REVIEW

Epilepsy-Dyskinesia Syndromes: The Venn Diagram of Genetic Epilepsy and Movement Disorders

Katerina Bernardi, MD,[1] Julian E. Alecu, MD,[1] Christelle Moufawad El Achkar, MD,[2] Laura Tochen, MD,[3] Phillip L. Pearl, MD,[2] and Darius Ebrahimi-Fakhari, MD, PhD[1*]

ABSTRACT: Epilepsy-dyskinesia syndromes cover a broad spectrum of neurogenetic disorders defined by the co-occurrence of epileptic and movement disorder phenotypes. Advances in next-generation sequencing have demonstrated more than 100 causative genes converging on shared molecular pathways regulating neuronal excitability, synaptic transmission, and neurodevelopment. Despite their clinical relevance, movement disorders in these conditions remain underrecognized and incompletely characterized. This review integrates recent clinical and molecular evidence to delineate the landscape of genetic epilepsy-dyskinesia syndromes, highlighting key mechanisms, including ion channel dysfunction, G-protein–coupled signaling, transcriptional regulation, synaptic vesicle cycling, and autophagy pathways, that underlie combined epilepsy-movement disorder phenotypes. We synthesize current knowledge of genotype–phenotype correlations, emphasizing phenotypic pleiotropy and recurrent variant hot spots that modulate disease severity and dominant movement phenomenology. Building on this framework, we propose complementary categorical and phenomenology-based classification systems to guide diagnosis and management. Finally, we discuss therapeutic implications, ranging from conventional pharmacological approaches and deep brain stimulation to emerging gene-directed and RNA-based precision therapies. Recognizing epilepsy-dyskinesia syndromes as a unified nosological spectrum provides a foundation for mechanistic understanding, improved diagnostic accuracy, and the development of targeted interventions addressing both seizures and movement disorders.

Key Words: dystonia; emerging therapies; epilepsy; gene therapy; neurogenetics

Epilepsy-dyskinesia syndromes (EDSs) cover a heterogeneous group of neurological conditions defined by the coexistence of both epilepsy and movement disorders.[1] Etiologies include acquired central nervous system (CNS) disorders and genetic causes.[2] Genetic EDSs comprise a rapidly expanding group of monogenic conditions that, although individually rare, collectively represent a substantial fraction of patients seen in epilepsy and movement disorder clinics.[3,4] Conceptually, EDSs can be understood as the overlapping intersection, the Venn diagram, of two rapidly expanding fields: the genetics of epilepsy and the genetics of movement disorders.[5-8]

EDSs present considerable clinical complexity, driven by both genetic heterogeneity, where distinct genes cause similar phenotypes, and phenotypic pleiotropy, where a single gene gives rise to multiple different clinical manifestations.[2] Movement disorders contribute substantially to the disease burden in EDSs, often persisting despite adequate seizure control and leading

[1]Movement Disorders Program, Department of Neurology & F.M. Kirby Neurobiology Center, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [2]Division of Epilepsy, Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [3]Department of Neurology, Children's National Hospital, Washington, District of Columbia, USA

*Correspondence to: Dr. Darius Ebrahimi-Fakhari, Movement Disorders Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School, 3 Blackfan Circle, Boston, MA 02115, USA; E-mail: darius.ebrahimi-fakhari@childrens.harvard.edu

Financial disclosures and conflicts of interest: Author disclosures are available in the Supporting Information.

Funding agencies: Research in the Ebrahimi-Fakhari laboratory was supported by the National Institute of Neurological Disorders and Stroke, National Institutes of Health (K08NS123552, 1U54NS148312), the Spastic Paraplegia Foundation, the CureAP4 Foundation, the Lilly & Blair Foundation, the CureSPG4 Foundation, EURO-HSP, the New England Epilepsy Foundation, the Dystonia Medical Research Foundation, the Boston Children's Hospital Translational Research Program, and the Boston Children's Hospital TIDO Accelerator Award.

Received: 20 February 2026; **Revised:** 27 May 2026; **Accepted:** 3 June 2026

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.70403

to impaired mobility, functional dependence, and reduced quality of life.[9] Yet, movement phenotypes remain underrecognized and underreported, because most published cohorts have focused primarily on epileptic manifestations.[10,11] Current therapeutic strategies are limited, and the interaction between antiseizure and movement disorder treatments is underexplored. However, the emergence of mechanism-targeting therapies, including small molecules, antisense oligonucleotides (ASOs), and gene replacement, has created new opportunities for disease modification.[12,13]

This review synthesizes current knowledge on the clinical and molecular spectrum of genetic EDSs (Supporting Information Data S1), proposes practical frameworks for classification, and discusses emerging therapeutic approaches that bridge the fields of epilepsy and movement disorders.

Defining Genetic Epilepsy-Dyskinesia Syndromes

Genetic EDSs represent an expanding group of neurogenetic disorders in which pathogenic variants in a single gene give rise to both epilepsy and movement disorders. Although the term "dyskinesia" historically emphasized hyperkinetic movements, the clinical spectrum in EDS is broader, encompassing hyperkinetic and hypokinetic (parkinsonism) movement disorders, in addition to ataxia and spasticity.[14-16] Movement disorders may present with continuous or paroxysmal phenomenology and can precede, coincide with, or follow the onset of epilepsy. In some patients, movement abnormalities constitute the predominant neurological feature, whereas in others, epilepsy dominates the clinical picture. This reflects the shared neurobiological substrates of cortical excitability and motor circuit regulation, which translates into the co-occurrence of seizures and movement disorders within the EDS continuum.[2]

Key Molecular Mechanisms

The molecular mechanisms of EDSs include multiple pathways that include regulation of neuronal excitability, synaptic transmission, protein degradation, and protein transport[2] (Fig. 1).

Regulation of membrane potential and neuronal excitability involves genes encoding ion-transporting proteins that govern action potential generation and propagation.[17] These networks include sodium channels (*SCN1A*, *SCN2A*, *SCN8A*),[18-20] potassium channels (*KCNT1*, *KCNQ2*, *KCNB1*, *KCNA2*, *KCNJ10*, *KCNMA1*, *KCND3*),[21-23] calcium channels (*CACNA1A*, *CACNA1B*, *CACNA1E*),[24-26] and Na^+/K^+-ATPases (*ATP1A2*, *ATP1A3*).[27,28] Pathogenic variants in these genes disrupt neuronal excitability, producing epilepsy and paroxysmal movement disorders.[4]

Ionotropic glutamatergic receptor signaling involves *N*-methyl-D-aspartate (NMDA) receptor subunits (*GRIN1*, *GRIN2A*, *GRIN2B*, *GRIN2D*)[29-31] and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits (*GRIA3*, *GRIA4*), mediating fast excitatory neurotransmission and plasticity.[32] Dysregulation of these receptors disrupts excitation–inhibition balance within cortical and subcortical motor circuits.[33]

Inhibitory synapse assembly depends on γ-aminobutyric acid type A (GABA-A) receptor subunits (*GABRA1*, *GABRB2*, *GABRB3*, *GABRG2*)[34-37] and GABAergic scaffolding proteins such as *ARHGEF9*,[38] forming a functionally integrated network critical for inhibitory signaling and synaptic stability.

Another critical regulatory network consists of cyclic adenosine monophosphate–mediated signaling through G-protein–coupled receptors, which affects glutamatergic, dopaminergic, and cholinergic transmission.[39-41] This cluster includes heterotrimeric G-protein subunits (*GNAO1*, *GNB1*),[42-44] G-protein activators (*SYNGAP1*),[45] downstream effectors (*PLCB1*),[46] and cyclic nucleotide-metabolizing enzymes (*PDE10A*, *PDE2A*),[47] which collectively modulate intracellular signaling essential for motor control.

Regulation of neuronal transcription and translation orchestrates critical aspects of cortical development, including neural progenitor proliferation, neuronal migration, and dendritic spine formation. This regulatory network includes transcription factors (*MECP2*, *ARX*, *FOXG1*, *MEF2C*, *SETBP1*, *MYT1L*),[48-52] transcriptional modulators (*CDKL5*, *CSTB*, *WWOX*),[53,54] chromatin accessibility regulators (*HNRNPU*, *SMC1A*, *SETD5*),[9,55-57] and mediators of dendritic translation (*PURA*).[58]

Synaptic vesicle cycling and synapse organization are governed by genes regulating neurotransmitter release and presynaptic architecture.[59,60] These networks include SNARE complex components (*STXBP1*, *PRRT2*),[61,62] endocytic and vesicle recycling proteins (*SYNJ1*, *TBC1D24*, *DNM1*, *VAMP2*),[63-66] and presynaptic cytoskeletal organization (*SPTAN1*, *PCDH12*, *PCDH19*).[67-69] Defects in these proteins impair the exo-endocytic cycle and synaptic efficacy.

Macroautophagy and protein degradation pathways maintain neuronal homeostasis through autophagosome formation (*WDR45*, *EPM2A*),[70-72] maturation (*EPG5*, *SNX14*),[73,74] substrate targeting (*NHLRC1*, *UBE3A*, *UBA5*),[75-77] and ubiquitin-mediated proteolysis (*HACE1*).[78] Dysfunction in these pathways leads to impaired cellular homeostasis and accumulation of misfolded proteins.[79,80]

Transmembrane transport pathways govern the movement of essential substrates across membranes, including carboxylic acids (*SLC13A5*),[63] glucose (*SLC2A1*),[81] thyroid hormone,[82] and neurotransmitters

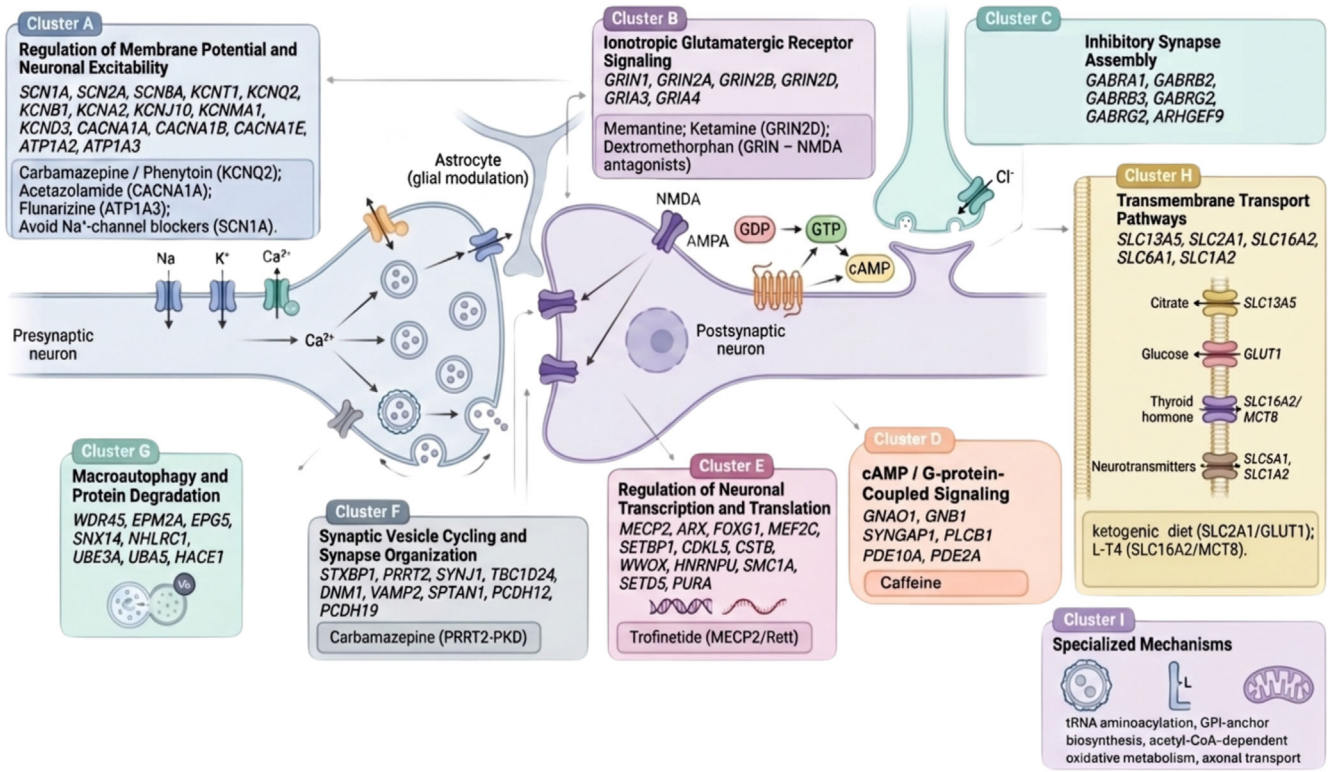

FIG. 1. Molecular pathway clusters in epilepsy-dyskinesia syndromes and associated therapeutic targets. Schematic overview of the principal molecular mechanisms underlying genetic epilepsy-dyskinesia syndromes, organized into nine functional clusters: (**A**) regulation of membrane potential and neuronal excitability; (**B**) ionotropic glutamatergic receptor signaling; (**C**) inhibitory synapse assembly; (**D**) cAMP-mediated signaling through G-protein–coupled receptors; (**E**) regulation of neuronal transcription and translation; (**F**) synaptic vesicle cycling and synapse organization; (**G**) macroautophagy and protein degradation; (**H**) transmembrane transport across different cell types: *SLC13A5* (neurons), *SLC2A1*/GLUT1 (endothelial cells, astrocytes, erythrocytes), *SLC16A2*/MCT8 (neurons, astrocytes, endothelial cells), *SLC6A1* (neurons, astrocytes), and *SLC1A2*/EAAT2 (astrocytes); (**I**) and specialized mechanisms. Representative disease-associated genes are listed within each cluster. Adjacent treatment boxes indicate pharmacological, dietary, or neuromodulatory therapies with a mechanistic rationale for the corresponding cluster or gene. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cAMP, cyclic adenosine monophosphate; GABA-A, γ-aminobutyric acid type A receptor; GDP, guanosine diphosphate; GPi, globus pallidus internus; GTP, guanosine triphosphate; NMDA, *N*-methyl-D-aspartate; TF, transcription factor; tRNA, transfer RNA. [Color figure can be viewed at wileyonlinelibrary.com]

(*SLC6A1*, *SLC1A2*).[83,84] These "transportopathies" produce combined metabolic and neurophysiological disturbances resulting in both epilepsy and movement manifestations.

Finally, additional specialized mechanisms include transfer RNA aminoacylation,[85] globus pallidus internus (GPI)-anchor biosynthesis (*PIGA*),[86,87] acetyl-coenzyme A–dependent oxidative metabolism,[88] axonal transport, clathrin-mediated endocytosis,[89] and cerebrovascular basement membrane integrity (*COL4A2*),[90] reflecting the molecular diversity underlying EDSs.

Phenotypic Pleiotropy, Genetic Heterogeneity, and Emerging Genotype–Phenotype Correlations

Phenotypic pleiotropy and genetic heterogeneity represent fundamental challenges in understanding EDSs.[2,91] Pathogenic variants within a single gene can produce remarkably diverse clinical manifestations, while conversely, a single clinical phenotype can arise from variants in different genes. This makes attributing a specific phenotype to a genotype and vice versa very challenging.[5,92] For instance, *PRRT2*-related disorders can present with one or more features including self-limited infantile epilepsy (SeLIE), paroxysmal kinesigenic dyskinesia (PKD), and episodic ataxia, among others.[93,94] Abnormalities in *ATP1A3* can result in at least four distinct phenotypes with or without overlapping features alongside atypical presentations of each phenotype.[95] *GNAO1*-related disorders similarly represent phenotypic variability, including severe dystonia, chorea, and life-threatening hyperkinetic crises, as well as less severe presentations with predominant neurodevelopmental disorders with variable epilepsy.[39,43,96] Pathogenic variants in *SLC2A1* can result in paroxysmal exercise–induced dyskinesia (PED), epilepsy syndromes with variable severity, or combined phenotypes,[97] and variants in *SCN8A* are associated with at least five distinct phenotypes, the milder of which include SeLIE and paroxysmal dyskinesias with or without epilepsy, and the most severe being early-onset

epileptic encephalopathy with variable movement disorders.[20,98]

Genotype–phenotype correlation remains largely imprecise in multiple conditions, likely because of several factors, including reduced penetrance, variable expressivity, and other genetic and epigenetic co-occurrences that are poorly understood to date.

In some genetic conditions, however, clearer correlation has emerged through better understanding of the wide range of phenotypes and pathophysiology caused by the genotype. A variant's functional classification can predict the phenotype in several conditions. Gain-of-function variants in *SCN1A* are strongly associated with an early-onset developmental epileptic encephalopathy (DEE) different from Dravet syndrome and with more likelihood of early movement disorders than loss-of-function variants that are associated with a spectrum ranging from febrile seizures to Dravet syndrome, with the latter being associated with gait disorders and parkinsonism during adolescence and adulthood.[99] *SCN8A* gain-of-function variants are typically associated with either SeLIE, moderate DEE, or severe DEE, with the latter two also demonstrating early hyperkinetic movements, whereas some loss-of-function variants are associated with chronic ataxia and neurodevelopmental disorders, with or without epilepsy.[98,100] Some variant type and location further refine phenotypic expression. *CDKL5* missense mutations at the Arg178 hot spot are linked to particularly severe DEE and poor developmental outcomes.[101] In *FOXG1*-related disorder, deletions confer a heavier epilepsy burden with medically refractory seizures, whereas missense variants tend to produce more pronounced movement disorders and milder or absent epilepsy.[102] Recurrent *GNAO1* hot spot mutations (p.R209, p.G40, p.G203R) yield distinct phenotypic profiles ranging from severe movement disorder–predominant presentations to developmental and epileptic encephalopathy.[43,103,104] Recently, *GNAO1* variants causing presumed haploinsufficiency have been associated with milder, later-onset familial dystonia, challenging the earlier gain- versus loss-of-function dichotomy.[104]

The Clinical Spectrum of EDS

Epilepsy Spectrum

Several well-defined epilepsy syndromes arise within the EDS spectrum, and the same etiologies can be associated with chronological progression from one syndrome to another or with more than one syndrome. Epilepsy of infancy with migrating focal seizures (EIMFS) has been reported with *KCNT1*, *GNAO1*, and *SCN1A* gain-of-function variants.[19,40,105] Early-onset epilepsy presenting with focal, tonic, or myoclonic seizures, which may progress to infantile epileptic spasms syndrome (IESS), and subsequently to Lennox-Gastaut syndrome, is associated with *CDKL5*, *FOXG1*, *GNAO1*, *SCN2A*, *SCN8A*, *STXBP1*, *ARX*, *GABRB3*, and some of the *GRIN* genes.[29,35,48,106] Dravet syndrome is characteristically linked to *SCN1A* with a phenotypically similar presentation reported in homozygous loss-of-function *SCN1B* variants.[18,20,36,107] Self-limited familial neonatal and/or infantile epilepsy occurs in *PRRT2*, *SCN2A*, and *SCN8A*.[94,98]

Distinct gene–syndrome associations have diagnostic value: *SCN2A*, *SCN8A*, and *CDKL5* variants show particularly strong linkage to IESS,[108] and *SCN1A* loss-of-function variants are identified in more than 90% of patients with Dravet syndrome.[105] Seizure outcomes vary markedly by genetic etiology and epilepsy syndrome: seizures are self-limited and resolve by age 2 years in *PRRT2*-related epilepsy[93]; seizures are refractory in most cases of *CDKL5*-deficiency disorder[108] and variable in disorders such as *MECP2* and *ATP1A3*, where a subset of patients might achieve seizure control or even remission.[109,110]

Movement Disorder Spectrum

Movement disorders in EDS are predominantly hyperkinetic, representing cardinal and often the most functionally disabling features of these conditions. Dystonia and motor stereotypies emerge as the most prevalent phenomenologies, followed by chorea, ataxia, myoclonus, and tremor.[3,10] Hypokinetic features, including bradykinesia and rigidity, are less common in childhood but may emerge with disease progression in specific syndromes.[2,72]

Importantly, approximately half of all patients exhibit mixed movement and motor disorders, with multiple phenomenologies coexisting rather than isolated pure phenotypes. Common combinations include dystonia with choreoathetosis, dystonia with spasticity, and ataxia with tremor.[5]

Dystonia demonstrates remarkable gene-specific clustering, with the strongest associations observed with *GNAO1*, *ARX*, *UBA5*, and *RHOBTB2*.[104,111-113] It can present as focal, segmental, or generalized, with severity ranging from mild posturing to life-threatening status dystonicus. *GNAO1*-related disorder characteristically presents with a combination of severe dystonia and chorea in the majority of patients.[103] Dystonia is also seen in sodium channelopathies (*SCN1A*, *SCN8A*), NMDA-receptor subunit genes (*GRIN1*, *GRIN2B*, *GRIN2D*),[29,114-116] and synaptic vesicle disorders (*STXBP1*), although generally milder.[1] Status dystonicus has been documented with variants in *GNAO1*, *ARX*, *GNB1*, *ATP1A3*, *MECP2*, *SCN2A*, and *UBA5*, among others.[2,111,117-120]

Motor stereotypies are hallmark features of transcriptional dysregulation disorders, particularly *MECP2*-,

CDKL5-, *FOXG1*-, and *STXBP1*-related disorders, manifesting as characteristic midline hand stereotypies (hand wringing, hand washing, hand clapping) or stereotypies involving the craniocervical region.[62,101,102,110]

Chorea shows strong gene-specific associations, most prominently with *GNAO1* and *FOXG1*.[102,117] In *FOXG1*-related disorder, chorea is the dominant movement abnormality and often occurs as early as infancy.[102,117]

Nonepileptic myoclonus appears as multifocal or action-induced jerks, often co-occurring with other movement disorders. It predominates in *TBC1D24*-related disease[121] and is also seen with variants in *KCNA2*, *STXBP1*, *SCN1A*, and *SCN8A*.[122-124]

Ataxia occurs across several genes, most notably *CACNA1A*, *SLC2A1*, and *SCN1A*.[97,99,125] *CACNA1A*-related disease encompasses a continuum from episodic ataxia type 2 to progressive cerebellar ataxia and ataxia associated with DEE.[125]

Paroxysmal movement disorders occur in several EDS genes, most characteristically with *PRRT2*, *SLC2A1*, and *ATP1A3*.[126,127]

Parkinsonism, characterized by bradykinesia, combined with either rest tremor or rigidity, is uncommon in childhood but emerges in several disorders, including in disorders related to *DNAJC6*, *ATP7A*, *STXBP1*, *SYNJ1*, *DHDDS*, and *KCNQ2*.[5,128-130] Hypokinetic features can evolve over time, as in *MECP2*-related Rett syndrome and *WDR45*-related β-propeller protein-associated neurodegeneration (BPAN), which transition from early hyperkinetic phases to dystonia-parkinsonism in adolescence or adulthood.[71,131] *ATP1A3* variants demonstrate exceptional phenotypic diversity, spanning dystonia, parkinsonism, chorea, ataxia, stereotypies, and myoclonus.[28]

To systematically delineate this landscape, we clustered data from the largest published cohorts with detailed movement disorder phenotyping, encompassing 696 patients across 109 genes and 13 defined movement disorder phenomenologies[2,3,9,10,124] (Fig. 2).

Temporal Patterns

Across the EDS spectrum, epilepsy often presents during the first year of life, whereas movement disorders are typically recognized later, commonly between 1 and 3 years of age, although considerable variation exists across genes.[3,9,10] The age of movement disorder onset ranges from the neonatal period to adulthood, reflecting diverse pathogenic mechanisms and developmental regulation of gene expression.[11,92,124]

In the majority of conditions, including *CDKL5*-, *GNAO1*-, *PRRT2*-, *WDR45*-, and *SLC2A1*-related disorder, seizures manifest before movement disorders, often with seizure onset clustering in the neonatal or early infantile period, while movement disorders emerge months to years later.[2] Subsets of phenotypes related to *ATP1A3*, *STXBP1*, and *FOXG1* might show concurrent onset of seizures and movement disorders in infancy.[102,132,133] With some presentations of *ARX*, *ATP1A3*, *MECP2*, and *CACNA1A*-related disorders, movement disorders may precede or occur independently of seizures, with characteristic age dependence.[125,134]

Clinical Classification

We propose two complementary clinical classification systems: a categorical classification based on overarching clinical trajectories and a phenomenology-based system centered on the leading motor phenotype.

Categorical Classification

The categorical classification organizes EDS into six broad groups based on overall clinical syndrome and disease trajectory, providing a complementary framework to the phenomenology-based approach (Fig. 3). First, *DEE with hyperkinetic movement disorders* represents the largest category, encompassing the majority of EDS cases where severe early-onset epilepsy co-occurs with prominent hyperkinetic movement disorders, including dystonia, chorea, stereotypies, and myoclonus. This heterogeneous group includes genes affecting diverse molecular pathways: synaptic transmission (*STXBP1*, *TBC1D24*, *DNM1*),[64,135,136] transcriptional regulation (*MECP2*, *CDKL5*, *FOXG1*, *ARX*, *MEF2C*, *PURA*),[50,53,108,111,137,138] signal transduction (*GNAO1*, *GNB1*, *SYNGAP1*),[47,139] ion channels (*SCN1A*, *SCN2A*, *SCN8A*, *KCNQ2*, *KCNT1*, *CACNA1A*),[140-142] glutamatergic neurotransmission (*GRIN1*, *GRIN2B*, *GRIN2D*),[29,114-116] and GPI-anchor biosynthesis (*PIGA*).[143,144] Patients typically present with medically refractory epilepsy and significant neurodevelopmental impairment. Second, *DEE with parkinsonism* represents a smaller but clinically important category characterized by DEE and hypokinetic phenomenology. This phenotype can emerge in *KCNQ2*- and *DNAJC6*-related disorders, as well as other rare genetic disorders related to *ATP7A*, *STXBP1*, *SYNJ1*, and *DHDDS*.[5,62,145] Importantly, some conditions show age-dependent evolution from early hyperkinetic to later hypokinetic features, as exemplified by *MECP2*-related Rett syndrome and *WDR45*-related BPAN.[72,134,146] Third, *epilepsy with paroxysmal movement disorders* encompasses conditions where paroxysmal dyskinesias (PKD, paroxysmal non-kinesigenic dyskinesia [PNKD], PED) occur alongside epilepsy. This category includes the classic genetic causes of paroxysmal movement disorders (*PRRT2*, *SLC2A1*), as well as *KCNMA1* and *CACNA1A*. *ATP1A3*-related disorder can present with paroxysmal hemiplegic or quadriplegic episodes and dystonic attacks that must be distinguished

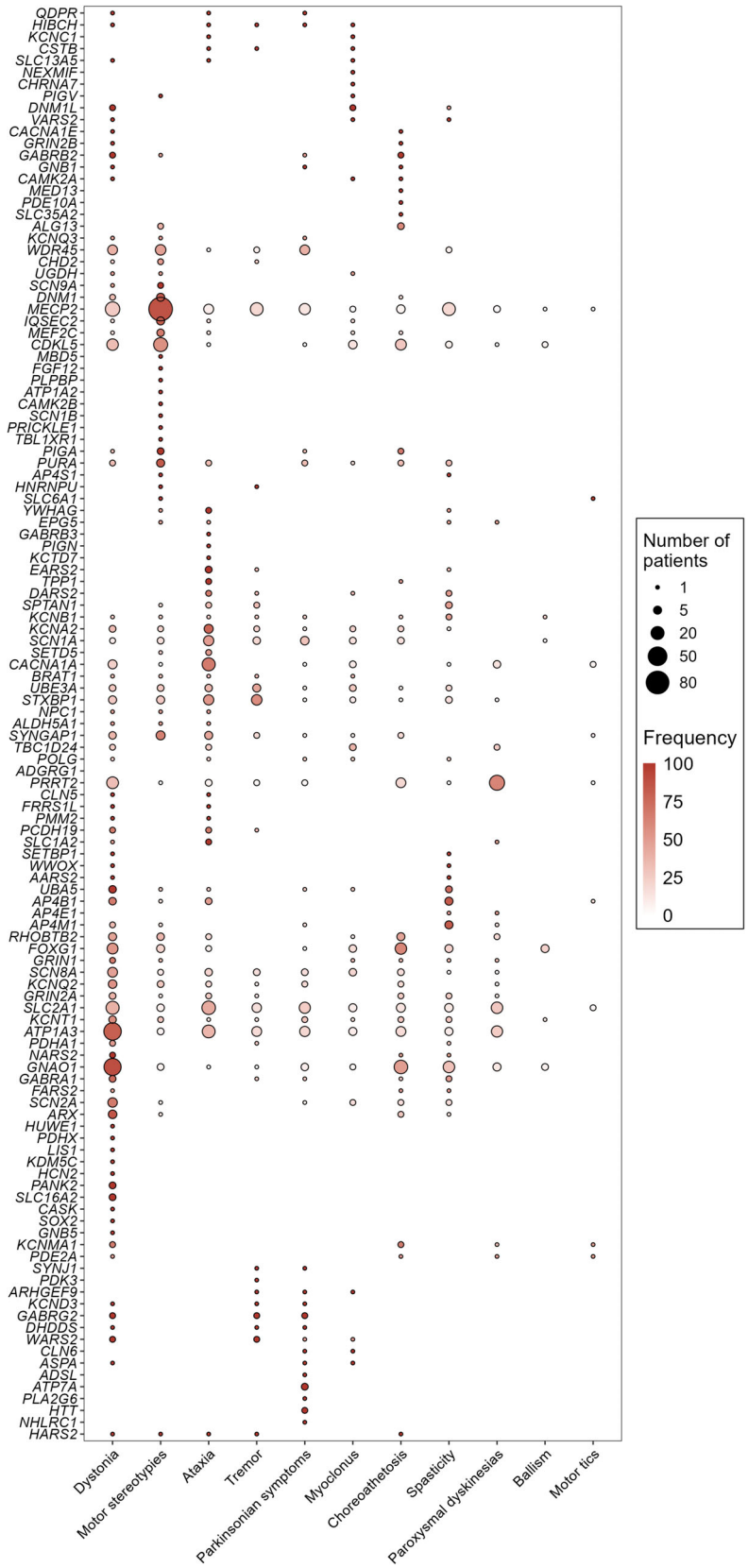

FIG. 2. Gene-specific movement disorder profiles in epilepsy-dyskinesia syndromes. Comprehensive movement disorder landscape across 767 patients with genetic epilepsy-dyskinesia syndromes from the largest published cohorts to date affecting 121 genes. The bubble plot displays the frequency and statistical significance of associations between each gene (*y*-axis) and movement disorder phenomenologies (*x*-axis). Circle size represents the number of patients with each gene–phenotype combination; color intensity (red gradient) indicates the frequency of occurrence within each genetic group. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 3. Categorical classification of epilepsy-dyskinesia syndromes. Sunburst diagram illustrating the categorical organization of genetic epilepsy-dyskinesia syndromes into six major groups. The inner ring represents the six broad categories; the outer ring displays individual genes within each category. DEE, developmental epileptic encephalopathy. [Color figure can be viewed at wileyonlinelibrary.com]

from seizures through video-electroencephalography (EEG) monitoring.[94,126,127] Fourth, *progressive myoclonic epilepsies* comprise a distinct group characterized by myoclonic seizures, progressive action-induced myoclonus, and neurological deterioration, including Unverricht-Lundborg disease (*CSTB*), Lafora disease (*EPM2A*, *NHLRC1*), and several neuronal ceroid lipofuscinoses, typically presenting in later childhood or adolescence with progressive functional decline.[147-149] Additional genetic etiologies include *GOSR2*, *KCNC1*, *PRICKLE1*, *SCARB2*, and *KCTD7*.[150-154] Fifth, inborn errors of metabolism includes disorders where EDS arises from disrupted metabolic pathways, such as glucose transporter deficiency (*SLC2A1*), mitochondrial disorders, and certain disorders of neurotransmitter metabolism, often with manifestations beyond the CNS and potential for targeted metabolic therapies.[1,81,155,156] Sixth, *neurodegenerative diseases* encompass progressive disorders with characteristic temporal evolution and often distinctive neuroimaging findings, including BPAN

(*WDR45*) with brain iron accumulation, juvenile Huntington's disease (*HTT*) with progressive chorea and cognitive decline, and various mitochondrial disorders, distinguished by progressive worsening, accumulation of pathological substrates, and typically later disease onset.[72,157] Neuronal ceroid lipofuscinoses similarly present with therapy-resistant myoclonic epilepsy alongside progressive movement disorders, including nonepileptic myoclonus, dystonia, chorea, ataxia, and parkinsonism.[158]

It is important to acknowledge that the categorical classification of EDS is not static, because age-dependent phenotypic evolution may occur in a subset of patients. For example, patients with *SCN1A*-related Dravet syndrome or *MECP2*-related Rett syndrome may transition from DEE with hyperkinetic movement disorders to parkinsonism during adolescence or adulthood.[99,134] Periodic reassessment is therefore recommended as phenotypes evolve.

Phenomenology-Based Clinical Classification

Most EDSs present with mixed movement disorder phenotypes. The differential can be approached through three sequential bedside questions. First, is the movement disorder paroxysmal (discrete, often triggered or spontaneous episodes) or continuous (present throughout wakefulness)? A paroxysmal presentation should focus attention on *PRRT2*, *SLC2A1*, *KCNMA1*, *ATP1A3*, and *CACNA1A*, stratified by trigger and episode character. Second, if continuous, is the motor phenotype predominantly hyperkinetic or hypokinetic? Hypokinetic presentations should raise *DNAJC6*, *ATP7A*, *SYNJ1*, *DHDDS*, *KCNQ2*, and *STXBP1*, bearing in mind that several predominantly hyperkinetic disorders (*MECP2*, *WDR45*, *SCN1A*) transition toward parkinsonism in adolescence or adulthood. Third, within the hyperkinetic group, what is the leading phenomenology: dystonia with frequent status dystonicus, dystonia, chorea, stereotypies, or myoclonus? Each is discussed in turn in the following sections, and Table 1 provides a gene-by-gene index organized in the same phenomenological hierarchy for rapid bedside reference.

Early-Onset DEE with Status Dystonicus

This severe phenotype combines early-onset epileptic encephalopathy with recurrent episodes of status dystonicus.[159] The epileptic phenotype typically manifests as severe, pharmaco-resistant DEE with onset in the neonatal period or early infancy, with multiple seizure types often coexisting and evolving over time.

GNAO1-related disorder represents the prototypical etiology, with hyperkinetic crises as a hallmark feature. These crises often combine severe dystonia with chorea, athetosis, and ballismus, frequently triggered by fever, infection, or stress, and accompanied by dysautonomia. Treatment in the intensive care unit is often required, and there is an evolving understanding of the response to deep brain stimulation (DBS). Epilepsy typically presents in the first months of life as early infantile DEE with tonic seizures and suppression-burst EEG pattern, or as EIMFS. Additional seizure types include epileptic spasms, myoclonic seizures, and focal seizures with impaired awareness. The epilepsy is typically medically refractory, although seizure burden may not correlate with the severity of hyperkinetic crises.[39,42,103,104,117,160]

ARX-related disorder demonstrates progressive dystonia beginning with characteristic hand involvement evolving to generalized distribution, alongside early infantile DEE or IESS with predominantly male involvement because of X-linked inheritance. The epilepsy phenotype is severe, with seizure onset typically in the neonatal period or first months of life. Seizure types include epileptic spasms, tonic seizures, myoclonic seizures, and focal seizures. Many patients have the characteristic triad of infantile spasms, developmental delay, and hand dystonia. Dystonia may be present from early infancy, progressing from focal hand dystonia to more generalized involvement, with status dystonicus documented in severe cases.[48,111,161]

UBA5-related disorder is an ultra-rare disease that can present with severe hyperkinetic crises resembling those of *GNAO1*-related disorder, with early-onset DEE manifesting as multiple seizure types, including tonic seizures, epileptic spasms, myoclonic seizures, and focal seizures, typically beginning in the neonatal period or early infancy. Epilepsy is generally pharmacoresistant, and the combination of severe movement disorder crises with refractory epilepsy creates substantial clinical burden.[77,112,118,162]

DEE with Prominent Dystonia

This category encompasses patients for whom dystonia represents the leading and most disabling movement disorder. The functional impact ranges from mild motor impairment to severe disability affecting mobility, self-care, and communication. Notably, genes previously discussed in the status dystonicus category (*ARX*, *GNAO1*, *STXBP1*, *RHOBTB2*) present with dystonia as the primary feature when episodes do not reach the severity of status dystonicus.

MECP2-related disease demonstrates characteristic age-dependent evolution, with progressive dystonia typically emerging during late childhood or adolescence after initial regression and loss of purposeful hand skills. Epilepsy occurs in 60% to 80% of patients, with seizure onset typically between ages 2 and 4 years. Seizure types are variable and may include focal seizures, generalized tonic-clonic seizures, myoclonic seizures, and absence seizures. Approximately 40% achieve seizure

TABLE 1 *Phenomenology-based classification centered on the leading motor phenotype*

Phenomenology	Gene	Inheritance	Molecular mechanism	Movement disorder features	Epilepsy features
Early-onset EE with status dystonicus	GNAO1	AD	G-protein signaling	Status dystonicus, dystonia, chorea, orolingual dyskinesia, complex stereotypies	DEE, EIDEE, EIMFS-like, early-onset
	ARX	X-linked	Transcription factor	Progressive generalized dystonia, hand dystonia (infancy), status dystonicus	Early infantile DEE, IESS, myoclonic seizures
	UBA5	AR	UFM1 conjugation pathway	Dystonia, paroxysmal dystonia, status dystonicus	Early-onset DEE
DEE with prominent dystonia	MECP2	X-linked	Transcriptional regulation	Generalized dystonia, hand stereotypies, bruxism, status dystonicus (rare)	DEE with multiple seizure types
	CACNA1A	AD	P/Q-type calcium channel	Dystonia, torticollis, paroxysmal tonic upgaze, episodic ataxia	Absence epilepsy, GTCS, IESS
	SCN2A	AD	Voltage-gated Na^+ channel (Nav1.2)	Severe dystonia, chorea (especially neonatal onset), oculogyric crises, episodic ataxia, status dystonicus (rare)	DEE, EIDEE, EIMFS, self-limited familial neonatal-infantile epilepsy
	SCN8A	AD	Voltage-gated Na^+ channel (Nav1.6)	Dystonia, choreoathetosis, tremor, ataxia, paroxysmal dyskinesia	IESS, Lennox-Gastaut syndrome, Dravet syndrome, multiple seizure types
	ATP1A3	AD	Na^+/K^+-ATPase	Dystonia-parkinsonism, paroxysmal dystonic episodes, chronic dystonia, status dystonicus (rare)	Variable epilepsy (AHC, CAPOS)
	STXBP1	AD	Synaptic vesicle trafficking	Truncal and limb dystonia, head stereotypies, status dystonicus (rare)	Early infantile developmental and epileptic encephalopathy, IESS, early DEE
	RHOBTB2	AD	Rho GTPase signaling	Dystonia, chorea, ataxia	Early-onset DEE
DEE with prominent chorea	FOXG1	AD	Transcription factor	Generalized chorea appearing in infancy, motor stereotypies	DEE (infantile epileptic spasms, multifocal seizures)
	CDKL5	X-linked	Serine/threonine kinase	Generalized chorea, stereotypies	Early-onset DEE, infantile epileptic spasms, myoclonic seizures
	SCN8A	AD	Voltage-gated Na^+ channel	Generalized chorea, ataxia, dystonia, exaggerated startle, hand stereotypies	DEE, EIMFS, multiple seizure types
	MEF2C	AD	Transcription factor	Chorea, dystonia, dyskinesia, MECP2-like hand stereotypies	DEE, infantile epileptic spasms, myoclonic seizures
	KCNB1	AD	Voltage-gated K^+ channel	Chorea, myoclonus, hand-wringing stereotypies	DEE
DEE with prominent stereotypies	MECP2	X-linked	Transcriptional regulation	Hand stereotypies (hand wringing, hand-mouthing), bruxism, ataxia, chorea, dystonia	DEE (focal, generalized seizures)

(Continues)

TABLE 1 *Continued*

Phenomenology	Gene	Inheritance	Molecular mechanism	Movement disorder features	Epilepsy features
	CDKL5	X-linked	Serine/threonine kinase	Stereotypies (hand wringing, leg-crossing)	Early-onset DEE, infantile epileptic spasms, myoclonic seizures
	STXBP1	AD	Synaptic vesicle trafficking	Hands, trunk, head, and neck stereotypies (figure-of-eight)	Early infantile DEE, IESS (formerly West syndrome), early DEE
	SCN1A	AD	Voltage-gated Na^+ channel	Eyelid stereotypies	Dravet syndrome, genetic epilepsy with febrile seizures plus (GEFS+), EIMFS
	KCNA2	AD	Voltage-gated K+ channel	Stereotypies, generalized myoclonus	Childhood-onset epilepsy GTCS, myoclonic, absence epilepsy
	SYNGAP1	AD	Synaptic GTPase-activating protein	Stereotypies, hand-flapping	DEE, infantile epileptic spasms
Epilepsy with paroxysmal dyskinesia	PRRT2	AD	Synaptic vesicle priming	PKD, PNKD	Self-limited familial infantile epilepsy, febrile seizures, absence epilepsy, GTCS, photosensitive epilepsy
	SLC2A1	AD	GLUT1 glucose transporter	PED, ataxia	Absence epilepsy, myoclonic-atonic seizures
	ATP1A3	AD	Na^+/K^+-ATPase	Alternating hemiplegia episodes, paroxysmal dystonia, PED	Variable epilepsy types (more common in AHC)
	KCNMA1	AD	BK channel (large conductance Ca^{2+}-activated K^+ channel)	PNKD, ataxia, myoclonus	Generalized epilepsy
	CACNA1A	AD	P/Q-type calcium channel	Episodic ataxia type 2, paroxysmal tonic upgaze	Absence epilepsy, variable

Abbreviations: EE, epileptic encephalopathy; AD, autosomal dominant; EIMFS, epilepsy of infancy with migrating focal seizures; IESS, infantile epileptic spasms syndrome; AR, autosomal recessive; EIDEE, early infantile developmental epileptic encephalopathy; DEE, developmental epileptic encephalopathy; GTCS, generalized tonic-clonic seizures; AHC, altering hemiplegia of childhood; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; PED, paroxysmal exercise–induced dyskinesia.

control, and seizure burden may decrease with age even as dystonia and parkinsonian features worsen during adolescence and adulthood. Early childhood is dominated by midline hand stereotypies, whereas dystonia progressively emerges during the second decade, often with parkinsonian features including bradykinesia and rigidity.[53,110,134,163,164]

STXBP1-associated disorders typically present with early-onset DEE with seizure onset in the neonatal period or first months of life. The epilepsy phenotype may include early infantile DEE with suppression-burst pattern, IESS, or evolution to Lennox-Gastaut syndrome. Seizure types are diverse, including tonic seizures, epileptic spasms, focal seizures with or without impaired awareness, and myoclonic seizures. Dystonia can be severe and persistent and can occur alongside other movement features, including ataxia, tremor, and stereotypies, creating a complex mixed movement disorder.[62,132,136,165-167]

RHOBTB2-related disorder presents with paroxysmal dystonic episodes and hemiplegic attacks, which can be severe and recurrent. When epilepsy is present, seizure types may include focal seizures, generalized tonic-clonic seizures, or multiple seizure types.[113,168,169]

CACNA1A-related disorder, particularly in DEE presentations with haploinsufficiency variants, shows early-onset seizures, including absence, focal, myoclonic, or multiple seizure types occurring alongside dystonia and developmental impairment.[125,170,171]

Alternating hemiplegia of childhood (AHC) related to variants in *ATP1A3* presents with epilepsy in approximately 50% of patients, typically developing after the onset of hemiplegic episodes and paroxysmal dystonia, although seizures may occasionally represent the initial

clinical manifestation. When present, seizure types include focal seizures, generalized tonic-clonic seizures, or multiple seizure types, with variable severity ranging from rare seizures to frequent events. Some patients may present with isolated DEE or isolated dystonia.[27,28,109,172]

SCN2A-related DEE is associated with prominent dystonia and chorea that can appear within the first weeks of life, at times preceding or coinciding with epilepsy onset. Status dystonicus can occur.[19,106,120,173]

DEE with Prominent Chorea

FOXG1-related syndrome is the prototypical disorder in this category with chorea and seizures typically emerging concurrently in early infancy. The choreiform movements are generalized and continuous from early childhood, often accompanied by dystonia, myoclonus, and distinctive, often unilateral, hand stereotypies. Early-onset seizures manifest as infantile spasms. Additional seizure types include focal seizures and generalized seizures (tonic, myoclonic, or tonic-clonic). Epilepsy may be severe and medically refractory or show variable response to antiseizure medications. The combination of prominent early-onset chorea, infantile spasms, and congenital microcephaly in a male patient without developmental regression can distinguish *FOXG1*-related disorder from other etiologies.[11,49,102]

CDKL5-related disorder is associated with generalized chorea alongside prominent hand and leg stereotypies, bruxism, ataxia, dystonia, and myoclonus, with seizures typically preceding or coinciding with onset of movement disorders. Severe early-onset DEE can manifest within the first weeks of life, often progressing into epileptic spasms and evolving to include other generalized seizure types (tonic, myoclonic, tonic-clonic), focal seizures (with or without impaired awareness), and myoclonic seizures. The epilepsy burden is among the highest across all EDS genes, with less than 20% of patients achieving complete seizure control.[101,105]

SCN8A-related disorders demonstrate variable chorea severity across its broad phenotypic spectrum. Severe or intermediate DEE with seizure onset in the first weeks to months of life is associated with gain-of-function variants. In these cases, the epilepsy is typically severe and pharmaco-resistant. Nonepileptic paroxysmal manifestations, including nonepileptic myoclonus, generalized tremor, and hyperekplexia-like startles, are often seen in early childhood. Loss-of-function variants can manifest with DEE, although more commonly with neurodevelopmental disorders with or without later-onset epilepsy. Movement disorders including chorea, ataxia, and myoclonus develop variably in patients with loss-of-function variants, often with less severe motor impairment compared with gain-of-function variants.[20,98,100]

GABA transaminase deficiency, an autosomal recessive disease caused by pathogenic *ABAT* variants, is associated with a severe early infantile epileptic encephalopathy and continuous choreoathetosis during wakefulness.[174]

GNAO1- and *SCN2A*-related disorders, as previously discussed, are also included in this category when chorea is the predominant movement disorder.

DEE with Prominent Stereotypies

MECP2-related disorder including typical Rett syndrome presents with characteristic midline hand stereotypies (hand wringing, washing, or clapping) representing a cardinal feature occurring in virtually all patients and persisting throughout life. Additional stereotypies involve trunk, head, and neck. The movements are continuous during wakefulness and increase with excitement or concentration.[175] A similar spectrum is seen in *CDKL5*-related disorder where stereotypies are prominent and include characteristic leg-crossing and hand stereotypies recognized within the first months to years of life.[53] *STXBP1*-related disorder demonstrates a distinct set of stereotypies involving hands, trunk, head, and neck, including the characteristic but nonpathognomonic "figure-of-eight" sequence. Stereotypies co-occur with additional movement features, including ataxia, intention tremor, dyskinetic movements, and dystonia.[62,136]

Epilepsy with Paroxysmal Dyskinesia

This group includes paroxysmal dyskinesias, sometimes requiring differentiation from epileptic seizures by video-EEG. PKD, most strongly associated with variants in *PRRT2*, presents with brief episodes (typically <1 minute) triggered by sudden movement, startle, or transitions from rest to activity. Episodes manifest as dystonic posturing or choreiform movements, usually affecting one side of the body. The epileptic phenotype with *PRRT2* variants most commonly consists of SeLIE or SeLFIE, with focal seizures that can be generalized and that are easily controlled with antiseizure medications, especially sodium channel blockers, and resolve spontaneously before age 2 years. Importantly, PKD typically begins years after epilepsy has remitted, emerging in later childhood or adolescence, and is associated with normal cognitive development and an excellent overall response to therapy.[61,93,94] Paroxysmal dyskinesia can also occur in succinic semialdehyde dehydrogenase deficiency, the most common inherited disorder of GABA degradation.[176]

PNKD with epilepsy is found with variants in *PRRT2* and *KCNMA1*. Episodes are typically longer (minutes to hours) and are triggered by stress, emotional excitement, caffeine, alcohol, or fatigue, or occur spontaneously at rest without specific triggers. The movements

are typically dystonic or choreiform and may be unilateral or bilateral. In *KCNMA1*-related disorder, epilepsy may manifest as generalized or focal seizures with variable onset ranging from infancy to childhood.[23,126]

PED is a hallmark of *SLC2A1*-related GLUT1 deficiency. Episodes are triggered by sustained exercise and consist of dystonic posturing or choreiform movements affecting the exercised limbs. Movements typically begin during or immediately after exertion, may be unilateral, and gradually resolve with rest. Neonatal and early infantile seizures are characteristic of the classical form, as well as paroxysmal eye-head movements. The latter, representing aberrant gaze saccades, manifest as episodic multidirectional jerks of the eyes and head that occur in the same direction and may precede the onset of seizures. The epilepsy phenotype may also manifest in early childhood, with focal seizures, early-onset absence seizures, myoclonic seizures, atonic seizures, and generalized tonic-clonic seizures. Other paroxysmal symptoms such as intermittent ataxia, confusion, altered mental status, or headaches can occur during fasting, illness, or periods of increased metabolic demand when cerebral glucose availability is further reduced. Hypoglycorrhachia (low CSF glucose with normal serum glucose; CSF-to-blood glucose ratio < 0.4 measured 4 hours postprandial) is a diagnostic feature, although ratios up to 0.5 have been reported.[84,127]

Paroxysmal tonic upgaze (PTU), associated with variants in *CACNA1A*, consists of recurrent episodes of sustained upward eye deviation, sometimes occurring multiple times per day and accompanied by a head tilt or ataxia during the event. Additional paroxysmal non-epileptic manifestations in *CACNA1A*-related disease include episodic ataxia and hemiplegic migraine.[126,170]

Therapeutic Approaches

Management of EDSs requires integrated treatment strategies addressing both epilepsy and movement disorders, with attention to gene-specific responses and potential therapeutic synergies.[2,92]

Several medications show distinct gene-specific efficacy profiles. Carbamazepine and other sodium channel blockers are highly effective for *PRRT2*-related PKD, often at low doses.[93,177] Acetazolamide reduces episodic manifestations, including ataxia in *CACNA1A*-related disorder.[178] The ketogenic diet serves as a disease-modifying therapy for *SLC2A1* deficiency, improving both seizures and movement disorders.[179] Sodium channel blockers can be effective against symptoms associated with *SCN2A* and *SCN8A* gain-of-function variants.[180]

DBS has emerged as an important therapy for medically refractory movement disorders in EDS, particularly for life-threatening hyperkinetic crises or status dystonicus.[11,181] The strongest evidence supports benefit in *GNAO1*- and *UBA5*-related disorders, with multicenter data demonstrating efficacy across additional etiologies, including *SCN2A*, *MECP2*, *ARX*, and *GNB1*.[111,118,120,182] Target selection generally involves global pallidus interna or the subthalamic nuclei for movement disorders, whereas alternative targets such as the anterior or centromedian nuclei of the thalamus may be considered for epilepsy control when indicated.[183]

For patients with coexisting refractory epilepsy and movement disorders, multitarget DBS, in which two electrodes per hemisphere are used to modulate both a movement disorder target (GPi or subthalamic nucleus) and an epilepsy-directed target (anterior nucleus of the talamus or centromedian nucleus of the thalamus), is emerging as a feasible strategy, with early reports suggesting safety and efficacy in complex cases.[184,185]

Emerging Precision Medicine Approaches

The treatment landscape for EDSs is rapidly evolving, with multiple strategies in preclinical or clinical development (Table 2). Although not strictly limited to a precise gene or gene variant, a number of small-molecule therapies have already reached regulatory approval for several genetic epilepsies based on efficacy experienced in these specific conditions.[12] For *SCN1A*-related Dravet syndrome, stiripentol, cannabidiol, and fenfluramine demonstrated efficacy in randomized controlled trials.[107] Trofinetide received approval for *MECP2*-related Rett syndrome[186] and ganaxolone for *CDKL5*-related epilepsy.[187] Additional small-molecule therapies under investigation include zinc acetate and caffeine for *GNAO1*-related disorders.[188,189] Sodium channel modulators for SCN2A- and SCN8A-related DEEs such as relutrigine are currently in phase 3 clinical trials, and studies have been extended to other types of genetic epilepsies.

In terms of precision medicine, ASO therapies represent one of the fastest-advancing approaches.[190] For gain-of-function mutations such as *SCN8A*-related DEE, ASOs downregulating the sodium channel subunit NaV1.6 have shown efficacy in reducing seizures and mortality in mouse models.[191] ASO therapies have also demonstrated promise in preclinical models of progressive myoclonic epilepsies, Timothy syndrome (*CACNA1C*), and Angelman syndrome (*UB3A*) both in preclinical and phase 1/2 trials, with some showing efficacy even with prenatal delivery in animal models.[192-194] Personalized allele-specific ASOs have been developed for the *GNAO1* p.E246K variant, selectively reducing mutant protein while preserving wild-type expression.[195] A major clinical milestone was reached with the first ASO therapy administered to infants with *KCNT1*-associated EIMFS.[196]

TABLE 2 *Emerging precision medicine strategies for epilepsy-dyskinesia syndromes*

Gene	Specific/Novel therapy	Indication/Notes
PRRT2	Carbamazepine (low dose)	PKD—dramatic efficacy, gold standard
SCN1A	Stiripentol, cannabidiol, fenfluramine	Dravet syndrome—FDA approved
	AVOID: sodium channel blockers	Worsen both seizures and movements
	Ketogenic diet	Effective for seizures and movements
	ASO therapy (TANGO)—zorevunersen	Phase 1/2 clinical trial
	Gene therapy (ETX101)	Clinical trial planned
SCN2A	Sodium channel blockers	Effective for GoF variants
	ASO therapy	In development for GoF variants
SCN8A	Sodium channel blockers (phenytoin)	Effective for GoF variants
	Topiramate may worsen symptoms	Caution in use
	ASO therapy	Preclinical—downregulates NaV1.6 in GoF
GNAO1	Zinc acetate, caffeine	Under investigation—targeting downstream signaling
	DBS (GPi)	Strong evidence for hyperkinetic crises, status dystonicus
	AVOID: levodopa	May worsen motor symptoms
MECP2	Trofinetide	FDA approved—Rett syndrome
	Gene therapy (AAV-miRARE)	Clinical trials—with autoregulatory elements
	DBS (GPi)	For progressive parkinsonism
	AVOID: levodopa	May worsen symptoms
CDKL5	Ganaxolone	FDA approved—reduces seizure frequency
	Cannabidiol	Documented efficacy
	Ketogenic diet	Documented efficacy
	Fenfluramine	Documented benefit
	Gene therapy (AAV9)	Preclinical success—gene replacement
STXBP1	DBS (GPi)	For severe dystonia and Lennox-Gastaut–like parkinsonian symptoms
ATP1A3	Flunarizine (AHC)	For hemiplegic episodes
	High-flow oxygen (AHC)	During hemiplegic attacks
ARX	DBS (GPi)	For severe dystonia, status dystonicus
UBA5	DBS (GPi)	Strong evidence for status dystonicus
SLC2A1	Ketogenic diet	Disease modifying—bypasses glucose transport defect; gold standard treatment
CACNA1A	Acetazolamide	Highly effective for EA2, hemiplegic migraine, paroxysmal tonic upgaze
	4-Aminopyridine	Alternative for episodic ataxia
	Lamotrigine	Documented benefit *for epilepsy*

(Continues)

TABLE 2 *Continued*

Gene	Specific/Novel therapy	Indication/Notes
CACNA1E	Topiramate	Selective efficacy—AED with consistent benefit
	DBS (GPi)	For severe dystonia, status dystonicus
KCNQ2	Sodium channel blockers, carbamazepine, phenytoin	Can be effective for early onset
KCNMA1	Lisdexamfetamine	PNKD—reduces episode frequency
KCNT1	ASO therapy	Breakthrough—2 patients successfully treated (EIMFS)
KCNA2	4-Aminopyridine	Promising treatment for GoF encephalopathy
SLC6A1	Valproate	Preferential response
gRIN1, *GRIN2B*, *GRIN2D*	GoF: memantine, dextromethorphan, radiprodil	NMDA antagonists—radiprodil is GluN2B selective
	GoF: ketamine, magnesium	NMDA modulators
	LoF: L-serine	NMDA co-agonist
GNB1	DBS (GPi)	For severe hyperkinetic movements with DEE
AP4M1	Gene therapy (AAV9)	Phase 1/2 clinical trial demonstrating safety
AP4B1	Gene therapy (AAV9)	Phase 1/2 clinical trial planned to start
EPM2A	Gene therapy (AAV9)	Preclinical success
POLG	AVOID: valproate	Can precipitate fatal hepatic failure; screen POLG before valproate use
UB3A	ASO therapy	Phase 1/2 clinical trial

Abbreviations: AED, antiepileptic drug; AAV-miRARE, microRNA artifical repressor. Mechanisms of action of non–antiseizure medications listed in this table: trofinetide (MECP2/Rett): synthetic analog of glycine-proline-glutamate, the N-terminal tripeptide of insulin-like growth factor 1; putative mechanisms include modulation of synaptic signaling and neuroinflammation. Ganaxolone (CDKL5): synthetic analog of the endogenous neurosteroid allopregnanolone; positive allosteric modulator of synaptic and extrasynaptic GABA-A receptors, with preferential activity at δ-subunit–containing receptors. Zinc acetate (GNAO1): putatively restores GTPase activity of mutant Gαo protein, thereby normalizing downstream cAMP/G-protein signaling; clinical evidence remains investigational. Caffeine (GNAO1): adenosine receptor antagonist; proposed to modulate cAMP levels downstream of Gαo dysfunction. Flunarizine (ATP1A3/AHC): calcium channel blocker; proposed to stabilize neuronal membrane excitability and reduce frequency and severity of hemiplegic attacks. High-flow oxygen (ATP1A3/AHC): induces cerebral vasoconstriction, reducing cerebral blood flow and thereby shortening the duration of hemiplegic attacks. Acetazolamide (CACNA1A): carbonic anhydrase inhibitor; reduces neuronal hyperexcitability, with a probable membrane-stabilizing effect on calcium channel function. 4-Aminopyridine (CACNA1A, KCNA2-GoF): voltage-gated potassium channel blocker; increases cerebellar Purkinje cell firing rate. Lisdexamfetamine (KCNMA1): prodrug of dextroamphetamine; proposed to modulate dopaminergic and noradrenergic signaling, reducing paroxysmal dyskinesia episode frequency. Memantine/Dextromethorphan/Radiprodil (GRIN GoF): NMDA receptor antagonists, reducing pathological overactivation of gain-of-function glutamate receptor variants; radiprodil is GluN2B selective. Ketamine (GRIN GoF): noncompetitive NMDA receptor antagonist acting via open-channel block. Magnesium (GRIN GoF): physiological voltage-dependent blocker of the NMDA receptor channel pore, reducing conductance under conditions of partial depolarization. L-serine (GRIN LoF): NMDA receptor co-agonist at the glycine-binding site, compensating for reduced receptor activity in loss-of-function variants.
Abbreviations: PKD, paroxysmal kinesigenic dyskinesia; FDA, US Food and Drug Administration; ASO, antisense oligonucleotide; TANGO, Targeted Augmentation of Nuclear Gene Output; GoF, gain of function; DBS, deep brain stimulation; GPi, globus pallidus internus; AHC, altering hemiplegia of childhood; PNKD, paroxysmal nonkinesigenic dyskinesia; EIMFS, epilepsy of infancy with migrating focal seizures; NMDA, *N*-methyl-D-aspartate; LoS, loss of function; DEE, developmental epileptic encephalopathy; cAMP, cyclic adenosine monophosphate.

ASOs can also increase protein expression in loss-of-function disorders through a mechanism termed Targeted Augmentation of Nuclear Gene Output (TANGO).[190] This has shown preclinical and phase 1/2 trials success in Dravet syndrome.[197]

For monogenic loss-of-function epilepsies, gene replacement has shown success in preclinical models of Lafora disease (*EPM2A*) and *CDKL5* deficiency using intraventricular AAV9 delivery.[198,199] Intrathecal AAV9 gene therapy is in clinical trials for hereditary spastic paraplegia type 50 (*AP4M1*)[200] and Rett syndrome.[201] For Dravet syndrome, the large size of *SCN1A* complicates packaging in AAV vectors. Solutions include dual-AAV split-intein systems or transactivation therapy using engineered transcription factors to selectively upregulate endogenous *SCN1A* in GABAergic interneurons, a strategy that has demonstrated safety in nonhuman primates and is now advancing to clinical trials.[107]

CRISPR-Cas9 provides the ability to precisely disrupt pathogenic alleles. Preclinical proof-of-concept studies

have shown seizure reduction in *SCN8A*-related DEE models.[202] However, challenges include off-target effects, variable editing efficiency, and delivery constraints.[203] Alternative approaches using dCas9 fused to transcriptional activators have successfully restored interneuron function and reduced seizures in Dravet models.[204] Prime editing rescued clinically relevant phenotypes, including ATPase activity, paroxysmal spells, motor defects, and cognition deficits, and lifespan in a mouse model of *ATP1A3*-related disorder.[205]

Collectively, these emerging therapies represent a paradigm shift from symptom-directed treatment toward disease-modifying and potentially curative approaches for EDS. Key challenges include achieving therapeutic CNS exposure, navigating host immune responses, defining meaningful clinical endpoints for ultra-rare and heterogeneous disorders, optimizing intervention timing relative to neurodevelopmental windows, and addressing the substantial financial costs associated with individualized genetic therapies.[206]

Conclusion and Future Directions

EDSs constitute a rapidly expanding group of genetic disorders that require coordinated, multidisciplinary care that integrates epilepsy and movement disorder expertise, leverages synergistic therapies, and targets shared molecular pathways. Progress hinges on robust genotype–phenotype correlations from systematic natural history studies and on validated, disease-specific outcome measures suitable for ultra-rare conditions. Although DBS shows promise for severe, refractory movement disorders and select epilepsy cases, key questions remain regarding patient selection, targets, timing, and integration with other surgical approaches. The growing therapeutic pipeline, spanning gene replacement, ASOs, and precision small molecules, signals a shift toward disease-modifying interventions. Continued advances in genetics, mechanisms, and clinical phenotyping, alongside sustained collaboration among clinicians, researchers, and patient advocates, will be essential to translate these gains into improved outcomes and access to care. ■

Author Roles: (1) Research Project: A. Conception, B. Design, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.
K.B.: 1A, 1B, 1C, 3A, 3B.
D.E.-F.: 1A, 1B, 1C, 3B.
J.A.A.: 1B, 1C, 3B.
C.M.E.A.: 1B, 1C, 3B.
L.T.: 1B, 1C, 3B.
P.L.P.: 1B, 1C, 3B.

Financial Disclosures and Conflicts of Interest: Katerina Bernardi: Employment: Boston Children's Hospital. Julian E. Alecu: Employment, Boston Children's Hospital. Christelle Moufawad El Achkar: Employment: Boston Children's Hospital. Laura Tochen: Employment: Children's National Hospital. Phillip L. Pearl: Employment: Boston Children's Hospital. Darius Ebrahimi-Fakhari: Consultancies: Guidepoint LLC, Fondazione Telethon, German Center for Neurodegenerative Diseases, University of Texas Southwestern; Advisory Boards: Scientific advisory board (unpaid): CureAP4 Foundation, The Maddie Foundation, SPG69/Warburg Micro Research Foundation, The Lilly & Blair Foundation, The Maurya Koduri Foundation, Genetic Cures for Kids Inc; Employment: Boston Children's Hospital; Honoraria: speaker honoraria from the Movement Disorders Society; Royalties: Cambridge University Press; Patents: PCT/US2024/029856; Grants: National Institute of Neurological Disorders and Stroke, National Institutes of Health (1U54NS148312, 5K08NS123552), CureAP4 Foundation, Spastic Paraplegia Foundation, New England Epilepsy Foundation, BCH Office of Faculty Development, BCH Translational Research Program, BCH Technology and Innovation Development Office. Author disclosures are available in the Supporting Information.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

References

1. Papandreou A, Danti FR, Spaull R, Leuzzi V, McTague A, Kurian MA. The expanding spectrum of movement disorders in genetic epilepsies. Dev Med Child Neurol 2020;62(2):178–191.
2. Quiroz V, Alecu JE, Zubair U, Bernardi K, Zaman Z, Rong J, et al. Molecular and clinical spectrum of epilepsy-dyskinesia syndromes: a cross-sectional study of 609 patients. Brain 2026;149(2):563–578.
3. van der Veen S, Tse GTW, Ferretti A, Garone G, Post B, Specchio N, et al. Movement disorders in patients with genetic developmental and epileptic encephalopathies. Neurology 2023;101(19):e1884–e1892.
4. Spagnoli C, Fusco C, Percesepe A, Leuzzi V, Pisani F. Genetic neonatal-onset epilepsies and developmental/epileptic encephalopathies with movement disorders: a systematic review. Int J Mol Sci 2021;22(8):4202.
5. Mastrangelo M, Galosi S, Cesario S, Renzi A, Campea L, Leuzzi V. Presenting patterns of genetically determined developmental encephalopathies with epilepsy and movement disorders: a single tertiary center retrospective cohort study. Front Neurol 2022;13:855134.
6. Ruggiero SM, Xian J, Helbig I. The current landscape of epilepsy genetics: where are we, and where are we going? Curr Opin Neurol 2023;36(2):86–94.
7. McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol 2016;15(3):304–316.
8. Oliver KL, Scheffer IE, Bennett MF, Grinton BE, Bahlo M, Berkovic SF. Genes4Epilepsy: an epilepsy gene resource. Epilepsia 2023;64(5):1368–1375.
9. Kobayashi Y, Tohyama J, Kato M, et al. High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders. Brain Dev 2016;38(3):285–292.
10. Dzinovic I, Skorvanek M, Necpal J, Boesch S, Svantnerova J, Wagner M, et al. Dystonia as a prominent presenting feature in developmental and epileptic encephalopathies: a case series. Parkinsonism Relat Disord 2021;90:73–78.
11. Perez-Duenas B, Gorman K, Marce-Grau A, Ortigoza-Escobar JD, Macaya A, Danti FR, et al. The genetic landscape of complex childhood-onset hyperkinetic movement disorders. Mov Disord 2022;37(11):2197–2209.
12. Sullivan J, Hood V. Emerging genetic therapies in epilepsy. Semin Neurol 2025;45(2):298–302.
13. Samanta D, Bhatia S, Hunter SE, et al. Current and emerging precision therapies for developmental and epileptic encephalopathies. Pediatr Neurol 2025;168:67–81.
14. Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. Mov Disord 2010;25(11):1538–1549.

15. Gardiner AR, Jaffer F, Dale RC, et al. The clinical and genetic heterogeneity of paroxysmal dyskinesias. Brain 2015;138(Pt 12): 3567–3580.

16. Lange LM, Gonzalez-Latapi P, Rajalingam R, et al. Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society task force – an update. Mov Disord 2022;37(5):905–935.

17. Meisler MH, Hill SF, Yu W. Sodium channelopathies in neurodevelopmental disorders. Nat Rev Neurosci 2021;22(3): 152–166.

18. Scheffer IE, Nabbout R. SCN1A-related phenotypes: epilepsy and beyond. Epilepsia 2019;60(Suppl 3):S17–S24.

19. Howell KB, McMahon JM, Carvill GL, Tambunan D, Mackay MT, Rodriguez-Casero V, et al. SCN2A encephalopathy: a major cause of epilepsy of infancy with migrating focal seizures. Neurology 2015;85(11):958–966.

20. Gardella E, Marini C, Trivisano M, et al. The phenotype of SCN8A developmental and epileptic encephalopathy. Neurology 2018;91(12):e1112–e1124.

21. Fitzgerald MP, Fiannacca M, Smith DM, et al. Treatment responsiveness in KCNT1-related epilepsy. Neurotherapeutics 2019;16(3): 848–857.

22. Miceli F, Soldovieri MV, Weckhuysen S, Cooper E, Taglialatela M. KCNQ2-related disorders. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.

23. Zhang ZB, Tian MQ, Gao K, Jiang YW, Wu Y. De novo KCNMA1 mutations in children with early-onset paroxysmal dyskinesia and developmental delay. Mov Disord 2015;30(9):1290–1292.

24. Epi KC, Epilepsy Phenome/Genome P, Allen AS, Berkovic SF, Cossette P, Delanty N, et al. De novo mutations in epileptic encephalopathies. Nature 2013;501(7466):217–221.

25. Reinson K, Oiglane-Shlik E, Talvik I, Vaher U, Ounapuu A, Ennok M, et al. Biallelic CACNA1A mutations cause early onset epileptic encephalopathy with progressive cerebral, cerebellar, and optic nerve atrophy. Am J Med Genet A 2016;170(8):2173–2176.

26. Helbig KL, Lauerer RJ, Bahr JC, et al. De novo pathogenic variants in CACNA1E cause developmental and epileptic encephalopathy with contractures, macrocephaly, and dyskinesias. Am J Hum Genet 2018;103(5):666–678.

27. Paciorkowski AR, McDaniel SS, Jansen LA, et al. Novel mutations in ATP1A3 associated with catastrophic early life epilepsy, episodic prolonged apnea, and postnatal microcephaly. Epilepsia 2015; 56(3):422–430.

28. Vezyroglou A, Akilapa R, Barwick K, et al. The phenotypic continuum of ATP1A3-related disorders. Neurology 2022;99(14):e1511–e1526.

29. Ohba C, Shiina M, Tohyama J, et al. GRIN1 mutations cause encephalopathy with infantile-onset epilepsy, and hyperkinetic and stereotyped movement disorders. Epilepsia 2015;56(6):841–848.

30. Li D, Yuan H, Ortiz-Gonzalez XR, Marsh ED, Tian L, McCormick EM, et al. GRIN2D recurrent De novo dominant mutation causes a severe epileptic encephalopathy treatable with NMDA Receptor Channel blockers. Am J Hum Genet 2016;99(4): 802–816.

31. Platzer K, Yuan H, Schutz H, Winschel A, Chen W, Hu C, et al. GRIN2B encephalopathy: novel findings on phenotype, variant clustering, functional consequences and treatment aspects. J Med Genet 2017;54(7):460–470.

32. Martin S, Chamberlin A, Shinde DN, et al. De novo variants in GRIA4 Lead to intellectual disability with or without seizures and gait abnormalities. Am J Hum Genet 2017;101(6):1013–1020.

33. Traynelis SF, Wollmuth LP, McBain CJ, et al. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev 2010;62(3):405–496.

34. Kodera H, Ohba C, Kato M, et al. De novo GABRA1 mutations in Ohtahara and west syndromes. Epilepsia 2016;57(4):566–573.

35. Moller RS, Wuttke TV, Helbig I, Marini C, Johannesen KM, Brilstra EH, et al. Mutations in GABRB3: from febrile seizures to epileptic encephalopathies. Neurology 2017;88(5):483–492.

36. Shen D, Hernandez CC, Shen W, et al. De novo GABRG2 mutations associated with epileptic encephalopathies. Brain 2017; 140(1):49–67.

37. Ishii A, Kang JQ, Schornak CC, et al. A de novo missense mutation of GABRB2 causes early myoclonic encephalopathy. J Med Genet 2017;54(3):202–211.

38. Kalscheuer VM, Musante L, Fang C, et al. A balanced chromosomal translocation disrupting ARHGEF9 is associated with epilepsy, anxiety, aggression, and mental retardation. Hum Mutat 2009;30(1):61–68.

39. Kelly M, Park M, Mihalek I, et al. Spectrum of neurodevelopmental disease associated with the GNAO1 guanosine triphosphate-binding region. Epilepsia 2019;60(3):406–418.

40. Nakamura K, Kodera H, Akita T, Shiina M, Kato M, Hoshino H, et al. De novo mutations in GNAO1, encoding a Galphao subunit of heterotrimeric G proteins, cause epileptic encephalopathy. Am J Hum Genet 2013;93(3):496–505.

41. Huang Y, Thathiah A. Regulation of neuronal communication by G protein-coupled receptors. FEBS Lett 2015;589(14):1607–1619.

42. Danti FR, Galosi S, Romani M, et al. GNAO1 encephalopathy: broadening the phenotype and evaluating treatment and outcome. Neurol Genet 2017;3(2):e143.

43. Feng H, Sjogren B, Karaj B, Shaw V, Gezer A, Neubig RR. Movement disorder in GNAO1 encephalopathy associated with gain-of-function mutations. Neurology 2017;89(8):762–770.

44. Wang D, Dao M, Muntean BS, Giles AC, Martemyanov KA, Grill B. Genetic modeling of GNAO1 disorder delineates mechanisms of Galphao dysfunction. Hum Mol Genet 2022;31(4): 510–522.

45. Dwivedi R, Kaushik M, Tripathi M, Dada R, Tiwari P. Unraveling the genetic basis of epilepsy: recent advances and implications for diagnosis and treatment. Brain Res 2024;1843:149120.

46. Kurian MA, Meyer E, Vassallo G, et al. Phospholipase C beta 1 deficiency is associated with early-onset epileptic encephalopathy. Brain 2010;133(10):2964–2970.

47. Galosi S, Pollini L, Novelli M, Bernardi K, Di Rocco M, Martinelli S, et al. Motor, epileptic, and developmental phenotypes in genetic disorders affecting G protein coupled receptors-cAMP signaling. Front Neurol 2022;13:886751.

48. Guerrini R, Moro F, Kato M, Barkovich AJ, Shiihara T, McShane MA, et al. Expansion of the first PolyA tract of ARX causes infantile spasms and status dystonicus. Neurology 2007;69(5): 427–433.

49. Ba R, Yang L, Zhang B, Jiang P, Ding Z, Zhou X, et al. FOXG1 drives transcriptomic networks to specify principal neuron subtypes during the development of the medial pallium. Sci Adv 2023;9(7): eade2441.

50. Zweier M, Gregor A, Zweier C, et al. Mutations in MEF2C from the 5q14.3q15 microdeletion syndrome region are a frequent cause of severe mental retardation and diminish MECP2 and CDKL5 expression. Hum Mutat 2010;31(6):722–733.

51. Coe BP, Witherspoon K, Rosenfeld JA, van Bon BW, Vulto-van Silfhout AT, Bosco P, et al. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat Genet 2014;46(10):1063–1071.

52. Yen A, Sarafinovska S, Chen X, et al. MYT1L deficiency impairs excitatory neuron trajectory during cortical development. Nat Commun 2024;15(1):10308.

53. Guerrini R, Parrini E. Epilepsy in Rett syndrome, and CDKL5- and FOXG1-gene-related encephalopathies. Epilepsia 2012;53(12): 2067–2078.

54. Suzuki H, Katayama K, Takenaka M, Amakasu K, Saito K, Suzuki K. A spontaneous mutation of the Wwox gene and audiogenic seizures in rats with lethal dwarfism and epilepsy. Genes Brain Behav 2009;8(7):650–660.

55. Yates TM, Vasudevan PC, Chandler KE, et al. De novo mutations in HNRNPU result in a neurodevelopmental syndrome. Am J Med Genet A 2017;173(11):3003–3012.

56. Deardorff MA, Kaur M, Yaeger D, et al. Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of cornelia de Lange syndrome with predominant mental retardation. Am J Hum Genet 2007;80(3):485–494.

57. Grozeva D, Carss K, Spasic-Boskovic O, et al. De novo loss-of-function mutations in SETD5, encoding a methyltransferase in a 3p25 microdeletion syndrome critical region, cause intellectual disability. Am J Hum Genet 2014;94(4):618–624.

58. Lalani SR, Zhang J, Schaaf CP, et al. Mutations in PURA cause profound neonatal hypotonia, seizures, and encephalopathy in 5q31.3 microdeletion syndrome. Am J Hum Genet 2014;95(5): 579–583.

59. Verhage M, Sorensen JB. SNAREopathies: diversity in mechanisms and symptoms. Neuron 2020;107(1):22–37.

60. Chanaday NL, Cousin MA, Milosevic I, Watanabe S, Morgan JR. The synaptic vesicle cycle revisited: new insights into the modes and mechanisms. J Neurosci 2019;39(42):8209–8216.

61. Yang K, Quiroz V, Ebrahimi-Fakhari D. PRRT2-related disorder. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews ((R)). Seattle (WA):University of Washington; 1993.

62. Xian J, Parthasarathy S, Ruggiero SM, et al. Assessing the landscape of STXBP1-related disorders in 534 individuals. Brain 2022; 145(5):1668–1683.

63. Hardies K, Cai Y, Jardel C, et al. Loss of SYNJ1 dual phosphatase activity leads to early onset refractory seizures and progressive neurological decline. Brain 2016;139(Pt 9):2420–2430.

64. Falace A, Filipello F, La Padula V, Vanni N, Madia F, De Pietri Tonelli D, et al. TBC1D24, an ARF6-interacting protein, is mutated in familial infantile myoclonic epilepsy. Am J Hum Genet 2010;87(3):365–370.

65. von Spiczak S, Helbig KL, Shinde DN, et al. DNM1 encephalopathy: a new disease of vesicle fission. Neurology 2017;89(4): 385–394.

66. Salpietro V, Malintan NT, Llano-Rivas I, et al. Mutations in the neuronal vesicular SNARE VAMP2 affect synaptic membrane fusion and impair human neurodevelopment. Am J Hum Genet 2019;104(4):721–730.

67. Saitsu H, Tohyama J, Kumada T, et al. Dominant-negative mutations in alpha-II spectrin cause west syndrome with severe cerebral hypomyelination, spastic quadriplegia, and developmental delay. Am J Hum Genet 2010;86(6):881–891.

68. Giansante G, Mazzoleni S, Zippo AG, et al. Neuronal network activity and connectivity are impaired in a conditional knockout mouse model with PCDH19 mosaic expression. Mol Psychiatry 2024;29(6):1710–1725.

69. Rakotomamonjy J, Rylaarsdam L, Fares-Taie L, et al. PCDH12 loss results in premature neuronal differentiation and impeded migration in a cortical organoid model. Cell Rep 2023;42(8): 112845.

70. Shukla M, Chugh D, Ganesh S. Neuromuscular junction dysfunction in Lafora disease. Dis Model Mech 2024;17(10):dmm050905.

71. Ji C, Zhao YG. The BPAN and intellectual disability disease proteins WDR45 and WDR45B modulate autophagosome-lysosome fusion. Autophagy 2021;17(7):1783–1784.

72. Saitsu H, Nishimura T, Muramatsu K, Kodera H, Kumada S, Sugai K, et al. De novo mutations in the autophagy gene WDR45 cause static encephalopathy of childhood with neurodegeneration in adulthood. Nat Genet 2013;45(4):445–449. 9e1

73. Lv S, Jiang H, Yu L, Zhang Y, Sun L, Xu J. SNX14 inhibits autophagy via the PI3K/AKT/mTOR signaling cascade in breast cancer cells. J Mol Histol 2024;55(4):391–401.

74. Cheung YWS, Nam SE, Fairlie GMJ, et al. Structure of the human autophagy factor EPG5 and the molecular basis of its conserved mode of interaction with Atg8-family proteins. Autophagy 2025; 21(6):1173–1191.

75. Hao X, Sun J, Zhong L, Baudry M, Bi X. UBE3A deficiency-induced autophagy is associated with activation of AMPK-ULK1 and p53 pathways. Exp Neurol 2023;363:114358.

76. Chan EM, Young EJ, Ianzano L, et al. Mutations in NHLRC1 cause progressive myoclonus epilepsy. Nat Genet 2003;35(2): 125–127.

77. Colin E, Daniel J, Ziegler A, et al. Biallelic variants in UBA5 reveal that disruption of the UFM1 Cascade can result in early-onset encephalopathy. Am J Hum Genet 2016;99(3):695–703.

78. Hollstein R, Parry DA, Nalbach L, et al. HACE1 deficiency causes an autosomal recessive neurodevelopmental syndrome. J Med Genet 2015;52(12):797–803.

79. Gomez-Sanchez R, Pizarro-Estrella E, Yakhine-Diop SM, Rodriguez-Arribas M, Bravo-San Pedro JM, Fuentes JM, et al. Routine Western blot to check autophagic flux: cautions and recommendations. Anal Biochem 2015;477:13–20.

80. Ishimura R, El-Gowily AH, Noshiro D, Komatsu-Hirota S, Ono Y, Shindo M, et al. The UFM1 system regulates ER-phagy through the ufmylation of CYB5R3. Nat Commun 2022;13(1):7857.

81. Xu JJ, Chen YL, Yu H, Chen DF, Li HF, Wu ZY. Genetic and clinical features of SLC2A1-related paroxysmal exercise-induced dyskinesia. Pediatr Neurol 2025;170:31–37.

82. Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet 2004;74(1):168–175.

83. Johannesen KM, Gardella E, Linnankivi T, Courage C, de Saint Martin A, Lehesjoki AE, et al. Defining the phenotypic spectrum of SLC6A1 mutations. Epilepsia 2018;59(2):389–402.

84. Kovermann P, Bayat A, Fenger CD, et al. The severity of SLC1A2-associated neurodevelopmental disorders correlates with transporter dysfunction. EBioMedicine 2025;114:105648.

85. Ognjenovic J, Simonovic M. Human aminoacyl-tRNA synthetases in diseases of the nervous system. RNA Biol 2018;15(4–5): 623–634.

86. Krawitz PM, Schweiger MR, Rodelsperger C, Marcelis C, Kolsch U, Meisel C, et al. Identity-by-descent filtering of exome sequence data identifies PIGV mutations in hyperphosphatasia mental retardation syndrome. Nat Genet 2010;42(10):827–829.

87. Maydan G, Noyman I, Har-Zahav A, et al. Multiple congenital anomalies-hypotonia-seizures syndrome is caused by a mutation in PIGN. J Med Genet 2011;48(6):383–389.

88. Patel MS, Nemeria NS, Furey W, Jordan F. The pyruvate dehydrogenase complexes: structure-based function and regulation. J Biol Chem 2014;289(24):16615–16623.

89. Abela L, Gianfrancesco L, Tagliatti E, et al. Neurodevelopmental and synaptic defects in DNAJC6 parkinsonism, amenable to gene therapy. Brain 2024;147(6):2023–2037.

90. Zagaglia S, Selch C, Nisevic JR, Mei D, Michalak Z, Hernandez-Hernandez L, et al. Neurologic phenotypes associated with COL4A1/2 mutations: expanding the spectrum of disease. Neurology 2018;91(22):e2078–e2088.

91. Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain 2019;142(8):2303–2318.

92. Garris J, Abbott M, Axeen E, Tochen L, Schreiber JM. Evaluation, diagnosis, and treatment of concomitant movement disorders in genetic epilepsies. Epilepsy Curr 2025;25(6):378–388.

93. Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. Brain 2015;138(Pt 12):3476–3495.

94. Doring JH, Saffari A, Bast T, et al. The phenotypic Spectrum of PRRT2-associated paroxysmal neurologic disorders in childhood. Biomedicine 2020;8(11):456.

95. Salles PA, Mata IF, Brunger T, Lal D, Fernandez HH. ATP1A3-related disorders: an ever-expanding clinical Spectrum. Front Neurol 2021;12:637890.

96. Ludlam WG, Soliani L, Dominguez-Carral J, Cordelli DM, Marchiani V, Gorria-Redondo N, et al. Diverse faces of GNAO1:

mild forms in epilepsy and autism. J Neurol 2024;271(7):3777–3781.

97. Bourque DK, Cordeiro D, Nimmo GAM, Kobayashi J, Mercimek-Andrews S. Phenotypic and genotypic Spectrum of glucose Transporter-1 deficiency syndrome. Can J Neurol Sci 2021;48(6):826–830.
98. Johannesen KM, Liu Y, Koko M, et al. Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications. Brain 2022;145(9):2991–3009.
99. Gallagher D, Perez-Palma E, Bruenger T, et al. Genotype-phenotype associations in 1018 individuals with SCN1A-related epilepsies. Epilepsia 2024;65(4):1046–1059.
100. Hack JB, Horning K, Juroske Short DM, Schreiber JM, Watkins JC, Hammer MF. Distinguishing loss-of-function and gain-of-function SCN8A variants using a random Forest classification model trained on clinical features. Neurol Genet 2023;9(3):e200060.
101. Demarest ST, Olson HE, Moss A, et al. CDKL5 deficiency disorder: relationship between genotype, epilepsy, cortical visual impairment, and development. Epilepsia 2019;60(8):1733–1742.
102. Mitter D, Pringsheim M, Kaulisch M, Plumacher KS, Schroder S, Warthemann R, et al. FOXG1 syndrome: genotype-phenotype association in 83 patients with FOXG1 variants. Genet Med 2018;20(1):98–108.
103. Briere L, Thiel M, Sweetser DA, Koy A, Axeen E. GNAO1-related disorder. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.
104. Wirth T, Garone G, Kurian MA, et al. Highlighting the dystonic phenotype related to GNAO1. Mov Disord 2022;37(7):1547–1554.
105. Carranza Rojo D, Hamiwka L, McMahon JM, et al. De novo SCN1A mutations in migrating partial seizures of infancy. Neurology 2011;77(4):380–383.
106. Wolff M, Johannesen KM, Hedrich UBS, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain 2017;140(5):1316–1336.
107. Chilcott E, Diaz JA, Bertram C, Berti M, Karda R. Genetic therapeutic advancements for Dravet syndrome. Epilepsy Behav 2022;132:108741.
108. Olson HE, Demarest ST, Pestana-Knight EM, et al. Cyclin-dependent kinase-like 5 deficiency disorder: clinical review. Pediatr Neurol 2019;97:18–25.
109. Brashear A, Sweadner KJ, Haq I, Napoli E, Ozelius L. ATP1A3-related disorder. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.
110. Percy AK, Ananth A, Neul JL. Rett syndrome: the emerging landscape of treatment strategies. CNS Drugs 2024;38(11):851–867.
111. Akula SK, Quiroz V, D'Gama AM, et al. The spectrum of movement disorders in young children with ARX-related epilepsy-dyskinesia syndrome. Ann Clin Transl Neurol 2024;11(6):1643–1647.
112. Briere LC, Walker MA, High FA, et al. A description of novel variants and review of phenotypic spectrum in UBA5-related early epileptic encephalopathy. Cold Spring Harb Mol Case Stud 2021;7(3):a005827.
113. de Pedro Baena S, Sariego Jamardo A, Castro P, Lopez Gonzalez FJ, Sanchez Carpintero R, Cerisola A, et al. Exploring the Spectrum of RHOBTB2 variants associated with developmental encephalopathy 64: a case series and literature review. Mov Disord Clin Pract 2023;10(11):1671–1679.
114. Platzer K, Krey I, Lemke JR. GRIN2D-related developmental and epileptic encephalopathy. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.
115. Platzer K, Lemke JR. GRIN2B-related neurodevelopmental disorder. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.
116. Platzer K, Lemke JR. GRIN1-related neurodevelopmental disorder. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.
117. Novelli M, Galosi S, Zorzi G, et al. GNAO1-related movement disorder: an update on phenomenology, clinical course, and response to treatments. Parkinsonism Relat Disord 2023;111:105405.
118. Zaman Z, Straka N, Pinto AL, et al. Deep brain stimulation for medically refractory status dystonicus in UBA5-related disorder. Mov Disord 2023;38(9):1757–1759.
119. Jones HF, Morales-Briceno H, Barwick K, Lewis J, Sanchis-Juan A, Raymond FL, et al. Myoclonus-dystonia caused by GNB1 mutation responsive to deep brain stimulation. Mov Disord 2019;34(7):1079–1080.
120. Mithani K, Breitbart S, Fasano A, Gorodetsky C, Ibrahim GM. Deep brain stimulation for status dystonicus in a toddler with SCN2A-related disorder. Childs Nerv Syst 2023;39(11):3033–3035.
121. Zhang J, Chen J, Zeng Q, et al. Infantile epilepsy with multifocal myoclonus caused by TBC1D24 mutations. Seizure 2019;69:228–234.
122. Canafoglia L, Castellotti B, Ragona F, et al. Progressive myoclonus epilepsy caused by a gain-of-function KCNA2 mutation. Seizure 2019;65:106–108.
123. Loussouarn A, Doummar D, Beaugendre Y, et al. Tremor-like subcortical myoclonus in STXBP1 encephalopathy. Eur J Paediatr Neurol 2021;34:62–66.
124. Caputo D, Solazzi R, Castellotti B, Panteghini C, Sciacca FL, Visani E, et al. Genetic complexity in pediatric onset epilepsy-movement disorder syndromes: insights from a cohort of 97 subjects. Epilepsia 2026;67(1):299–314.
125. Indelicato E, Boesch S. From genotype to phenotype: expanding the clinical Spectrum of CACNA1A variants in the era of next generation sequencing. Front Neurol 2021;12:639994.
126. Erro R, Bhatia KP, Espay AJ, Striano P. The epileptic and non-epileptic spectrum of paroxysmal dyskinesias: channelopathies, synaptopathies, and transportopathies. Mov Disord 2017;32(3):310–318.
127. de Gusmao CM, Garcia L, Mikati MA, Su S, Silveira-Moriyama L. Paroxysmal genetic movement disorders and epilepsy. Front Neurol 2021;12:648031.
128. Kurian MA, Abela L. DNAJC6 Parkinson disease. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.
129. Williams LJ, Waller S, Qiu J, et al. DHDDS and NUS1: a converging pathway and common phenotype. Mov Disord Clin Pract 2024;11(1):76–85.
130. Quadri M, Fang M, Picillo M, et al. Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset parkinsonism. Hum Mutat 2013;34(9):1208–1215.
131. Schmitt I, Evert BO, Sharma A, Khazneh H, Murgatroyd C, Wullner U. The alpha-synuclein gene (SNCA) is a genomic target of methyl-CpG binding protein 2 (MeCP2)-implications for Parkinson's disease and Rett syndrome. Mol Neurobiol 2024;61(10):7830–7844.
132. Dong M, Zhang T, Hu R, Li M, Wang G, Liu X. Genotype and phenotype spectrum of 10 children with STXBP1 gene-related encephalopathy and epilepsy. Front Pediatr 2022;10:1010886.
133. Capuano A, Garone G, Tiralongo G, Graziola F. Alternating hemiplegia of childhood: understanding the genotype-phenotype relationship of ATP1A3 variations. Appl Clin Genet 2020;13:71–81.
134. Leonard H, Cobb S, Downs J. Clinical and biological progress over 50 years in Rett syndrome. Nat Rev Neurol 2017;13(1):37–51.
135. Kim J, Teng LY, Shaker B, et al. Genotypes and phenotypes of DNM1 encephalopathy. J Med Genet 2023;60(11):1076–1083.
136. Stamberger H, Crosiers D, Balagura G, Bonardi CM, Basu A, Cantalupo G, et al. Natural history study of STXBP1-developmental and epileptic encephalopathy into adulthood. Neurology 2022;99(3):e221–e233.

137. Yu Q, Zhao MW, Yang P. LncRNA UCA1 suppresses the inflammation via modulating miR-203-mediated regulation of MEF2C/NF-kappaB signaling pathway in epilepsy. Neurochem Res 2020;45(4):783–795.

138. Kofoed AWS, Kristiansen SS, Miranda MJ, Rubboli G, Johannesen KM. Differences in manifestations of epilepsy and developmental delay in PURA syndrome and 5q31 microdeletions. Clin Genet 2024;106(4):386–393.

139. Vlaskamp DRM, Shaw BJ, Burgess R, et al. SYNGAP1 encephalopathy: a distinctive generalized developmental and epileptic encephalopathy. Neurology 2019;92(2):e96–e107.

140. Dhamija R, Goodkin HP, Bailey R, Chambers C, Brenton JN. A case of KCNQ2-associated movement disorder triggered by fever. J Child Neurol 2017;32(14):1123–1124.

141. Gertler T, Bearden D, Bhattacharjee A, Carvill G. KCNT1-related epilepsy. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.

142. Meisler MH, Kearney JA, Sprunger LK, MacDonald BT, Buchner DA, Escayg A. Mutations of voltage-gated sodium channels in movement disorders and epilepsy. Novartis Found Symp 2002;241:72–81.

143. Tarailo-Graovac M, Sinclair G, Stockler-Ipsiroglu S, van Allen M, Rozmus J, Shyr C, et al. The genotypic and phenotypic spectrum of PIGA deficiency. Orphanet J Rare Dis 2015;10:23.

144. Franquelim C, Romana A, Rachao A, Martins JS, Monteiro JP, Carvalho J. Early-onset dystonia and visual impairment preceding epileptic encephalopathy associated with PIGA gene mutation. Neuropediatrics 2024;55(4):265–268.

145. Olgiati S, Quadri M, Fang M, Rood JP, Saute JA, Chien HF, et al. DNAJC6 mutations associated with early-onset Parkinson's disease. Ann Neurol 2016;79(2):244–256.

146. Hor CHH, Tang BL. Beta-propeller protein-associated neurodegeneration (BPAN) as a genetically simple model of multifaceted neuropathology resulting from defects in autophagy. Rev Neurosci 2019;30(3):261–277.

147. Turnbull J, Tiberia E, Striano P, Genton P, Carpenter S, Ackerley CA, Minassian BA. Lafora disease. Epileptic Disord 2016;18(S2):38–62.

148. Tegelberg S, Joensuu T, Lehesjoki AE. Progressive myoclonus epilepsy: Unverricht-Lundborg disease. In: Noebels JL, Avoli M, Rogawski MA, Vezzani A, Delgado-Escueta AV, eds. Jasper's Basic Mechanisms of the Epilepsies. 5th ed. New York: Oxford Universuty Press; 2024:1085–1098.

149. Malik K, Santucci K, Sremba L, Steenari M, Miele A, Demarest S, et al. Neuronal ceroid lipofuscinoses overview. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.

150. Burke EA, Sturgeon M, Zastrow DB, et al. Compound heterozygous KCTD7 variants in progressive myoclonus epilepsy. J Neurogenet 2021;35(2):74–83.

151. Atasu B, Acarli ANO, Bilgic B, Baykan B, Demir E, Ozluk Y, et al. Genotype-phenotype correlations of SCARB2 associated clinical presentation: a case report and in-depth literature review. BMC Neurol 2022;22(1):122.

152. Mastrangelo M, Caputi C, Esposito D, Leuzzi V. PRICKLE1-related disorders. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.

153. Carpenter JC, Mannikko R, Heffner C, Heneine J, Sampedro-Castaneda M, Lignani G, et al. Progressive myoclonus epilepsy KCNC1 variant causes a developmental dendritopathy. Epilepsia 2021;62(5):1256–1267.

154. Hentrich L, Parnes M, Lotze TE, et al. Novel genetic and phenotypic expansion in GOSR2-related progressive myoclonus epilepsy. Genes (Basel) 2023;14(10):1860.

155. Mastrangelo M, Tolve M, Artiola C, et al. Phenotypes and genotypes of inherited disorders of biogenic amine neurotransmitter metabolism. Genes (Basel) 2023;14(2):263.

156. Ebrahimi-Fakhari D, Van Karnebeek C, Munchau A. Movement disorders in treatable inborn errors of metabolism. Mov Disord 2019;34(5):598–613.

157. Oosterloo M, Touze A, Byrne LM, Achenbach J, Aksoy H, Coleman A, et al. Clinical review of juvenile Huntington's disease. J Huntingtons Dis 2024;13(2):149–161.

158. Mole SE, Anderson G, Band HA, et al. Clinical challenges and future therapeutic approaches for neuronal ceroid lipofuscinosis. Lancet Neurol 2019;18(1):107–116.

159. Vogt LM, Yang K, Tse G, et al. Recommendations for the Management of Initial and Refractory Pediatric Status Dystonicus. Mov Disord 2024;39(9):1435–1445.

160. Thiel M, Bamborschke D, Janzarik WG, et al. Genotype-phenotype correlation and treatment effects in young patients with GNAO1-associated disorders. J Neurol Neurosurg Psychiatry 2023;94(10):806–815.

161. Rodgers J, Calvert S, Shoubridge C, McGaughran J. A novel ARX loss of function variant in female monozygotic twins is associated with chorea. Eur J Med Genet 2021;64(11):104315.

162. Cinnirella C, Cinnirella G, Campanella C, Maccarelli F, Accorsi P, Giordano L. UBA5-epileptic encephalopathy: new patient, a novel variant, and a review of epileptic phenotypes. Epileptic Disord 2025;27:1275–1281.

163. Jan TY, Wong LC, Yang MT, Huang CJ, Hsu CJ, Peng SS, et al. Correlation of dystonia severity and iron accumulation in Rett syndrome. Sci Rep 2021;11(1):838.

164. Takeshita E, Saito Y, Nakagawa E, et al. Late-onset mental deterioration and fluctuating dystonia in a female patient with a truncating MECP2 mutation. J Neurol Sci 2011;308(1–2):168–172.

165. Freibauer A, Wohlleben M, Boelman C. STXBP1-related disorders: clinical presentation, molecular function, treatment, and future directions. Genes (Basel) 2023;14(12):2179.

166. Spaull R, Steel D, Barwick K, Prabhakar P, Wakeling E, Kurian MA. STXBP1 stop-loss mutation associated with complex early onset movement disorder without epilepsy. Mov Disord Clin Pract 2022;9(6):837–840.

167. Stamberger H, Nikanorova M, Willemsen MH, et al. STXBP1 encephalopathy: a neurodevelopmental disorder including epilepsy. Neurology 2016;86(10):954–962.

168. Hoang PT, Bledsoe IO, San Luciano M. Abrupt and severe onset of dystonia, chorea and hemiplegic episodes in a Young boy with a novel heterozygous missense variant in the GTPase domain of RHOBTB2. Mov Disord Clin Pract 2025;12(Suppl 2):S13–S15.

169. Langhammer F, Maroofian R, Badar R, et al. Genotype-phenotype correlations in RHOBTB2-associated neurodevelopmental disorders. Genet Med 2023;25(8):100885.

170. Lipman AR, Fan X, Shen Y, Chung WK. Clinical and genetic characterization of CACNA1A-related disease. Clin Genet 2022; 102(4):288–295.

171. Rinaldi D, Tangari MM, Ledda C, Dematteis F, Rizzone MG, Lopiano L, Artusi CA. CACNA1A variant associated with generalized dystonia. Neurol Sci 2024;45(9):4589–4592.

172. Yu L, Peng G, Yuan Y, et al. ATP1A3 mutation in rapid-onset dystonia parkinsonism: new data and genotype-phenotype correlation analysis. Front Aging Neurosci 2022;14:933893.

173. Alagia M, Fecarotta S, Romano A, Parrini E, Auricchio G, Miano MG, Terrone G. A novel splicing SCN2A mutation in an adolescent with low-functioning autism, acute dystonic movement disorder, and late-onset generalized epilepsy. Pediatr Neurol 2023; 138:58–61.

174. Koenig MK, Hodgeman R, Riviello JJ, et al. Phenotype of GABA-transaminase deficiency. Neurology 2017;88(20):1919–1924.

175. Spagnoli C, Fusco C, Pisani F. Rett syndrome Spectrum in monogenic developmental-epileptic encephalopathies and epilepsies: a review. Genes (Basel) 2021;12(8):1157.

176. Tokatly Latzer I, Pearl PL, Roullet JB. Succinic Semialdehyde Dehydrogenase Deficiency. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews((R)). Seattle (WA):University of Washington; 1993.

177. Li HF, Chen WJ, Ni W, et al. PRRT2 mutation correlated with phenotype of paroxysmal kinesigenic dyskinesia and drug response. Neurology 2013;80(16):1534–1535.

178. Indelicato E, Boesch S. CACNA1A-related channelopathies: clinical manifestations and treatment options. Handb Exp Pharmacol 2023;279:227–248.

179. Klepper J, Akman C, Armeno M, et al. Glut1 deficiency syndrome (Glut1DS): state of the art in 2020 and recommendations of the international Glut1DS study group. Epilepsia Open 2020;5(3): 354–365.

180. Conecker G, Xia MY, Hecker J, Achkar C, Cukiert C, Devries S, et al. Global modified Delphi consensus on diagnosis, phenotypes, and treatment of SCN8A-related epilepsy and/or neurodevelopmental disorders. Epilepsia 2024;65(8):2322–2338.

181. Gelineau-Morel R, Kruer MC, Garris JF, et al. Deep brain stimulation for pediatric dystonia: a review of the literature and suggested programming algorithm. J Child Neurol 2022;37(10–11):813–824.

182. Decraene B, Smeets S, Remans D, et al. Deep brain stimulation for GNAO1-associated dystonia: a systematic review and meta-analysis. Neuromodulation 2024;27(3):440–446.

183. Piper RJ, Ibrahim GM, Tisdall MM. Deep brain stimulation for children with generalized epilepsy. Neurosurg Clin N Am 2024; 35(1):17–25.

184. Muthiah N, Willie JT. New and old targets: evolving framework for personalized DBS in refractory epilepsy. Stereotact Funct Neurosurg 2025;103(5):470–481.

185. Yang AI, Isbaine F, Alwaki A, Gross RE. Multitarget deep brain stimulation for epilepsy. J Neurosurg 2024;140(1):210–217.

186. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. Nat Med 2023; 29(6):1468–1475.

187. Knight EMP, Amin S, Bahi-Buisson N, 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 2022;21(5):417–427.

188. Larasati YA, Thiel M, Koval A, Silachev DN, Koy A, Katanaev VL. Zinc for GNAO1 encephalopathy: preclinical profiling and a clinical case. Med 2025;6(1):100495.

189. di Rocco M, Galosi S, Follo FC, Lanza E, Folli V, Martire A, et al. Phenotypic assessment of pathogenic variants in GNAO1 and response to caffeine in C. Elegans models of the disease. Genes (Basel) 2023;14(2):319.

190. Roberts TC, Langer R, Wood MJA. Advances in oligonucleotide drug delivery. Nat Rev Drug Discov 2020;19(10):673–694.

191. Lenk GM, Jafar-Nejad P, Hill SF, et al. Scn8a antisense oligonucleotide is protective in mouse models of SCN8A encephalopathy and Dravet syndrome. Ann Neurol 2020;87(3):339–346.

192. Milazzo C, Mientjes EJ, Wallaard I, Rasmussen SV, Erichsen KD, Kakunuri T, et al. Antisense oligonucleotide treatment rescues UBE3A expression and multiple phenotypes of an Angelman syndrome mouse model. JCI Insight 2021;6(15):e145991.

193. Nitschke S, Minassian BA. Antisense oligonucleotide therapy for progressive myoclonus epilepsies. In: Noebels JL, Avoli M, Rogawski MA, Vezzani A, Delgado-Escueta AV, eds. Jasper's Basic Mechanisms of the Epilepsies. 5th ed. New York: Oxford University Press; 2024:1161–1174.

194. Chen X, Birey F, Li MY, et al. Antisense oligonucleotide therapeutic approach for Timothy syndrome. Nature 2024;628(8009): 818–825.

195. Shomer I, Mor N, Raviv S, et al. Personalized allele-specific antisense oligonucleotides for GNAO1-neurodevelopmental disorder. Mol Ther Nucleic Acids 2025;36(1):102432.

196. Golinski SR, Soriano K, Briegel AC, et al. Gene therapy for targeting a prenatally enriched potassium channel associated with severe childhood epilepsy and premature death. Nat Commun 2024.

197. Han Z, Chen C, Christiansen A, et al. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. Sci Transl Med 2020;12(558):eaaz6100.

198. Mitra S, Gumusgoz E, Minassian BA. Lafora disease: current biology and therapeutic approaches. Rev Neurol (Paris) 2022;178(4): 315–325.

199. Fuchs C, Trazzi S, Torricella R, Viggiano R, De Franceschi M, Amendola E, et al. Loss of CDKL5 impairs survival and dendritic growth of newborn neurons by altering AKT/GSK-3beta signaling. Neurobiol Dis 2014;70(100):53–68.

200. Chen X, Dong T, Hu Y, De Pace R, Mattera R, Eberhardt K, et al. Intrathecal AAV9/AP4M1 gene therapy for hereditary spastic paraplegia 50 shows safety and efficacy in preclinical studies. J Clin Invest 2023;133(10):e164575.

201. Gadalla KKE, Vudhironarit T, Hector RD, et al. Development of a novel AAV gene therapy cassette with improved safety features and efficacy in a mouse model of Rett syndrome. Mol Ther Methods Clin Dev 2017;5:180–190.

202. Gumusgoz E, Kasiri S, Youssef I, et al. Focused ultrasound widely broadens AAV-delivered Cas9 distribution and activity. Gene Ther 2025;32(3):237–245.

203. Wong JC, Grieco SF, Dutt K, et al. Autistic-like behavior, spontaneous seizures, and increased neuronal excitability in a Scn8a mouse model. Neuropsychopharmacology 2021;46(11):2011–2020.

204. Yamagata T, Raveau M, Kobayashi K, et al. CRISPR/dCas9-based Scn1a gene activation in inhibitory neurons ameliorates epileptic and behavioral phenotypes of Dravet syndrome model mice. Neurobiol Dis 2020;141:104954.

205. Sousa AA, Terrey M, Sakai HA, Simmons CQ, Arystarkhova E, Morsci NS, et al. In vivo prime editing rescues alternating hemiplegia of childhood in mice. Cell 2025;188(16):4275–4294.e23.

206. Walker MC. State-of-the-art gene therapy in epilepsy. Curr Opin Neurol 2025;38(2):128–134.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.