Movement Disorders
CLINICAL PRACTICE

REVIEW

Movement Disorders in Developmental and Epileptic Encephalopathies

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Abstract: Background: Monogenic developmental and epileptic encephalopathies (DEE) frequently feature co-occurring movement disorders. Gene discovery has expanded epilepsy-dyskinesia syndromes (EDS) from classic associations such as stereotypies in Rett syndrome to PRRT2-related infantile seizures with paroxysmal dyskinesia and crouched gait in SCN1A-associated Dravet syndrome.

Objectives: To outline the movement disorders spectrum in EDS, propose a pragmatic syndrome-based clinical framework, group implicated genes into mechanistic categories, highlight selected genotype–phenotype correlations, and summarize symptomatic and precision therapeutic options.

Methods: A non-systematic, structured literature review identified monogenic disorders reported with EDS, grouping publications into four tiers: multi-etiology cohorts; small series and narrative/systematic reviews; single-gene or pathway-focused reports; and mechanistic/therapeutic studies.

Results: Eight cohort studies and multiple tier 2–3 series and reviews yielded 245 single-gene associations, most mapping to ion channel and synaptic signaling pathways. Across DEE cohorts, movement disorders occurred in roughly one-quarter to over one-half of patients, were often hyperkinetic (notably dystonia and stereotypies), and frequently combined multiple phenomenologies. We grouped clinical presentations into early and late infantile-onset EDS, Rett and Rett-like syndromes, paroxysmal/episodic and relapsing–remitting disorders, disorders with severe acute motor exacerbations, and hypokinetic/progressive phenotypes. Treatments are guided by gene- and mechanism-informed strategies including sodium-channel blockers, glutamatergic modulators, ketogenic diet, agents for paroxysmal dyskinesias, and deep brain stimulation in life-threatening crises.

Conclusions: Movement disorders are common, often severe, and genetically heterogeneous across EDS. A syndrome-based approach integrating clinical features, neuroimaging, and broad genetic testing (including copy number variants and repeat expansions) can guide symptomatic management and emerging precision therapies.

Developmental and Epileptic Encephalopathies (DEE) represent a heterogeneous group of disorders characterized by early-onset epilepsy and developmental delay or regression.[1] This review provides an outline of the movement disorders described in monogenic disorders that are known to cause DEE and, more broadly, epilepsy. It emphasizes the importance of clinical phenotyping to navigate the complexities of genetic disorders, considering common and rare differential diagnoses. We also summarize current and emerging therapeutic options. We have included genetic associations that may cause epilepsy but not always DEE as part of the epilepsy dyskinesia syndromes (EDS).

Methods

Although this was not a systematic review, we aimed to summarize the breadth of literature describing cohorts of EDS, as well

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as recent studies describing new genotype–phenotype associations and advances in therapeutics. A stepwise search was undertaken in PubMed and Medline by two independent reviewers (SSM and HMB) to identify monogenic disorders described with DEE and movement disorders (Supporting Information, Section-S1). Acquired disorders were excluded.

The search results were grouped as the following: tier 1—cohort studies including multiple genetic aetiologies; tier 2—case series with ten or fewer cases described with movement disorders, narrative reviews and systematic reviews; tier 3—case reports, cohort studies and reviews on individual genes or genes belonging to a common pathway (eg, glutaminergic disorders or sodium channelopathies); and tier 4—publications focused on disease mechanisms or therapeutics (not describing clinical details of cases/cohorts). Citing articles were explored using Google Scholar for completion. A framework for clinical syndrome description was formulated from tier 1, tier 2 and tier 3 publications.

Results

We reviewed eight studies as tier 1 cohorts.[2–9] Three of these were cohorts of epilepsy patients where co-occurring movement disorders were described, while the others were movement disorder cohorts where co-occurring epilepsy was described (Table S1). The largest cohort from Quiroz et al included monogenic aetiologies that can present with DEE, but the entry criteria did not necessitate a history of epilepsy.[8] An outline of the cohort studies and their key findings is listed in Table S1. Tier 2 studies included three cohort studies with fewer individuals described to have movement disorders,[10–14] narrative reviews that covered a broad spectrum of disorders and narrative reviews that covered a subset of disorders based on either mechanistic pathways or phenotypic groups such as Rett syndrome, neonatal onset, progressive myoclonic epilepsies and myoclonus ataxia.[15–24] Studies reviewed as tier 3 and tier 4 are listed in Supporting Information, Section S2.

Two hundred and forty-five individual genetic associations (excluding CNVs) were reported across tier 1, 2, and 3 publications (Table S2). Almost all genomic associations that were reported in case series or reports (tier 3 publications) were already included in one or more cohort studies. Novel associations that were found in tier 3 studies but not included in cohort studies included *ABAT*, *CACNA2D1*, *CARS2*, *CWF19L1*, *DLG4*, *ELFN1*, *FOLR1*, *IRF2BPL*, *MOGS*, *NAA10*, *NR4A2*, *PI4K2A*, *RARS2*, *SNAP25*, *TMEM63B*, and *TWNK*. This list is expected to continue growing as genomic discoveries advance. Across the tier 1 cohort studies, 165 individual genetic associations (excluding CNVs) were described, of which the genes described in five or more cohort studies included *SLC2A1*, *STXBP1*, *SCN1A*, *SCN8A*, *SYNGAP1*, *ATP1A3*, *CACNA1A*, *CDKL5*, *KCNA2*, *KCNQ2*, *MECP2* and *SCN2A* in descending order of frequency. In the recent epilepsy dyskinesia study by Quiroz et al, the ten most common genetic associations described were *MECP2, ATP1A3*, *GNAO1*, *PRRT2*, *SLC2A1*, *CACNA1A, WDR45*, *CDKL5*, *FOXG1* and *STXBP1*. A detailed outline of the frequency with which genes were described across the reviewed literature is provided in Table S2.

We grouped all 245 genes described across tier 1, 2, and 3 publications into four broad mechanistic groups according to the Gene Ontology (biological process or molecular function) terms that the respective genes mapped to (Fig. 1A; methodology described in Supporting Information, Section S3). A more detailed breakdown by individual pathways is provided in Tables S3.1 and S3.2. Most genes that are described across the majority of cohort studies and reviews and are also the most common in larger cohort studies, map to the ion channels and synaptic signaling functions (Fig. 1, Table S3.1). Figure 1A shows the main mechanistic groups, with the 20 most common genes for each group. A hierarchical clinical approach to EDS is shown in Figure 1B.

Most of the tier 1 and 2 studies described single nucleotide variations. Copy number variants (CNV) such as deletions and duplications were also described. Some of these included one or more of the genes described with EDS, such as deletions that include *STXBP1*[25] and *UBE3A*[5] and the *MECP2* duplication[6] syndrome or larger deletions that span multiple genes, such as the entire sodium channel complex in the region 2q24.3q31.1.[26] Other CNVs are described without clarity about a particular gene in the involved region being responsible, such as deletions in the region of 22q11.2 and 6q26-q27 presenting with epilepsy in childhood and later onset of parkinsonism.[21] In particular, some genetic disorders like glucose transporter 1 deficiency syndrome (GLUT1-DS) have CNVs in up to 10% of described cases. This should be considered when requesting and interpreting genetic testing, as some panel and exome-based methods may not check for CNVs. In addition, some repeat-expansion disorders are also described with EDS, with the commonest described association being *ARX*-associated disease.[27] In addition, other disorders include juvenile Huntington's disease[28,29] described with refractory epilepsy in some cases and dentatorubral-pallidoluysian atrophy (DRPLA)[30,31] with progressive childhood onset epilepsy and neurodegeneration along with movement disorders, as well as *EPM1*-associated progressive myoclonic epilepsy (PME). Similarly, some other disorders that can present with EDS due to triplet repeats map to other PME and progressive myoclonus ataxia (PMA) syndromes.

The themes that emerged from the cohort studies were that movement disorders are overall common in DEE (25–58% in DEE cohorts; Table S1), and the functional impact of movement disorders is severe in most cases. It was also evident from the recent largest cohort study that many of these monogenic associations can manifest with movement disorders without reported seizures or DEE.[8] Hyperkinetic movement disorders dominated across all studies, with hypokinetic movements representing only a small fraction (pooled 3.4% across tier 1 studies; Table S4), though it must be noted that most of these studies were from pediatric centers and later onset of bradykinesia in some disorders, for example channelopathies, beta propeller protein-

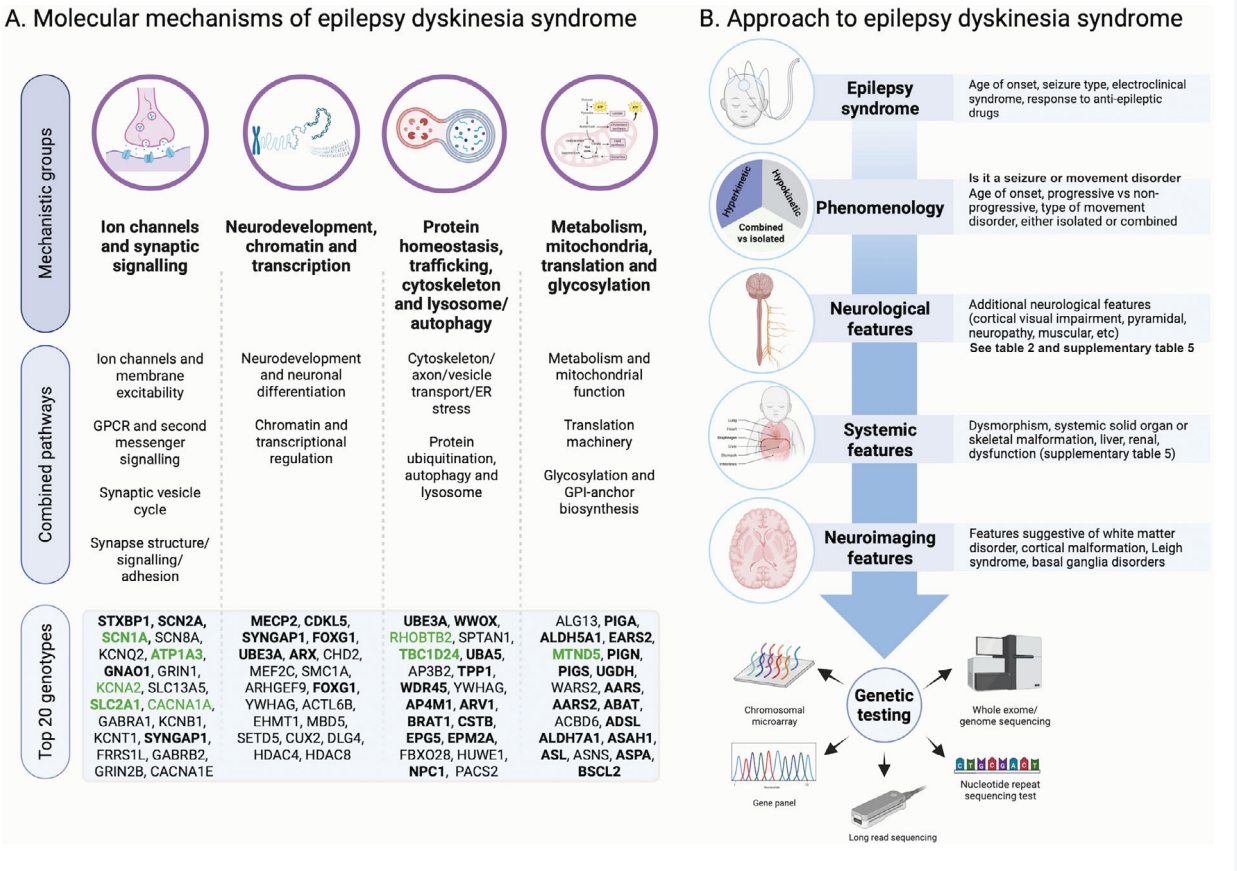

Figure 1. Main mechanistic groups and diagnostic approach of epilepsy-dyskinesia syndromes. All genotypes in bold indicate that some patients with these disorders can have a progressive course. Genotypes in green can present with paroxysmal or episodic movement presentations. Some examples of neurological, systemic and neuroimaging features that can assist in the approach are outlined in Tables 2 and 3 in the main manuscript and in Table S5.

associated neurodegeneration (BPAN or Rett syndrome, may not have been fully captured in these cohort studies. Multiple movement disorders in the same patients were described in a median of 46% (10–53.3%) of patients across cohort studies (Table S1). There was some variability in the spectrum of movement disorder phenomenology across the different studies, but dystonia and stereotypies were the most common, both reported in nearly a third of patients each across tier 1 cohort studies (Table S4). We have grouped phenomenological descriptions from tier 1, 2 and 3 studies in the following syndromic groups based on age, clinical phenomenology and progression. We describe these groups with a focus on selected features to help clinical grouping, diagnosis and in some cases, therapies. We refer the reader to more extensive reviews for some groups, such as progressive disorders with myoclonus[24] and ataxia.[18,22]

Syndromic groups based on phenomenological descriptions:

1. Early infantile-onset EDS
2. Late infantile-onset EDS
3. Rett syndrome and Rett-syndrome like disorders
4. Paroxysmal/Episodic and relapsing remitting movement disorders
5. Disorders with prominent SAME
6. Disorders with bradykinesia and progressive disorders

Early Infantile-Onset EDS

Many genetic EDS present in early infancy.[19] Some fulfill criteria for early infantile DEE, which in older literature were referred to as Ohtahara syndrome or early myoclonic encephalopathy. Some of the prototypic EDS genes such as *ARX*,[32] *GNAO1*[33] and *STXBP1*[34] were first described with a label of Ohtahara syndrome presentation, with their movement disorder spectrum described subsequently. Most of the seizure syndromes that present at this age are associated with burst suppression on EEG with tonic or myoclonic seizures, but some disorders such as *SCN2A, KCNQ2* and *PRRT2* can present with focal seizures that may be self-limited or easily treatable while a movement disorder phenotype may emerge through the ensuing months or years. A genotype–

phenotype trend is emerging with gain-of-function (GOF) variants in some genes, particularly channelopathies, described to present with a more severe, early infantile phenotype (Table 1). In many early infantile-onset EDS, the epilepsy severity is often a clinical priority and movement phenotypes emerge later. Some clinical and neuroimaging features can, however, be indicative of particular disorders. In early infancy, these features include the epilepsy syndrome, the presence of neonatal hypertonia, arthrogryposis or contractures and malformations on neuroimaging abnormalities as well as unique phenomena like paroxysmal head–eye movement episodes, a distinctive non-epileptic paroxysmal phenomenon in infancy described with glucose transporter 1 deficiency syndrome (GLUT1DS)[35] and rarely with few other associations (Table 2).

Late Infantile-Onset EDS

Representative DEE that manifest with seizures in late infancy and early childhood include Dravet syndrome and infantile epileptic spasms syndrome (IESS).[1] One of the cohort studies[7] outlined movement disorder associations in 72/124 infants with IESS with *ALDH7A1, SCN2A, CDKL5* and *ALG13* noted as relatively frequent associations. The onset of movement disorders, mainly in the form of stereotypies, was reported to be before the onset of IESS in 17/72 patients. Overall, both for

TABLE 1 *EDS genes where a genotype–phenotype correlation is established*

Gene	Genotype–Phenotype correlation described
ATP1A3	Distinct recurrent missense variants: some variants (eg, around p.Asp801) enriched in alternating hemiplegia of childhood. Variants in transmembrane/cytoplasmic regions enriched in rapid-onset dystonia–parkinsonism or CAPOS/RECA-like phenotypes
FOXG1	Larger deletions and truncating variants, particularly affecting the forkhead domain or N-terminus, associate with more severe microcephaly, corpus callosum abnormalities and early-onset epilepsy Some missense or 3′ variants correlate with relatively milder psychomotor delay and structural changes
GNAO1	LOF/markedly reduced Gαo activity—DEE-predominant phenotype with early refractory seizures GOF or near-normal-function variants, especially in the 207–246 hotspot—hyperkinetic movement-disorder–dominant presentations with dyskinetic crises, often with fewer seizures
GRIN1	Heterozygous missense variants—infantile DEE, absent speech, evolving hyperkinetic movement disorder. Biallelic nonsense variants described are more severe with progression and death in infancy[36]
GRIN2A	Heterozygous LOF/hypomorphic variants—epilepsy–aphasia spectrum (Landau–Kleffner, CSWS/ECSWS, atypical rolandic). Potential benefit from L-serine for LOF variants.[37] Functional severity loosely tracks with language and epilepsy severity, but no simple domain rule
GRIN2B	GOF missense variants enriched in early infantile DEE and epileptic spasms Some LOF or truncating variants—ID/autism with absent or milder epilepsy
KCNQ2	Inherited truncating/haploinsufficient variants—self-limited familial neonatal epilepsy with relatively good outcome; de novo dominant-negative or severe missense (voltage-sensor/pore) variants—neonatal-onset DEE with persistent ID. Some GOF variants—infantile spasms without neonatal seizures
MECP2	Early truncations or variants affecting the methyl-CpG-binding or transcriptional repression domains—more severe classic Rett with profound ID and early loss of skills. C-terminal truncations or some missense variants—milder/variant Rett phenotypes with better ambulation and hand function; X-inactivation further modulates expressivity. DUP *MECP2*: *MECP2* duplication syndrome; larger or higher-expression duplications correlate with more severe ID, epilepsy and infections, while smaller or mosaic duplications may have milder phenotypes.
SCN1A	LOF variants—classic Dravet syndrome and can manifest with a crouch gait in the second decade: Cases with c.677C>T (p.Thr226Met) have been described with chorea without DEE. GOF variants—neonatal encephalopathy, DEE, arthrogryposis.[38–41]
SCN2A	GOF variants—neonatal/very-early DEE or self-limited neonatal–infantile epilepsy, usually sodium-channel-blocker responsive. LOF variants→ later-onset epilepsy and/or ID/ASD, often worsened by sodium-channel blockers
SCN8A	GOF variants—early-onset DEE with refractory seizures. LOF variants—ID with milder or late-onset epilepsy or ataxia
SLC2A1	Variants causing near-complete loss of GLUT1 function (large deletions, early truncations, severe missense) → classic GLUT1 deficiency with early encephalopathy, microcephaly, complex movement disorder and epilepsy; partial-loss missense or mosaic variants → milder phenotypes (absence epilepsy, paroxysmal dyskinesia) with better preserved cognition

Abbreviations: ASD, autism spectrum disorder; GOF, gain of function; ID, intellectual disability; LOF, loss of function.

TABLE 2 *Clinical and neuroimaging features in Infantile onset disorders with epilepsy and movement disorders*

Key features	Selected genetic disorders where these features are reported
Epilepsy syndrome	
Early infantile DEE (previous terminologies include Ohtahra syndrome and EME)	*ARX*,[27] *CDKL5*,[42] *GABRA1*,[43] *GNAO1*,[33] *KCNQ2*,[11] *SCN2A*,[44] *STXBP1*[45]
Epilepsy of infancy with migrating focal seizures	*ATP1A3*,[46] *KCNT1*,[47] *SCN2A*,[48] *TBC1D24*[49]
Fever/vaccination triggered seizures	*FBXO28*,[50] *GABRB2*,[51] *GABRB3*,[52] *GABRD*,[53] *GABRG2*,[53] *RHOBTB2*,[54] *SCN1A*,[55] *SCN1B*,[10] *SCN8A*,[56] *SCN9A*,[57] *SLC32A1*,[58] *TMEM63B*,[59] *WDR45*,[60] *YWHAG*,[61] Creatine deficiency disorders[62]
Infantile epileptic spasm syndrome*	*CDKL5*,[42] *DNM1*,[63] *GABRB2*,[51] *IRF2BPL*,[64] *KCNQ3*,[65] *RHOBTB2*,[54] *SCN1B*, *STXBP1*,[45] *UBA5*,[10] *WWOX*[66]
Reflex seizures (stimulus provoked)	*STXBP1*,[67] *SYNGAP1*[68]
Neonatal hypertonia	*ATAD1*,[69] *BRAT1*,[70] *GRIA2*,[71] *SCN1A(GOF)*,[41] *SCN2A(GOF)*,[47] *SCN8A (GOF)*,[72] *CACNA1E*,[73] *GABRA1*[74]
Excessive startle/hyperekplexia	*ARHGEF9*,[75] *GRIA2*,[71] *GRIA3*,[76] *KCNQ2*,[77] *PURA*,[78] *STXBP1*,[79] *SCN1A*,[41] *SCN2A*,[80] *SCN8A*,[81] *WWOX*,[66] *YWHAG*[61]
Abnormal eye movements	
Oculogyric episodes	*ATP1A3*,[82] *GRIA2*,[83] *GRIN1*,[36] *ITPA*,[84] *SCN2A*[80]
Paroxysmal rotatory movements/rotatory nystagmus	*ATP1A3*,[85] *CDKL5*[86]
Paroxysmal head eye movements	Side to side movements—*PLPBP*[87], *RHOBTB2*,[88] *SLC2A1*[35] (most common association) Tonic upgaze with head *nodding*—*CACNA1A*[89] Paroxysmal eye and head deviation—*ATP1A3*[90]
Tonic upgaze	*CACNA1A*,[91] *SCN8A*[92]
Restricted vertical gaze	*GNB1*,[93] *NUS1*[94]
Self-limited focal seizures with later onset movement disorders	*KCNQ2*,[95] *SCN2A*,[96] *SCN8A*,[97] *PRRT2*[98]
Arthrogryposis/contractures	*ATP1A2*,[99] *CACNA1E*,[73] *PIEZO2*,[100] *SCN1A*,[41] *SCN8A*[101]
Neuroimaging abnormalities	
Cerebellar atrophy	*CWF19L1*,[102] *FOLR1*,[103] *FRRS1L*,[104] *KCNA2*,[105] *SPTAN1*[106]
Corpus callosum abnormalities	*ARX*,[107] *FOXG1*,[108] *NAA10*,[109] *RHOBTB2*,[54] *TMEM63B*,[59] *UBA5*,[110] *WWOX*[66]
Delayed myelination	*CACNA1E*,[73] *FOLR1*,[103] *SLC13A5*,[111] *SLC25A2*,[112] *UBA5*[110]
Malformations of cortical development (eg. Polymicrogyria, cortical dysplasia)	*ARX*,[32] *ATP1A3*,[113] *ATP1A2*,[46] *GRIA3*,[114] *GRIN1*,[115] *GRIN2B*,[116] *SCN1A*,[40]
Progressive cortical atrophy through childhood	*SCN8A(GOF)*,[97] *SCN2A(GOF)*,[117] *CACNA1E*,[73] *GABRA1*[74]
White matter changes	*CACNA1B*,[118] *GABRB2*,[119] *GABRB3*,[120] *GRIA2*,[83] *NAA10*,[109] *WWOX*[66]

Abbreviations: DEE, Developmental and epileptic encephalopathy; EME, Early myoclonic encephalopathy; GOF, gain of function.
*A comprehensive cohort described by Nagarajan et al.[7]

early and late infantile onset disorders, seizures are usually reported to occur before movement disorders. Some infants with IESS may develop movement disorders as an adverse effect of vigabatrin use, with typical MRI changes, though this association may not always be clear.[121] Drug induced movements should always be a consideration in individuals with epilepsy, and this has been summarized in recent reviews.[122,123] Although there is a spectrum of DEE subtypes that can be associated with the same gene similar to pleiotropy in movement disorder presentations, we highlight selected disorders in Table 2 that a clinician should

consider as differentials with both early and late infantile epilepsy syndromes.

The observations from *SCN1A*-associated Dravet syndrome have paved the way for similar observations in other monogenic DEE. Historically, a crouched gait was described in the second decade in individuals who had Dravet syndrome,[124] followed by the observation of chorea, particularly associated with some missense variants.[125] More recently, a severe neonatal DEE with arthrogryposis has been described associated with gain-of-function (GOF) *SCN1A* variants.[38–41] A genotype–phenotype association has not been consolidated for many DEE/epilepsy genes that can present with movement disorders, but we summarize those where a clinical association with particular genotypes has been established so far (Table 2). Similar to *SCN1A*, a more severe early-onset DEE is also described in other sodium channel disorders such as *SCN2A* and *SCN8A*, while loss of function (LOF) variants may present with a later or milder phenotype in some cases. A second group comprises genes involved in glutamatergic neurotransmission, where functional effects on NMDA receptor signaling correlate with both phenotype and potentially with treatment implications.[37] Some genotypes such as biallelic truncating *GRIN1* variants and GOF *GRIN2B* variants associate with very severe early infantile DEE phenotypes, higher mortality and presentation with IESS, whereas LOF variants may present either with infantile DEE or with later acquired epileptic aphasia (*GRIN2A*) and neurodevelopmental delay and autism (*GRIN2B*). Genotype-dependent nuances are also noted in several other commonly described DEE genes, including neuronal signaling genes such as *GNAO1* and *ATP1A3*, where gain- versus loss-of-function variants influence seizure-predominant or movement disorder–predominant phenotypes, as well as in genes affecting transcriptional or metabolic pathways including *MECP2*, *FOXG1*, and *SLC2A1*, where variant type and functional severity correlate with differences in clinical severity and associated neurological features (Table 1).

Rett Syndrome and Rett-Syndrome like Disorders

Rett syndrome due to *MECP2* variants is one of the prototypic EDS that features prominently in several cohort studies. The key diagnostic criteria for Rett syndrome consist of a period of developmental regression followed by stagnation, loss of hand skills, speech regression, hand stereotypies and gait abnormalities with an evolving autistic phenotype. While diagnostic criteria define a "typical" Rett phenotype, atypical forms have been described with some *MECP2* variants, and a larger spectrum of "Rett-syndrome-like" disorders has emerged with genomic discovery. A recent review outlined some of these disorders with their phenotypic features.[20] *CDKL5*, *STXBP1*, *SCN2A(LOF)*, *FOXG1*, *GABRB2*, and *WDR45*-associated DEE and movement disorders are some other common monogenic associations described with both typical and atypical Rett syndrome in many cohort studies. In addition, from our literature review, the term "Rett-syndrome like" was also used for cases with *ARX*, *GRIN1*, *KCNA2*, *RHOBTB2*, *VAMP2* and *WDR45*. Overall, autism and hand stereotypies are common across various genetic disorders associated with epilepsy and neurodevelopmental disorders, and these are sometimes loosely grouped as "Rett-syndrome like." We have highlighted key features of selected genetic disorders that can present with Rett syndrome or Rett-syndrome like features chosen based on them being relatively common, or, having distinctive clinical or investigation parameters or, being potentially treatable (Table 3). It is important to note that many of these disorders, including *MECP2*-associated Rett syndrome,[126] can present with a variety of movement disorders rather than motor stereotypies only. Many of the disorders that manifest with this phenotype in childhood are now also described to progress to a parkinsonian or akinetic-rigid phenotype with age as their natural history becomes clearer.[21]

Paroxysmal/Episodic and Relapsing Remitting Movement Disorders

The overlap of epilepsy and movement disorders was initially emphasized by the description of monogenic associations with paroxysmal movement disorders in conditions like *PRRT2*-associated disorder and GLUT1DS. While heterozygous *PRRT2* variants usually associate with self-limited infantile seizures, CNVs involving *PRRT2* and biallelic variants have been described with refractory epilepsy and autism spectrum disorder along with paroxysmal kinesigenic dyskinesia.[127] A wide spectrum of genetic associations of DEE genes has now described with episodic movement disorders—both paroxysmal dyskinesia and episodic ataxia—sometimes with seizures meeting criteria for DEE and at other times with relatively easy-to-control or self-limited seizures. In addition, there are some disorders that can have episodic presentations separated by longer periods of time, with "stroke-like" clinical or both clinical and neuroradiological correlates. Selected disorders are summarized in Table 4 and have been reviewed in recent work.[128,129]

Disorders with Severe Acute Motor Exacerbations (SAME)

Several studies have highlighted the predilection for some of the EDS genetic associations for movement disorder exacerbations described as status dystonicus or, more recently, as severe acute motor exacerbations (SAME).[130] Although such exacerbations may happen with any underlying disorder, some associations, such as *GNAO1*[131] and *ARX*,[8,132] are over-represented. In addition to these genes, in our literature review, such exacerbations were also described with the following genes—*ATP1A3*,[8] *AGAT*,[130] *GAMT*,[130] *CACNA1B*,[130] *CLN3*,[130] *CLN8*,[130] *DHDDS*,[130] *DNM1*,[130] *FOXG1*,[5] *GNB1*,[133–135] *MECP2*,[8] *NARS*,[8] *RHOBTB2*,[8] SCN1A,[130] SCN8A,[130] *SLC13A5*[8] and *STXBP1*,[8,25] *SYNGAP1*,[5] *KCNQ2*,[130] *SCN2A*,[130] *TBC1D24*,[130] *UBA5*.[8] Deep brain stimulation (DBS) is described as life-saving in severe presentations of *GNAO1*-related disorder[131,136] but also described to have had benefit in some other conditions, such as *GABRB2*,[119] *GNB1*,[93,137] *SCN2A*[138] and *UBA5*.[139] In addition to

TABLE 3 *Clinical and neuroimaging features in selected Rett-like syndromes that can present with epilepsy and movement disorders*

Genetic disorder	Selected features*
CDKL5	Rett and Rett like presentations comprise about a quarter of described cases[86] Profound neurodevelopmental delay and hypotonia are common Regression is uncommon DEE onset in the first 3 months of life, IESS and tonic spasms are common Stereotypies commonly reported, often with self-stimulation like phenomenology Other movements described include choreoathetosis, akathisia, dystonia, and parkinsonism with severe, episodic, hyperkinetic movement disorder exacerbations in some cases[86]
STXBP1	Atypical Rett syndrome in some reported cases (~2–3%) Periods of regression in many cases[140] Neonatal onset seizures, IESS, hand stereotypies, bruxism[67] Cases are described with tremor, myoclonus and ataxia without seizures[141]
FOXG1	Rett and Rett like cases described in some cases (~10%) Regression like Rett syndrome is rare Mixed hyperkinetic movement disorders—orofacial dyskinesia, chorea, stereotypies[142] Corpus callosum, fornix and midline neuroimaging abnormalities, simplified gyral patterns[108]
ARX	Neonatal onset seizures, IESS Ambiguous genitalia and other genital abnormalities in males Microcephaly, cataracts Dystonia from late infancy and status dystonicus described in some cases[27] Neuroimaging may show malformations of cortical development, callosal abnormalities, hydrocephalus[107]
WDR45 (BPAN)	Mild to severe epileptic phenotypes in early childhood Seizure control can improve in second decade of life with evolving dystonia or parkinsonism or both T1W hyperintensities in the substantial nigra, sometimes with nigral swelling with acute encephalopathy in early childhood. Brain iron deposition in later childhood and young adulthood in the nigra and pallidum[143,144]
*KCNA2***	Some cases with severe early infantile DEE and evolving ataxia through childhood Other cases with milder self-limited epilepsy, evolving spastic paraparesis and some with episodic ataxia[145]
Creatine deficiency disorders (*GAMT, AGAT, SLC6A8*)	Infantile onset DEE Stereotypies are common; periods of regression described. Dystonia in some cases in second decade of life[146,147] Globus pallidus hyperintensities and absent creatine peak on MR spectroscopy Cases with *GAMT* or *AGAT* variants respond to creatine supplementation
GRIN1	Either epilepsy or movement disorder may appear first in early infancy Severe developmental delay and hand stereotypies[148] Oculogyric crises reported in some cases Malformations of cortical development (polymicrogyria) reported in some cases[115]

Abbreviations: BPAN, Beta propeller protein associated neurodegeneration; DEE, Developmental and epileptic encephalopathy; IESS, Infantile epileptic spasm syndrome.
*Moderate to severe intellectual disability is a common feature of all these disorders.
**Autism is reported only in a small proportion of cases.

these genetic conditions, additional EDS genes that are listed in the collaborative DBS matchmaker platform (https://dbsmatchmaker.com; last accessed December, 12 2025) with some reported benefit from implantation include *ARX*, *MECP2*, *CACNA1G*, *FOXG1* and *WDR45*.

Disorders with Hypokinesia and Progressive Disorders

The natural history of many disorders that present with EDS is still evolving. Over the last decade motor phenotypes that evolve in adulthood in many of these disorders have been described such as gait progression in loss of function *SCN1A* variants that presented with Dravet syndrome in childhood[124,149] and prominent non-epileptic myoclonus in many cases and a parkinsonian gait in adults with *STXBP1*.[140] A comprehensive description can be found in recent reviews on parkinsonism reported in several genetic disorders in adulthood with a history of epilepsy in childhood.[21] Hypokinesia in childhood (described as parkinsonism, bradykinesia or hypokinesia) has been described in a very small proportion of cohort studies of EDS. One important segment consists of neonates and infants who are described with hypokinetic rigid syndromes, many of which overlap with

TABLE 4 *Selected genetic associations of episodic movement disorders that can also present with epilepsy*

Feature	Genetic associations described
PKD	*KCNA1*,[150] *PRRT2, SCN8A*[151]
PNKD	*CACNA1A, KCNA1, KCNMA1*,[152] *PRRT2*,[8] *TBC1D24*
PED	*TBC1D24, SLC2A1*
Episodic Ataxia	*SLC2A1, SCN2A, CACNA1A, KCNA1*
Episodic/Alternating hemiplegia	*ATP1A2*,[153] *ATP1A3, CACNA1A, RHOBTB2, SCN1A, SLC2A1*
Stroke-like episodes with MRI changes	*ATP1A2*,[153] *CACNA1A*,[154] *SLC2A1*,[155] *RHOBTB2*[156]

Abbreviations: PKD, paroxysmal kinesigenic dyskinesia; PED, paroxysmal exercise induced dyskinesia; PNKD, paroxysmal non-kinesigenic dyskinesia.

disorders presenting with severe DEE and hypertonia in the neonatal period that are listed in Table 2. Many of the other genetic associations that have been described with hypokinesia in childhood associated with epilepsy include disorders such as neuronal ceroid lipofuscinoses that can also be grouped under the umbrella of progressive myoclonic epilepsies and progressive myoclonus ataxia. A comprehensive approach to these disorders has been summarized in recent reviews.[18,22,24] In addition, hypokinesia is also described in some cases of Rett syndrome and "Rett-like" presentations[6] and can be a prominent feature early on in some disorders such as *ATP1A3*, *ECHS1*,[5] *SYNGAP1*,[5] *WARS2*.[6] Recent reports that have described prominent EDS genes that can overlap with the spectrum of progressive myoclonic epilepsies and ataxia include *DHDDS*,[157,158] *FBXO8*,[50] *GOSR2*,[159] *IRF2BPL*,[64,160] *NGLY1*[161,162] and *NUS1*.[94,163,164] Some EDS that can present with progressive movement disorders, such as DRPLA, are triplet repeat disorders as highlighted before.

Treatment Strategies in EDS

The exponential increase in genetic discovery has held out the promise of precision therapies for genetic neurological disorders, including many EDS. While gene-based potentially disease-modifying therapies are being explored and developed,[165] symptomatic medication choices dependent on the genotype are increasingly important considerations for clinicians to be aware of. The clearest example is seen in voltage-gated sodium channel disorders, where GOF variants in *SCN1A*, *SCN2A* and *SCN8A* increase neuronal excitability and may respond to sodium channel–blocking anti-seizure medications like carbamazepine. In contrast, LOF variants reduce channel activity and impair neuronal firing, and sodium channel blockers may further suppress residual channel function and exacerbate seizures; accordingly, these agents are generally avoided in individuals with LOF-associated phenotypes such as classic *SCN1A*-related Dravet syndrome or later-onset *SCN2A* disorders.

A similar paradigm has been proposed for glutamatergic disorders associated with the GRIN family of genes encoding NMDA receptor subunits. LOF variants that reduce NMDA receptor function impair excitatory synaptic signaling and may respond to L-serine supplementation,[37] which increases availability of the NMDA receptor co-agonist D-serine. Conversely, GOF variants that enhance NMDA receptor activity may result in excessive excitatory neurotransmission and have been treated in selected cases with NMDA receptor antagonists such as memantine or dextromethorphan.[166] However, genotype-treatment correlations remain inconsistent across cohorts, and the clinical translation of these mechanism-based approaches remains to be clarified.

Symptomatic medications can also prove to be very effective in some disorders, even where the mechanistic basis of treatment response is only partially understood. In paroxysmal movement disorders with epilepsy, low dose carbamazepine has been shown to be useful for *PRRT2* (including biallelic cases) and other genetic associations such as *KCNA1*, possibly reflecting membrane stabilization through reduction of neuronal sodium channel–mediated excitability, which may counteract synaptic hyperexcitability associated with presynaptic release dysfunction. Acetazolamide, a carbonic anhydrase inhibitor that alters intracellular pH and neuronal excitability, has been reported to help episodic ataxia in *CACNA1A*, *SCN2A*, *KCNA1* and *RHOBTB2*. 4-aminopyridine, a potassium channel blocker that prolongs action potentials and enhances synaptic transmission, has been shown to benefit some cases of *KCNA2*[167] in addition to larger number of cases with *CACNA1A*. Some reports have described benefit from lisdexamphetamine[168] and more recently, paroxetine[169] in *KCNMA1* associated paroxysmal episodes, thought to be due to modulation of monoaminergic pathways influencing basal ganglia excitability.

Metabolic therapies represent another important class of mechanism-based treatment. The ketogenic diet continues to be the mainstay of treatment for GLUT1DS, where ketone bodies provide an alternative cerebral energy substrate in the setting of impaired glucose transport across the blood–brain barrier, while triheptanoin efficacy has not been consistently replicated across cohorts.[170] The recent EDS cohort study highlighted some novel symptomatic treatments that showed a favorable response, such as cannabidiol in *CDKL5* and gabapentin in *ATP1A3*, while highlighting a risk of movement disorder worsening with levodopa in *GNAO1* and *MECP2* and amantadine associated worsening in *ATP1A3*.[8] In addition some cases with *ATP1A2* have been described to have had benefit from memantine.[99]

While the role of DBS is constantly evolving in monogenic movement disorders, as described in the section above, patient and target selection as well as response in epilepsy syndromes is more limited. There have been reports of improvement in seizures and motor function in some cases of PME with *GOSR2* variants with zona incerta DBS[171] and the understanding of

patient selection for seizures may further evolve over the coming years.

Conclusion and Suggested Approach

We have provided a comprehensive overview of the interface between DEE and movement disorders and a pragmatic, syndrome based clinical approach (Fig. 1B). Delineating the epilepsy syndrome and movement disorder phenomenology forms the basis of this approach, including the age of onset and the progression of motor symptoms, as outlined in our clinical groups. In some conditions, associated neurological or systemic features, biomarkers or neuroimaging can provide valuable clues. We have highlighted some of these features in the Tables 2 and 3 and in Table S5. We have also outlined some aspects of nuanced therapeutic decision making that could potentially be guided by the genotype. It is important to recapitulate some salient points—accurate identification and description of clinical phenomenology is paramount. In this group of disorders, seizures should be distinguished from non-epileptic movements, with the use of EEG when required; seizures or movement disorders may co-occur with each other or independently in many of the disorders discussed here and the absence of one should not preclude the suspicion of a particular disorder. When faced with an individual who has an overlap of epilepsy and movement disorders the clinical approach should start with outlining the age of onset, the clinical trajectory, any salient accompanying clinical and neuroimaging features and any particular treatment response or worsening. The timing of movement disorder onset may sometimes necessitate the consideration of medication induced movements.

The diagnostic approach should include consideration of testing modalities that look for CNVs and triplet repeats in addition to single nucleotide variations (Fig. 1B), usually in a step wise manner. Newer technologies such as long read sequencing may provide a one-step option to cover these nuances but are still not available widely. Lastly, genetic confirmation can guide important therapeutic decision making with symptomatic therapies, counseling for interventions like DBS and hopefully, increasing number of disorders where gene-based therapies may become available.

Author Roles

(1) Research project: A. Conception, B. Organization, 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.

S.M.: 1A, 1B, 1C, 2A, 2B, 3A

D.E.F.: 1A, 1B, 1C, 2C, 3B

H.M.B.: 1A, 1B, 1C, 2C, 3B

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Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Supporting Information. Search methods and results

Table S1. Cohort studies that described genetic disorders with epilepsy and movement disorders.

Table S2. List of genes associated with epilepsy and movement disorders across reviewed studies.

Table S3. Grouping of 245 genes described to present with epilepsy and movement disorders according to Gene Ontology—Biological Process (BP) and Molecular Function (MF) terms into four simplified mechanistic groups.

Table S4. Pooled percentage of movement disorder type across tier 1 studies.

Table S5. Neurological and extra-neurological features related to developmental and epileptic encephalopathy with frequent hyperkinetic movement disorders.

Data S1. COI_disclosure.