevalence of ASD within DEEs is likely underestimated due to the absence of comprehensive diagnostic assessments utilizing gold-standardized tools such as Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and Autism Diagnostic Interview - Revised (ADI-R). Detailed clinical analysis showed a high prevalence of autism in many DEEs, with a percentage of autistic features in >60% individuals with *SCN1A*-positive Dravet syndrome,[8] >50% for patients with *KCN1B*-related DEE,[9] and up to 60% in children with *NRXN1*-related DEE.[10]

Genetic and clinical findings of the epilepsy–autism phenotype associated with DEE are summarized in Table 1.

Among the well-known DEEs, emerging studies are focusing on profiling ASD beyond the epilepsy phenotype, highlighting specific features of ASD in particular genetic conditions.

Large cohort studies have provided evidence of association between pathogenic gene variants and specific phenotype features, highlighting a wide range of possible scenarios even for the same gene.[11] The ASD profile of patients with *SCN1A*-related Dravet syndrome is characterized by a relative preservation of social skills.[12] In *PCDH19*

TABLE 1 Genetic and clinical findings of the epilepsy–autism phenotype associated with DEEs.

Gene	Epilepsy phenotype	Prevalence of ID	Prevalence of ASD	Cognitive and autism profile	Reference
SCN1A	DS Early onset DEE GEFS+ MAE EIMFS	Up to 77% (GEFS+ excluded)[a]	24%–61% in children, 61.5% in adults (GEFS+ excluded)	Expressive and receptive language deficits, visuospatial difficulties Relative preservation of social skills Poor peer relationships and lack of emotional reciprocity up to 79%, restricted interests up to 69%	8,11–14
SCN2A	SeLFNIE Episodic ataxia Early onset (<3 months) or late onset (>3 months) DEE	Only in DEE phenotype	Up to 50% in DEE phenotype	ID: + ➔ +++ Reduced social interaction and repetitive behaviors	15,16
SCN8A	SeLIE Intermediate focal epilepsy DEE Generalized epilepsy Unclassifiable epilepsy Neurodevelopmental disorder without epilepsy	Up to 67% in DEE phenotype	Up to 28% in DEE phenotype	SeLIE: normal cognition Intermediate focal epilepsy: + DEE: +++ Generalized epilepsy: +; autistic features Neurodevelopmental disorders group: +	17
KCNQ2	SeLNE Early onset DEE Sleep-activated epileptiform activity	Up to 77% in DEE phenotype	Up to 67% with autistic features in DEE phenotype	Prominent language impairment Difficulties in social interaction, understanding emotions, stereotypic movements	18,19
KCNQ3	SeLNE and SeLIE DEE Sleep-activated epileptiform activity	NA	Diagnosis of ASD up to 45%, autistic features up to 55% in DEE phenotype	Stereotypies, mouthing nonfood objects, and aggressive, impulsive, and self-injurious behaviors	20,21
TSC1/2	75% in *TSC1* 81% in *TSC2* Children with *TSC2* variants more prone to have ES	20% in *TSC1* 51% in *TSC2*	21.1%	ID: + ➔ +++ (mostly +/++) ADHD associated with both increased severity of epilepsy and features of autism/pervasive developmental disorder Early identifiers of autism or autisticlike features in patients with TSC: early DD or slowing in nonverbal cognition	22–24
SYNGAP-1	98.2%, mostly generalized seizures (96.5%)	96.5%	50%–73%	ID: ++ (87.7%) Restricted interests and repetitive behaviors, attention deficits	25,26

TABLE 1 (Continued)

Gene	Epilepsy phenotype	Prevalence of ID	Prevalence of ASD	Cognitive and autism profile	Reference
PCDH19	100%, clustered and fever-induced seizures, mostly focal seizures with affective symptoms	Up to 59%	50.8%	ID: + → ++ Communication and social interaction domains mostly affected; low rate of hand stereotypies, sensory interests, and self-injuries	27,28
STXBP1	Up to 89%, mainly in the first year of life, focal onset seizures as the most common seizure type	100%	42%	ID: +++ Stereotypies (hand, figure of eight head)	29–31

Note: Due to the great variability in early onset genetic DEEs, the rate of ID and ASD is highly variable and should be investigated in every child. Level of ID: + = mild to moderate, ++ = moderate to severe, +++ = severe to profound.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DD, developmental delay; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; EIMFS, epilepsy of infancy with migrating focal seizures; ES, epileptic spasms; GEFS+, genetic epilepsy with febrile seizure plus; ID, intellectual disability; MAE, myoclonic atonic epilepsy; NA, not available; SeLFNIE, self-limited familial neonatal–infantile epilepsy; SeLIE, self- limited (familial) infantile epilepsy; SeLNE, self-limited (familial) neonatal epilepsy.

[a]ID is a mandatory criterion in DS.[32]

clustering epilepsy (*PCDH19*-CE), the ASD profile shows a specific phenotype, with the communication and social interaction domains mostly affected, and a low rate of hand stereotypies, sensory interests, and self-injuries.[27,33] In *SYNGAP1*-related DEE, ASD is mainly characterized by restricted interests and repetitive behaviors.[25]

The severity of ASD is often linked with the severity of intellectual disability (ID) and in some conditions, ASD is related to an earlier age at onset.[34] These findings may suggest that early and severe epilepsy contribute to the deleterious consequences in addition to the impact of gene dysfunction.

Epilepsy and ASD can manifest different evolutions over time. In many genetic DEEs, such as Dravet syndrome,[35] *KCNQ2*-related DEE,[36] and *PCDH19*-CE, seizure frequency decreases with increasing age, whereas ASD, other behavioral disorders, and ID remain as the main clinical problems during adulthood.

ASD is increasingly linked to the genetic underlying pathophysiological mechanisms rather than being exclusively related to epilepsy. Alterations in developmental trajectories during cortical neurogenesis are emerging as major contributors to the etiology of both autism and epilepsy phenotypes. Dysregulated neurogenesis programs may lead to impaired neuronal wiring. This has been documented through in vitro studies on induced pluripotent stem cells and organoids,[37] as well as by means of morphometric analyses that document alterations in cortical thickness, local gyrification index, and reductions in surface area in temporolimbic cortices,[38] which are well known to be associated with ASD.

There is a well-recognized correlation between atypical mesiotemporal anatomy and autism. This correlation has been demonstrated through magnetic resonance imaging (MRI) and postmortem brain studies, revealing abnormalities in the hippocampus, amygdala, and connected limbic structures in individuals with autism. In *PCDH19*-CE, patients displayed bilateral reductions in the local gyrification index within limbic cortical areas, including the parahippocampal and entorhinal cortex, as well as the fusiform and lingual gyri. Additionally, they exhibited altered diffusivity features in the underlying white matter. These morphometric abnormalities were more prominent in patients with an earlier onset of seizures, confirming the detrimental effects of early and severe epilepsy on a developing brain, in addition to the impact of the genetic variant on neurogenesis.[38]

4 | NEWLY REPORTED DEEs ASSOCIATED WITH EPILEPSY–AUTISM PHENOTYPE

The genetic causes of early onset DEEs are increasingly recognized, and new rare gene variants are described

expanding the field of genetic DEEs. Table 2 summarizes the genetic and clinical findings of newly reported DEEs associated with epilepsy–autism phenotype. The following genes have been recently described and provide examples of a complex interplay between genes and neurodevelopment.

PPFIA3 encodes protein tyrosine phosphatase, receptor-type, F-polypeptide-interacting-protein-alpha-3, involved in synapse formation and function, synaptic vesicle transport, and presynaptic active zone assembly. A syndromic neurodevelopmental disorder characterized by developmental delay, ID, dysmorphisms, abnormal head size, hypotonia, ASD or autistic features, and epilepsy has been reported in cohort of 20 individuals with pathogenic variants in *PPFIA3*. A study of transgenic fruit flies showed that pathogenic *PPFIA3* variants are dominant-negative loss of function (LoF) alleles that perturb multiple developmental processes and synapse formation.[39]

MYCBP2 encodes an E3 ubiquitin-protein ligase with evolutionarily conserved functions in axon development. A neurodevelopmental disorder characterized by corpus callosum abnormalities, developmental delay, ID, epilepsy, and autistic features has been described in a cohort of eight patients with de novo LoF *MYCBP2* variants.[40]

An in vivo animal model (*Caenorhabditis elegans*) obtained with *CRISPR* gene editing showed that these variants result in abnormal axon development, increased axonal autophagosome formation, and abnormal behavioral habituation.[40]

The *DHX9* gene encodes for a BRCA1-interacting nuclear helicase. Two *DHX9*-associated disease traits have been recently described, including neurodevelopmental disorders and axonal Charcot–Marie–Tooth disease in 20 individuals with de novo, ultrarare, heterozygous missense variants with LoF effect. Functional studies demonstrated that pathogenic *DHX9* variants cause abnormal *DHX9* cellular distribution and in some cases alter helicase adenosine triphosphatase activity. The $Dhx9^{-/-}$ mouse model exhibited behavioral, neurological, and growth abnormalities.[41]

TMEM63B encodes for a stretch-activated ion channel. De novo heterozygous *TMEM63B* variants cause early onset DEEs, all associated with white matter disease, corpus callosum abnormalities, and variable cortical, cerebellar, and hematological abnormalities. The neurological phenotype is severe and includes autistic features. Variants affecting transmembrane domains of the channel demonstrated inward leak cation currents across the mutated channel even in isotonic conditions in transfected Neuro2a cells, and the response to hypo-osmotic challenge was impaired.[42]

RELN encodes for reelin, a large extracellular protein that plays several roles in brain development and function by regulating neuronal migration, laminar organization, dendritic morphogenesis, and neurotransmission. In humans, biallelic *RELN* pathogenic variants have been initially associated with a variant of lissencephaly with cerebellar hypoplasia.[44] The phenotypic spectrum has expanded since and monoallelic *RELN* variants have been associated with moderate frontotemporal lissencephaly, less severe than in biallelic individuals, with normal cerebellar structure and a constant association with ID and severe behavioral dysfunction.[43]

Because genetic DEE-associated epilepsy and ASD phenotypes are characterized by a clinical heterogeneity, it is reasonable to think that many different neurobiological mechanisms may be responsible, interacting together, and with a complex interplay between genetic, epigenetic, and environmental factors.

5 | MECHANISMS THAT POTENTIALLY LINK EPILEPSY AND AUTISM IN DEEs

The identification of specific genes involved in DEEs and ASD has led to the recognition of shared molecular pathways.[4] Causal mechanisms for both conditions include abnormalities in fundamental neurobiological processes such as γ-aminobutyric acidergic (GABAergic) signaling, synaptic plasticity, functional connectivity, and neuroimmune interactions.[45] Such mechanisms may be grouped into abnormalities of ion channel behavior, synaptic function and structure, and the mechanistic target of rapamycin (mTOR) pathway.[46,47] Disruptions within these processes can contribute to both DEEs and ASD, highlighting the complex interplay between genetics and neurodevelopment. These abnormalities underscore the intricate interplay of various factors contributing to the epilepsy–autism phenotype.

5.1 | Dysregulation of GABA system

GABA is the most abundant and widely distributed inhibitory neurotransmitter in the brain. Several clinical, neuroimaging, and neuropathological studies have shown that both epilepsy and ASD display abnormalities in GABA neurotransmission.[48,49] This neurodevelopmental defect in GABAergic circuitry is likely the common mechanism leading to an excitatory imbalance occurring in both diseases, possibly also explaining their high comorbidity rate.

The role of changes in GABA neurotransmission associated with epilepsy is very well known and has recently received increasing attention. Modulating GABAergic signaling remains an essential approach for epilepsy

TABLE 2 Genetic and clinical findings of newly reported developmental and epileptic encephalopathies associated with epilepsy–autism phenotype.

Gene	Patient	Epilepsy phenotype	Prevalence of ID	Prevalence of ASD	Cognitive and autism profile	Other findings	Reference
PPFIA3	20	6/20 (30%) 9/20 (45%) with EEG abnormalities Multiple sz types	18/20 (90%)[a]	4/20 (20%) with ASD 5/20 (25%) with autistic features	Delayed speech development (16/20, 80%)	Dysmorphic features (13/20, 65%) GI issues (10/20, 50%) Macro-/microcephaly (9/20, 45%) Hypotonus (8/20, 40%)	39
MYCBP2	8	3/8 (37%)	4/8 (50%)	5/8 (62%)	NA	Facial dysmorphisms (8/8, 100%) Corpus callosum defects (4/8, 50%) Bilateral hearing impairment (2/8, 25%)	40
DHX9	20[b]	6/17 (35%)	8/14 (57%)[c]	Neuropsychiatric disorders including autism in 8/17 (47%)	NA	Dysmorphic features (8/17, 47%) Axial hypotonia (7/17, 41%) Charcot–Marie–Tooth disease (3/17, 18%)	41
TMEM63B	17	17/17 (100%) Very early onset (from birth to 3 years)	17/17 (100%)	2/17 (12%)	Moderate to profound ID Severe motor impairment	Multiple MRI abnormalities (17/17, 100%) Dysphagia (11/17, 65%) Hematological issues (12/17, 71%)	42
RELN	19	7/16 (44%)[c]	19/19 (100%)	1 with ASD, 1 with autistic features	From borderline to severe More severe ID in frontotemporal LIS compared to anterior temporal LIS	Monoallelic *RELN* variants ➔ moderate frontotemporal LIS, less severe than in biallelic individuals, with normal cerebellar structure Behavioral issues	43

Abbreviations: ASD, autism spectrum disorder; EEG, electroencephalographic; GI, gastrointestinal; ID, intellectual disability; LIS, lissencephaly; MRI, magnetic resonance imaging; NA, not available; sz, seizure.

[a]Two individuals could not be assessed for this feature due to premature mortality.

[b]Clinical records for robust organismal phenotyping of 17 individuals with candidate disease-causing *DHX9* variants were available (14 with neurodevelopmental disorders and three with Charcot–Marie–Tooth disease).

[c]Available data.

treatment. GABAergic signaling potentiation is the cardinal mechanism of many antiseizure medications (e.g., benzodiazepines/phenobarbital, felbamate vigabatrin, tiagabine, gabapentin, valproate). Conversely, drugs blocking GABA type A receptors ($GABA_AR$s; bicuculline, pentylenetetrazol) can provoke seizures in experimental animal models. Furthermore, several hundred genetic variants in $GABA_AR$ subunits have been associated with epilepsy.[50]

Similarly, in past decades, increasing evidence confirmed the role of altered inhibitory/excitatory signaling in ASD. Functional neuroimaging and magnetic resonance spectroscopy studies documented the reduction of $GABA_AR$ activity and an altered excitatory/inhibitory signaling (lower GABA/glutamate ratio) in both adults and children with ASD.[51,52] Studies in both animal models and postmortem human samples confirmed the alteration of GABAergic neurons and circuits in ASD, further supporting the hypothesis that GABA/glutamate abnormalities underlie sensory challenges in ASD.[53] Finally, human genetic studies indicate an association between ASD, genes for $GABA_AR$ subunits, and genes controlling GABAergic neuron development or synaptic function.

The impaired GABAergic converging pathway for epilepsy and ASD may result from the dysfunction of different genes, with either an indirect (presynaptic) or direct (postsynaptic) mechanism.

Pathogenic variants in *MECP2* (Rett syndrome) cause an indirect decrease in the expression of the *GABRB3* gene.[54] Variants in other DEE genes (*STXBP1, DNM1, PRRT2*, *SCN1A*, and *TSC2*), with increased susceptibility to ASD, also indirectly impair GABA release through a presynaptic mechanism.[55,56]

Variants in genes coding for different $GABA_AR$ subunits (*GABRA1, GABRG2, GABRB2, GABRB3*) impair GABAergic signaling via postsynaptic mechanisms, altering the channel gating efficiency or the receptor expression. *GABRA1* variants with a gain of function (GoF) effect have been reported in severe DEEs.

Variants in the *GABRB3, GABRD*, and *GABRA1* genes have been phenotypically evaluated in cohort studies.[57–59] In all cases, both LoF and GoF were observed, the LoF variant leading to a milder phenotype with the largest ASD and attention-deficit/hyperactivity disorder comorbidities (up to 82%; Danish Epilepsy Center international registry). Neuronal chloride regulation, controlled by KCC2 and NKCC1 cotransporters, dynamically modulates GABAergic inhibition. Dysregulation of these transporters is linked to both ASD and epilepsy.[60,61]

The GABA transporter encoded by the *SLC6A1* gene plays a critical role in the reuptake of GABA from the synaptic cleft, thereby maintaining inhibitory neurotransmission homeostasis.[62] Genetic variants in *SLC6A1* can impair GABA clearance, leading to altered synaptic signaling, which is associated with the development of epilepsy and neurodevelopmental disorders such as ASD, due to disrupted inhibitory–excitatory balance in neuronal circuits.[63]

5.2 | Dysregulation of mTOR signaling cascade and neuroinflammation

Dysregulation of the mTOR pathway and neuroinflammation play pivotal roles in the complex landscape of epileptogenesis, extending seizure generation to encompass drug resistance and neuropsychiatric comorbidities, including the epilepsy–autism phenotype. This multifaceted process arises from a confluence of genetic and acquired factors, leading to a cascade of pathological changes that disrupt brain homeostasis.[64]

Recent advances in our comprehension of epileptogenesis highlight the need to target specific cellular and molecular pathways to interfere with its progression and associate comorbidities. Notably, both mTOR dysregulation and neuroinflammation have emerged as critical players, evident in human brain specimens from drug-resistant structural epilepsies and corresponding animal models.[65,66] Encouragingly, therapeutic interventions aimed at mitigating either mTOR hyperactivation or aberrant neuroinflammatory responses have shown promising efficacy.[65,67] Interestingly, the involvement of both mTOR and immune dysregulation in ASD is also an area of active research.[68–70]

mTOR and neuroinflammation are functionally intertwined at various levels. In animal models mimicking structural epilepsy etiologies, mTOR and neuroinflammation are upregulated in the same brain regions and cell types, activating convergent molecular mechanisms that greatly contribute to seizures, neuropathology, and comorbidities, including ASD.[65] Additionally, mTOR signaling modulates intracellular pathways and the expression of interleukins and their receptors in immune cells, influencing immune effector cell responses and functions.[71]

Hyperactivation of mTOR signaling may disrupt proper differentiation and function of both innate and adaptive immune cells.[71] mTOR also regulates transcription factors involved in inflammatory and anti-inflammatory gene transcription, including NF-κB, STAT3, HIF1α, and PPARγ, with a recognized direct role in the activation of inflammatory pathways in microglia. Reciprocally, cytokines and toll-like receptor ligands, central activators of the neuroinflammatory cascade in epilepsy, also induce mTOR signaling.[72] Excessive activation of mTORC1 in glial cells and neurons has been associated with decreased

activity of two crucial cellular pathways, the ubiquitin–proteasome system and autophagy.[65,73,74] Dysfunction in these systems leads to the accumulation of damaged organelles and proteins, activation of the inflammasome, and heightened oxidative stress. Moreover, experimental evidence indicates that impaired autophagy in microglia exacerbates neuroinflammation induced by various stimuli, highlighting its role in modulating inflammatory processes.[75]

Hyperactivation of mTOR has also been linked to cellular senescence.[76,77] Notably, senescent cells undergo changes in gene expression that result in the senescence-associated secretory phenotype, which chiefly includes pro-inflammatory cytokines (i.e., IL-1β, IL-6, IL-8) and matrix metalloproteinases (MMPs), thus contributing to a chronic inflammatory state.[78]

Preclinical data support further attempts to modulate seizures and epileptogenesis by targeting mTOR activity and neuroinflammation.[64,65,79] Further research is needed to directly compare the efficacy and safety of different inhibitors in monotherapy versus combination therapy in patients with epilepsy associated with hyperactivation of the mTOR pathway. For neuroinflammation, a very limited number of proof-of-concept clinical studies, or case report studies, have provided initial evidence of efficacy of some repurposed anti-inflammatory drugs against drug-resistant epilepsies caused by mTOR pathway genes.[65] The combination of drugs targeting mTOR and pathogenic inflammatory mediators may maximize the therapeutic effects of each treatment alone. In this context, gaining a deeper understanding of the cellular and molecular interactions between mTOR and neuroinflammation in DEEs may shed light on the underlying pathophysiological mechanisms of the epilepsy–autism phenotype and provide therapeutic avenues.[65]

5.3 | Abnormal functional connectivity

Networks with altered functional connectivity are increasingly recognized as underlying the co-occurrence of epilepsy and ASD,[80,81] and one example is the epilepsy–autism phenotype in the context of tuberous sclerosis complex (TSC).[82–86] Interestingly, pathological brain connectivity patterns have been identified in individuals with TSC, and ASD may reveal neurophysiological markers, facilitating early intervention.[87] Notably, research by Sato et al. suggests that white matter microstructural integrity is linked to connectivity dysfunction, which underlies co-occurring neurodevelopmental disorders.[83] Evidence indicates that large-scale network deviations are associated with both ASD and mTOR-related connectopathy (characterized by frontocorticostriatal hyperconnectivity and rescued by mTOR inhibition), as recently demonstrated using resting-state functional MRI, electrophysiology, and computational modeling in *Tsc2* haploinsufficient mice. Sleep disturbances are a prevalent neurological symptom and can diminish the quality of life in TSC patients. Examining atypical functional connectivity in TSC may elucidate novel mechanisms for sleep dysfunction, as reported in recent experimental models.[88] Moreover, reduction in connectivity has been documented also in a *SYNGAP1* rat model,[89] in Dravet syndrome,[90] in *SCN8A*-related epilepsy,[91] and in *STXBP1* encephalopathy.[92]

5.4 | Impaired synaptic plasticity

Synaptogenesis begins during prenatal development at approximately the 20th week of gestation. Synapse formation peaks during infancy, with synaptic density reaching its highest point at approximately 2–3 years of age. Subsequently, a phase of synaptic pruning occurs during childhood and adolescence, refining and strengthening the most relevant connections while eliminating redundant ones, thus shaping the mature neural circuitry of the brain.[93] Synaptic connectivity plays a pivotal role in various developmental processes within the nervous system. During neural differentiation, the formation of synapses facilitates the specialization of neurons into distinct cell types, guiding them toward specific functions within neural networks. Additionally, synaptic connections support the neuronal migration. As neural circuits begin to be established, synaptic connectivity enables the communication and coordination of neuronal activity, which is essential for the refinement and maturation of functional brain networks. This time window of synaptogenesis, like all steps of brain development, is a window of vulnerability to both genetic and environmental factors.[94]

Accumulating data on synaptic abnormalities in ASD, including postmortem studies, animal models, and neuroimaging findings, have raised concerns about the role of synapses in the neurobiology of ASD.[95] In the case of epilepsy, there is obviously aberrant synaptic activity contributing to the generation and propagation of seizures. Interestingly, gene-regulating synaptic functions have been described in patients with both ASD and epilepsy.[4] This could be in children with ASD who develop epilepsy or in patients with DEEs who could also have ASD (Figure 1).

Pathogenic gene variants of synaptic vesicle cycling (SVC) disorders that have been described in ASD and epilepsy could affect one of the specific subprocess of SVC,

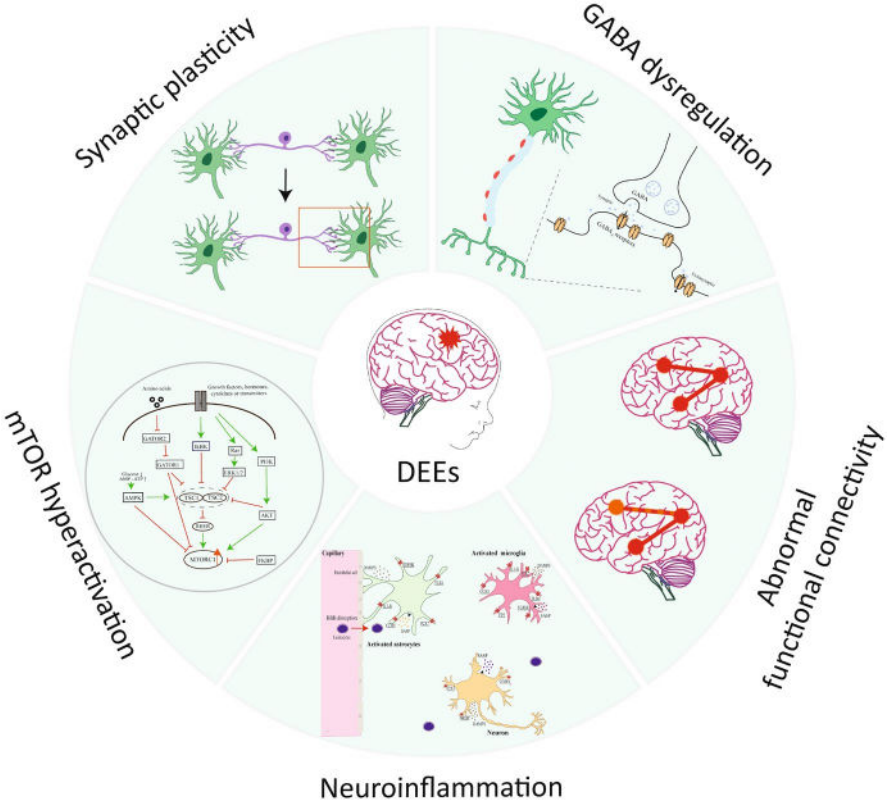

FIGURE 1 The importance of mechanistic target of rapamycin (mTOR) signaling and neuroinflammation in causing the epilepsy–autism phenotype. Such potentially different neurobiological mechanisms that can all produce an epilepsy–autism phenotype will likely require different therapeutic strategies. BBB, blood–brain barrier; DEE, developmental and epileptic encephalopathy; GABA, γ-aminobutyric acid.

including vesicle trafficking (e.g., *KIF1A* and *GDI1*), clustering (e.g., *TRIO, NRXN1*, and *SYN1*), docking and priming (e.g., *STXBP1*), fusion (e.g., *SYT1* and *PRRT2*), or reuptake (e.g., *DNM1, AP1S2*, and *TBC1D24*).[4,96]

Environmental factors may also play a role in the emergence of ASD and epilepsy. Inflammation during brain development can disrupt the formation of synapses. Inflammatory processes can lead to a decrease in synapse formation and an abnormal morphology of developing synapses.[97] During pregnancy, maternal immune responses with cytokine release during prenatal inflammation such as upon exposure to influenza viruses may affect the developing fetal brain and contribute to the development of ASD.[98] Although epidemiological evidence further strengthens the link, prenatal inflammation is more a risk factor or a contributing factor than a cause of ASD. Animal studies also demonstrate ASD-like behaviors in offspring exposed to prenatal inflammation.[68,99,100] Interestingly, maternal immune activation is also a risk factor for epilepsy. Using polyinosinic–polycytidylic acid to induce maternal immune activation in mice in which hippocampal kindling was used to assess epilepsy propensity and sociability test to evaluate autismlike behavior in the offspring, it has been shown that proinflammatory cytokines have different effects. Both IL-6 and IL-1β are necessary for priming offspring for epilepsy, and IL-6 was confirmed in its role in inducing autismlike behavior.[101]

6 | EARLY USE OF NEW THERAPEUTIC OPTIONS

6.1 | *KCNQ2* and *KCNT1*

Genetic variants in potassium channel-encoding genes are among the most frequent causes of early onset DEEs.[102] Among them, *KCNQ2*- and *KCNT1*-related disorders represent two paradigmatic DEEs in which personalized treatment approaches (with retigabine and quinidine, respectively) have been attempted. The *KCNQ2* activator retigabine (ezogabine), which was approved for clinical use as an add-on treatment of focal seizures in adults in 2011, was also shown to counteract the functional consequences of *KCNQ2* LoF variants in vitro[103] and attenuate drug-induced seizures in animal models of *KCNQ2* dysfunction.[104] Moreover, retigabine treatment also rescued neuronal excitability, juvenile seizure-related death, and ASD-related behavioral abnormalities (hyperactivity) in mice in which the gene for the neuronal scaffolding protein Ank2 was conditionally deleted in cortical and hippocampal excitatory neurons.[105] However, although early treatment with retigabine improved seizure and behavior phenotypes in children with *KCNQ2*-related DEE,[106,107] with drug weaning resulting in clear clinical worsening, a recent clinical trial with a pediatric formulation of retigabine has been terminated prematurely because of difficulties

in recruiting children fulfilling inclusion criteria (www.clinicaltrials.gov, NCT04639310). Moreover, retigabine was withdrawn from the market because of several pharmacological limitations, including (1) poor selectivity among *KCNQ* subtypes (resulting in side effects such as urinary retention), (2) short half-life (requiring three-times-per-day dosing), (3) poor brain penetration, and (4) retinal and mucocutaneous blue–gray discoloration due to photoinduced formation and accumulation of dimers in tissues.[108] Thus, no drug is currently on the market to test the potential of *KCNQ* activators as precision therapy in epilepsy and, possibly, developmental disorders including autism, in *KCNQ2*-related DEE. For this reason, efforts are ongoing to synthesize compounds with higher potency and efficacy as a Kv7 channel activator in vitro, no photoinduced dimer formation, higher brain/plasma ratio, and longer plasma half-life in vivo, when compared to retigabine.[109]

Genetic variants in the sodium- and chloride-gated potassium channel *KCNT1* cause severe, drug-resistant rare forms of early onset epilepsy such as epilepsy of infancy with migrating focal seizures; patients affected by *KCNT1*-related encephalopathies also display developmental plateauing or regression and psychiatric and intellectual disabilities.[110] It is noteworthy that *KCNT1* subunits interact directly with the fragile X mental retardation protein, a protein that when missing or mutated results in fragile X syndrome, the most common form of inherited ID and autism in humans.[111] Given that the largest majority of pathogenic *KCNT1* variants cause GoF effects in vitro,[112] *KCNT1* blockers such as quinidine have been proposed as possible precision therapy in patients affected by *KCNT1*-related diseases. However, heterogenous clinical responses have been obtained with quinidine[113]; several factors, including the natural history and severity of the underlying disease, the specific molecular defect, and the age of symptom onset and quinidine therapy initiation, in one with drug-specific pharmacokinetic and pharmacodynamic factors, might provide plausible explanations for such heterogeneity. Worldwide efforts to discover novel *KCNT1* blockers are currently ongoing, although none of the newly synthesized or repurposed compounds described has yet been tested in patients with *KCNT1*-related DEEs.[114–117]

A precision therapeutic approach using a gene-silencing antisense oligonucleotide (ASO) strategy in a mouse model of *KCNT1*-associated DEE has revealed that a single intracerebroventricular bolus injection of a Kcnt1 gapmer ASO in symptomatic mice, at postnatal day 40, significantly reduced seizure frequency, improved behavioral abnormalities (including impaired nesting behaviors and enhanced exploration of the open arm in the elevated plus maze test), and extended overall survival compared with mice treated with a control ASO.[118]

6.2 | SCN1A

Evidence from rodent models suggests that mice with *Scn1a* haploinsufficiency exhibit hyperactivity, stereotyped behaviors, social interaction deficits, and impaired context-dependent spatial memory.[119] Treatment with low-dose clonazepam rescued the abnormal social behaviors in the mouse model of Dravet syndrome, thus providing a potential therapeutic strategy for cognitive deficit and autism spectrum behaviors.[119] Equally, cannabidiol has been demonstrated to improve seizures and social deficits in a mouse model of Dravet syndrome, providing further evidence that antiseizure medications might improve not only the seizure burden but also the neuropsychiatric comorbidities.[120] Nevertheless, these observations from animal work have—so far—not been consistently replicated in human studies. Recent long-term prospective follow-up data appear to show an ever-widening gap in cognitive abilities and a marked increase in autistic features and other comorbidities over time in Dravet syndrome.[8,120] The rise in comorbidities is particularly marked in younger compared to older patients, and predictors of worse long-term developmental outcome include poorer baseline language ability as well as more severe baseline epilepsy severity.[8,120] Fenfluramine treatment in Dravet syndrome has been associated with an apparent dose-dependent, clinically meaningful improvement in behavior, emotion, cognition, and overall everyday executive function.[121] Natural history data show that language and communication delays are observed early, and developmental stagnation occurs after 2 years of age, suggesting an optimal therapeutic window before 3 years of age.[122] Accurate prediction of whether a young child with a pathogenic S*CN1A* variant will develop the severe epilepsy of Dravet syndrome or milder genetic epilepsy with febrile seizure plus (GEFS+) is challenging, and clinicians often miss the opportunity for early intervention as they wait for symptoms such as developmental delay to emerge. Advances in prediction modeling now allow objective estimation at disease onset regarding whether a child will develop Dravet syndrome versus GEFS+, assisting clinicians with prognostic counseling and decisions on early institution of therapies.[123]

6.3 | TSC1–2

Emerging clinical research is focusing on the mTOR pathway as a target for seizure control. Although initial investigations have primarily explored mTOR inhibitors, there is growing interest in other compounds affecting this pathway, such as *PI3K* and *AKT1*

inhibitors, which are also undergoing clinical evaluation.[124,125] Addressing the nonneurological side effects associated with mTOR inhibitors is crucial, as their use is hindered by issues like stomatitis and susceptibility to infections. Recent experimental studies propose potential solutions, including brain-specific rapalogs that selectively inhibit brain mTOR activity while sparing other tissues. This approach, utilizing brain-permeable and brain-impermeable mTOR inhibitors, holds promise for mitigating nonneurological side effects.[126] Moreover, targeting the mTOR pathway may offer benefits in managing epilepsy-associated comorbidities. Although current data are limited, a post hoc analysis of Japanese patients in the EXIST-3 study demonstrated improvements on the Pervasive Developmental Disorders–Autism Society Japan Rating Scale following treatment with everolimus. Further investigation is warranted to evaluate the impact of mTOR pathway modulation on comorbidities associated with mTORopathies.[127]

Given these recent advances, it remains to be shown whether very early treatment and new emerging therapies might be able to modify the natural history of DEEs and their neuropsychiatric comorbidities (Table 3 and Figure 2).

6.4 | Other nonpharmacological options for ASD in DEEs

The ASD phenotype in DEEs might diverge from "usual" ASD presentations. Understanding and addressing this distinct profile is crucial for developing effective interventions tailored to the specific needs of individuals with both DEEs and ASD and epilepsy. There is a gap in evidence-based studies investigating the effects of early behavioral intervention for ASD co-occurring with epilepsy. Early parent mediated interventions in children with DEEs at high risk of developing ASD are important to stimulate brain plasticity in social brain circuitry and to foster language and communication developmental trajectories.[128] The optimal therapeutical window to prevent language/communication delay is before 36 months of age in children with *SCN1A*- and TSC-related DEEs.[129] Recent studies from systematic review or small case series showed that the behavioral phenotype and the prognosis of autism can be modifiable with early intensive behavioral–cognitive therapy.[130,131]

Overall, the use of new therapeutic approaches for some genetic DEEs associated with ASD showed that evidence for efficacy on nonseizure symptoms, such as ASD and ID, is low, and more studies should be performed to reach a better understanding.

TABLE 3 Early use of disease-specific therapeutic options.

Gene variant	Drug	Dosage	Response	Level of evidence	Reference
SCN1A—DS	Fenfluramine	Max 0.7 mg/kg/day (or 0.4 mg/kg/day with STP)	Apparent dose-dependent, clinically meaningful improvement in regulating behavior, emotion, cognition, and overall everyday executive function	3	121
SCN1A—DS	Cannabidiol	100 mg/kg or 200 mg/kg, i.p.	Improve social deficits in a mouse model	Preclinical study	120
TSC1–2	Everolimus	3–7 ng/mL or 9–15 ng/mL	Improvements in the pervasive developmental disorders	1	127
KCNQ2 LoF	Retigabine	Not reported	Improved seizure and behavior phenotypes	3	107
KCNT1 GoF	Quinidine	30–90 mg/kg/day	Heterogenous clinical responses	3	113

Abbreviations: DS, Dravet syndrome; GoF, gain of function; i.p., intraperitoneal; LoF, loss of function; STP, stiripentol.

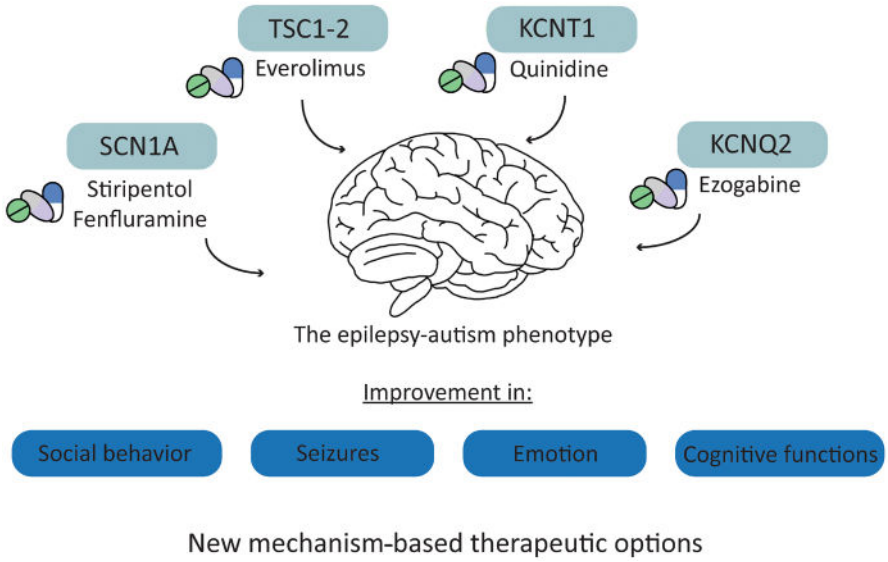

FIGURE 2 Overview of mechanism-based therapeutic options in DEE.

7 | CURRENT CHALLENGES AND FUTURE DIRECTIONS

Despite recent advances in understanding the cellular and molecular bases of different genetic syndromes, reducing the gap between the appearance of the first seizures and the definite early diagnosis, and addressing the treatment of DEE-associated epilepsy–autism phenotypes, remain challenging in clinical practice. Further exploration is required to better refine the clinical phenotype of various DEEs at the onset, and large cohorts would enhance the understanding of the natural history of the disorder, potentially identifying personalized therapeutic targets in children with genetic DEEs. Conducting functional analyses of gene variants and rigorous preclinical testing to elucidate the pathophysiological mechanisms behind the epilepsy–autism phenotype could shed light on why autistic symptoms persist even after seizure cessation in many DEEs.

Although recent advances in molecular genetic testing have facilitated greater recognition of early onset genetic DEEs, a substantial disparity persists between identifying genes linked to DEEs and devising effective targeted treatments. Given the identification of genetic causes, forthcoming clinical trials should embrace a precision health approach targeting the underlying disease mechanisms, assessing the efficacy not limited to seizure control but also including neurodevelopmental trajectories, ultimately aiming to prevent the epilepsy–autism phenotype.

Integrating genomic discoveries with functional investigations and animal models offers a holistic approach to deciphering the mechanisms behind these disorders, including the role of environmental factors. Such insights are crucial for devising precise interventions and enhancing our comprehension of the molecular underpinnings of neurodevelopmental disorders.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

N.S. has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Eisai, BioMarin, LivaNova, Sanofi, Jazz Pharmaceuticals, UCB, and Takeda; and has served as an investigator for Zogenix, Marinus, BioMarin, UCB, and Roche. E.A. has served as an investigator for UCB and Nutricia. No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. S.A. is deputy editor of *Epilepsia*; has served as a consultant or received honoraria for lectures from Angelini Pharma, Biocodex, BioMarin, Eisai, Encoded, Jazz Pharmaceuticals, GRIN Therapeutics, Neuraxpharm,

Nutricia, Orion, Proveca, Stoke, Takeda, UCB Pharma, and Xenon; and has been an investigator for clinical trials for Eisai, Marinus, UCB Pharma, Takeda, and Xenon. S.B. has been on an advisory board for Biocodex and has received speaker and consultant honoraria from Angelini, Biocodex, and Jazz Pharmaceuticals. A.B. has received honoraria for presenting at educational events, serving on advisory boards, and doing consultancy work for Biocodex, Jazz/GW Pharma, Encoded Therapeutics, Stoke Therapeutics, Nutricia, and UCB/Zogenix. E.G. has served on scientific advisory boards for UCB, Neurocrine Bioscience, and Encoded Therapeutics and has received speaker honoraria from Eisai, Jazz/GW Pharma, and UCB. M.Tr. has received speaker fees or funding or has participated on advisory boards for BioMarin and Biocodex. None of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. We confirm that we have used current ILAE seizure and epilepsy classification schemes (*Epilepsia* 2017;58:522–530 and *Epilepsia* 2017;58:512–521).[132,133]

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