Molecular and clinical spectrum of epilepsy-dyskinesia syndromes: a cross-sectional study of 609 patients

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Abstract

Epilepsy-dyskinesia syndromes (EDS) are a complex group of neurogenetic disorders characterized by the co-occurrence of epilepsy and movement disorders. Despite their increasing clinical recognition, the molecular and clinical spectrum of EDS remain poorly understood. While numerous genetic etiologies have been implicated, systematic characterization across diverse populations is lacking. This study aimed to delineate the molecular and clinical landscape of EDS

in a large, multinational cohort, focusing on movement disorder phenomenologies, genotype-phenotype correlations, and treatment responses.

We conducted a multicenter, cross-sectional study involving 609 patients with childhood-onset movement disorders associated with pathogenic variants in 105 predefined genes. Clinical data were collected from over 30 centers across 25 countries using a standardized survey, capturing movement disorder phenomenologies, seizure types, developmental trajectories, motor function, and treatment outcomes. We classified EDS-associated genes into biologically meaningful groups by performing unsupervised clustering, which integrated protein-protein interactions and functional data. Genotype-phenotype correlations were assessed using a one-versus-remainder approach to quantify differential enrichment of clinical manifestations and treatment responses.

Pathogenic variants were identified in 74 of the 105 predefined genes, with 12 genes accounting for two-thirds of cases. The most frequently reported genes were *MECP2, ATP1A3,* and *GNAO1*. Data-driven gene cluster analysis identified 12 functional groups, mapping EDS to relevant biological pathways and informing genotype-phenotype analyses. Dystonia (34.2%), stereotypies (24.6%), and ataxia (16.2%) were the most prevalent movement disorders, with gene- and pathway-specific movement disorder signatures extending beyond previously known associations. Notably, most patients exhibited mixed movement disorders, highlighting the phenotypic complexity of EDS. Epilepsy was diagnosed in only 66.8% of cases, suggesting that some EDS primarily manifest as movement disorders. Developmental trajectories varied by genetic etiology. Pharmacological responses demonstrated gene- and pathway-specific treatment effects, confirming established therapeutic associations (e.g., *PRRT2* variants responding to carbamazepine) and identifying previously unrecognized effects, such as exacerbation of motor symptoms with levodopa/carbidopa in *GNAO1* and *MECP2* variants.

This study provides a detailed characterization of EDS, identifying distinct genetic, phenotypic, and therapeutic patterns. The findings underscore the need for early recognition of movement disorders within epilepsy cohorts, offer immediate insights to improve anticipatory guidance and clinical management of EDS, and advocate for personalized treatment strategies. By laying the groundwork for longitudinal studies to refine genotype-phenotype correlations and establish a natural history, this work paves the way for interventional clinical trials and precision medicine approaches.

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Introduction

Epilepsy-dyskinesia syndromes (EDS) are a large and heterogeneous group of neurological conditions defined by the co-occurrence of epilepsy and movement disorders [1]. EDS arise from a range of etiologies, including acquired causes, such as hypoxic-ischemic injury, autoimmune encephalitis, central nervous system infections, and importantly, a growing number of genetic disorders. Over 100 genetic causes have now been identified, underscoring the rapidly expanding molecular landscape of genetic epilepsies [2,3], movement disorders [4-6] and their significant overlap.

Despite these advances, the cumulative prevalence of EDS remains unclear and likely underestimated. Systematic investigations on EDS are limited [1,7,8], as most published cohorts have primarily focused on epileptic or developmental encephalopathies, with movement disorders often described only incidentally or as secondary features. As a result, the understanding of the phenotypic spectrum and natural history of EDS, as well as the interplay between abnormal movements and seizures, is limited.

Considerable genetic heterogeneity and phenotypic pleiotropy add a layer of complexity to understanding EDS. Many genes are associated with overlapping phenotypes; for example, dystonia has been linked to more than 30 distinct genetic causes [5]. Conversely, a single gene may exhibit striking phenotypic pleiotropy, exemplified by *PRRT2*-related disorders, which range from benign familial epilepsy to paroxysmal dyskinesia to episodic ataxia [9,10], and *ATP1A3*-related conditions, which encompass at least four distinct canonical clinical entities with overlapping features [11]. These examples highlight the blurred boundaries between clinical phenotypes and the intricate molecular mechanisms underlying EDS. As the spectrum of EDS continues to expand, it has become clear that movement disorders significantly contribute to disease burden. However, large, systematically characterized cohorts - particularly those evaluated by movement disorder specialists - are rare. Such data are essential for refining clinical phenotypes, elucidating natural history, identifying genotype-phenotype correlations, and enhancing clinical trial readiness for these rare conditions.

To address this unmet need, we conducted the Epilepsy-Dyskinesia Spectrum Study (NCT06585605), a multicenter investigation designed to delineate the molecular and phenotypic spectrum of EDS. We present cross-sectional data from 609 individuals with childhood-onset EDS.

Materials and methods

This multicenter, cross-sectional observational study included patients with childhood-onset movement disorders (0–18 years) and confirmed genetic diagnoses from a predefined list of 105 genes associated with both movement disorders and epilepsy (Supplementary material, File 1). The genes included in the study were curated and selected through a multistep consensus process between the Movement Disorders Program at Boston Children's Hospital and the Steering Committee of the Pediatric Movement Disorders Special Interest Group (SIG) of the International Parkinson and Movement Disorder Society (MDS) while incorporating feedback from the membership of the SIG via email survey. Pediatric neurologists specializing in movement disorders contributed cases from over 30 centers across 25 countries. All clinical data were sourced from patients' medical records and anonymized. The study adhered to the Declaration of Helsinki, institutional policies at participating centers, and was approved by the Institutional Review Board at Boston Children's Hospital (IRB-P00043928) and registered at ClinicalTrials.gov (NCT06585605). Demographic and clinical data were collected through a standardized survey developed specifically for the study of EDS (Supplementary material, File 1). Additional methods, including gene cluster analyses and statistics are detailed in the Supplementary material, File 2.

Results

Demographic and Genetic Characteristics

A total of 609 patients were included in the analysis. Previously described cases in the literature accounted for 9.4% (Supplementary Table 1). The median age at last follow-up was 9.5 years (interquartile range [IQR]=10.17 years) (Figure S1A). Data were collected from over 30 centers

in 25 countries (Figure 1A), covering all continents except Africa. The highest representation was from the United States (34.4%), followed by Spain (11.4%), Canada (8.0%), Australia (7.3%), and Chile (7.3%). All submitters self-identified as movement disorder specialists (fellowship trained) or pediatric neurologists in diagnosing and managing movement disorders.

Pathogenic variants were identified in only 74 of the 105 predefined genes (Supplementary Table 2), highlighting the ultra-rare nature of some conditions. The ten most frequently affected genes were *MECP2* (14.8%, n=90), *ATP1A3* (7.4%, n=45), *GNAO1* (6.7%, n=41), *PRRT2* (6.4%, n=39), *SLC2A1* (5.8%, n=35), *CACNA1A* (5.3%, n=32), *WDR45* (5.1%, n=31), *CDKL5* (4.9%, n=30), *FOXG1* (3.3%, n=20), and *STXBP1* (3.1%, n=19) (Figure 1B, Supplementary Table 2).

54.6% of patients were female, with expected sex ratios for specific genes based on X-linked inheritance patterns (Figure 1D). At the time of reporting, 595 patients (97.7%) were alive, while 13 (2.1%) had died, with a median age at death of 6.2 years (IQR=6.1 years) (Figure 1E). The significant subset of deaths (n=4) was associated with *GNAO1* variants. Single deceased patients were also reported for variants in *ARX*, *GABRA1*, *GABRB2*, *KCNT1*, *NARS2*, *PCDH19*, *SCN8A*, *VARS2*, and *WWOX*.

We determined inheritance patterns through molecular testing for 65.7% (n=395) of patients, with 73.7% of variants occurring *de novo*. For several genes, including *WDR45*, *CDKL5*, *FOXG1*, *STXBP1* and *RHOBTB2*, all reported variants were *de novo* in origin (Figure 1F). Diagnostic approaches varied, with genetic diagnoses most frequently obtained through exome sequencing (46.5%, n=263), followed by targeted multigene panels (30.6%, n=173) and single-gene testing (11.0%, n=62) (Figure S2), likely reflecting both the clinical approach to some clinical entities (i.e. single-gene testing for *MECP2*- and *PRRT2*-related disorders) and availability of genetic technologies across different health care settings. The median age at genetic diagnosis was 4.4 years (IQR=8.8 years).

Genes associated with EDS form 12 biologically defined clusters

Previous studies have explored converging disease mechanisms across different forms of EDS by manually mapping associated genes to known biological pathways [1,8,12,13]. However, this approach relies on subjective categorizations, leading to potential biases and limited scope. To overcome these limitations, we employed a data-driven, unbiased methodology to systematically uncover functional associations among all EDS-associated genes in our study. Specifically, we integrated Gene Ontology (GO)-derived functional similarities with experimentally validated protein-protein interaction (PPI) data from three major databases, STRING, BioGRID, and IntAct [14-16]. Using network-based clustering, we identified 12 distinct gene clusters (Figure 1C), each characterized by shared biological functions and protein-level interactions. This systems-level perspective provides a comprehensive framework for understanding EDS pathogenesis. Detailed characterizations of all clusters are presented in Figures S3–S6; here, we focus on a subset of clusters with the highest prevalence in our cohort.

Among the identified clusters, Cluster 1 consists of genes encoding ion-transporting proteins, including voltage-gated sodium, potassium, and calcium channels, which mediate ion flux across membranes to regulate neuronal excitability and action potential propagation (Figure S3A&B). Cluster 2 is enriched for genes involved in cGMP-mediated signaling through heterotrimeric and monomeric G-protein-coupled receptors. This cluster includes G protein subunits (*GNAO1*, *GNB1*), G protein activators (*SYNGAP1*), downstream effectors (*PLCB1*), and cyclic nucleotide-metabolizing enzymes (*PDE10A*, *PDE2A*), forming a core regulatory network for metabotropic glutamate, dopamine, and acetylcholine signaling (Figure S3C&D) [17]. Cluster 3 encompasses genes that regulate neuronal transcription and translation, including transcription factors (*MECP2*, *ARX*, *FOXG1*, *MEF2C*, *SETBP1*), transcriptional modulators (*CDKL5*, *CSTB*, *WWOX*), chromatin accessibility regulators (*HNRNPU*, *SMC1A*, *SETD5*), and mediators of dendritic translation (*PURA*) (Figure S3E&F). These transcriptomic regulators orchestrate critical aspects of cortical development, including neural progenitor proliferation, neuronal migration, and dendritic spine formation [18-25]. Cluster 5 is enriched for genes essential for synapse function and architecture, particularly those involved in SNARE complex assembly (*STXBP1*, *PRRT2*), synaptic vesicle endocytosis (*SYNJ1*, *TBC1D24*, *DNM1*, *VAMP2*), and presynaptic cytoskeletal organization

(*SPTAN1*, *PCDH12*, *PCDH19*) (Figure S4C&D) [26-28]. Cluster 10 is associated with macroautophagy, featuring genes involved in autophagosome biogenesis (*WDR45*, *EPM2A*), maturation (*EPG5*, *SNX14*), and targeting proteins and organelles for degradation (*NHLRC1*, *UBE3A*, *UBA5*) [29-34]. Other clusters are centered on axonal protein transport, tRNA aminoacylation, post-translational glycolipidation of proteins, neuronal oxidative metabolism, ionotropic glutamatergic receptor signaling, and inhibitory synapse assembly. Collectively, these 12 gene clusters delineate distinct molecular networks underlying EDS pathogenesis.

Movement Disorders

At last follow-up, 96.1% (n=585) of patients exhibited a predominant movement disorder, with 76.4% (n=447) showing a hyperkinetic movement disorder and only 1.5% (n=9) displaying a hypokinetic movement disorder. Other movement disorders (spasticity or ataxia) were the leading phenomenology in 22.1% (n=129). Representative Supplementary Videos 1–23 are available at FigShare doi:10.6084/m9.figshare.c.7969280. Overall, dystonia (34.2%, n=200) was the most common primary movement disorder, followed by stereotypies (24.6%, n=144), and ataxia (16.2%, n=95).

Significant associations were observed between specific leading movement disorder phenomenologies and particular genes and pathway clusters (Figure 2A, Figure S8A&B). Stereotypies emerged as the phenomenology significantly overrepresented in patients with pathogenic *MECP2* (OR=21.4, 95%-CI =12.0–40.0, p_{adj}<1.0e-16) (Supplementary Video 1) and *WDR45* (OR=9.2, 95%-CI=3.8–24.6, p_{adj}=2.6e-8) variants, typically reflecting characteristic hand stereotypies seen in both conditions.

Dystonia was most frequent in patients with *GNAO1* (OR=6.0, 95%-CI=2.8–13.6, p_{adj}=7.1e-7) (Supplementary Videos 2-4), *ATP1A3* (OR=3.5, 95%-CI=1.8–7.0, p_{adj}=3.9e-4), and *PRRT2* (OR=2.7, 95%-CI=1.3–5.9, p_{adj}=1.9e-2) (Supplementary Video 5) variants. Overall, 43.3% (246/568) of patients in the cohort were reported having dystonia either as a leading

phenomenology or as additional finding (Figure S9A). The distribution of affected body regions was relatively similar across affected genes with most patients having limb dystonia (89.1%, 180/202), followed by truncal (32.3%, 65/201), cervical (23.4%, 47/201) and orofacial dystonia (20.0%, 40/200) (Figure S9A). Underscoring the severity of dystonia in a subset of patients with EDS (covering *GNAO1*, *STXBP1*, *MECP2*, *ARX*, *ATP1A3*, *UBA5*, *RHOBTB2*, *NARS*, and *SLC13A5*), 7.5% (15/200) had a history of status dystonicus with need for inpatient, often intensive care unit level, of care.

Ataxia was strongly associated with variants in *CACNA1A* (OR=12.7, 95%-CI=5.4–31.7, p_{adj}=5.8e-13) (Supplementary Video 6) and *SCN1A* (OR=11.1, 95%-CI=2.9–51.5, p_{adj}=8.1e-4) and was also more common in patients with *SLC2A1*-related disorder (OR=2.9, 95%-CI=1.3–6.4, p_{adj}=1.8e-2). Overall, 26.4% (149/564) of patients were reported having ataxia either as leading phenomenology or additional finding, mostly manifesting in the form of gait ataxia (83.9%, 109/130) and less frequently as truncal (29.2%, 38/130) or limb ataxia (28.5%, 37/130) (Figure S9C). Chorea was the leading phenotype only in patients with *FOXG1* variants (OR=10.4, 95%-CI=3.7–29.5, p_{adj}=3.8e-8) (Supplementary Video 7), though it was also significantly associated with *PRRT2* variants (OR=6.4, 95%-CI=2.8–14.4, p_{adj}=7.0e-7) (Supplementary Video 5), reflecting the often complex paroxysmal dyskinesia with combined dystonia and chorea seen with *PRRT2*-related disorder.

The second leading movement disorders also demonstrated gene-specific patterns (Figure 2A, Figure S8C&D). Spasticity was more frequently observed as an additional feature in patients with *GNAO1*-related disorder (OR=4.0, 95%-CI=1.5–9.8, p_{adj}=2.0 e-2) and *MECP2*-asssociated Rett syndrome (OR=3.3, 95%-CI=1.3–8.0, p_{adj}=4.7e-2). *GNAO1* variants were further associated with an increased likelihood of chorea as a second predominant manifestation (OR=3.8, 95%-CI=1.6–8.7, p_{adj}=1.6e-2). Ataxia was a second phenomenology more frequently observed in patients with variants in *STXBP1* (OR=5.2, 95%-CI=1.2–20.2, p_{adj}=4.7e-2) (Supplementary Video 8) and *SLC2A1* (OR=4.4, 95%-CI=1.5–12.4, p_{adj}=2.0e-2) variants. Patients with *CDKL5* variants exhibited a greater propensity for secondary myoclonus (OR=14.8, 95%-CI=2.8–69.9, p_{adj}=2.0e-

2) and stereotypies (OR=9.2, 95%-CI=2.1–37.5, p_{adj}=3.2e-3), including characteristic leg crossing stereotypies (Supplementary Video 9).

Essential to clinical practice, about half of all patients with EDS had a mixed movement disorder combining at least two different phenomenologies (53.3%, 298/559, Figure 2B) with certain combinations occurring significantly more frequently. Common combinations included dystonia as the leading and choreoathetosis as the second leading phenomenology (OR=6.3, 95%-CI=3.4–12.4, p_{adj}=1.8e-9) and vice versa (OR=9.7, 95%-CI=5.0–18.7, p_{adj}=1.0e-14), dystonia and spasticity (OR=3.4, 95%-CI=1.7–7.4, p_{adj}=2.7e-3), and ataxia with tremor (OR=5.0, 95%-CI =2.4–10.2, p_{adj}=7.3e-6). Among patients with a single isolated movement disorder phenomenology, stereotypies were the most frequently observed (33.8%, 98/290), followed by dystonia (27.9%, 81/290) and ataxia (19.3%, 56/290).

The patterns of movement disorders varied by phenomenology (Figure 2C). Overall, 55.7% (n=300) of patients experienced a persistent movement disorder as their primary disorder. However, 44.3% of the cohort exhibited fluctuating patterns, with 21.7% (n=117) experiencing both permanent movement disorders and paroxysmal episodes, and 22.6% (n=122) experiencing paroxysmal symptoms only. Among those with fluctuating symptoms, 12.6% (n=30) exhibited diurnal variations. While most phenomenologies were predominantly persistent, certain phenomenologies - such as dystonia, myoclonus, and stereotypies - were more frequently associated with fluctuating patterns, with fluctuations during periods of metabolic stress, i.e. fever or infection, or other acute triggers, as is commonly seen in childhood-onset hyperkinetic movement disorders.

Beyond associating individual gene variants with distinct movement disorder phenomenologies, we extended our analysis to functional gene clusters (Figures S7B, S8B&D). This approach identified several associations between clusters and specific movement phenotypes, overall and when stratified by leading movement disorder features, while accounting for imbalances in gene representation within clusters. Motor stereotypies as a secondary feature were significantly more

frequent in patients with pathogenic variants in genes involved in cortical development (Cluster 3) (OR=3.1, 95%-CI=1.1–8.7, p_{adj}=3.3e-2). Pathogenic variants in $GABA_A$-receptor subunit genes (Cluster 11) were strongly associated with tremor as a secondary movement disorder (OR=13.0, 95%-CI=1.2–141.8, p_{adj}=3.6e-2) and rigidity as an additional finding (OR=22.8, 95%-CI=4.4–117.8, p_{adj}=1.9e-4), a signal not apparent in gene-level analyses. Pathogenic variants in Cluster 2 - encompassing genes involved in cGMP-mediated signaling through heterotrimeric and monomeric G-protein-coupled receptors - were associated with chorea as a secondary finding (OR=3.5, 95%-CI=1.1–12.0, p_{adj}=4.7e-2), consistent with the role of these genes in neurotransmission.

Illustrative examples of movement disorders in EDS

Our systematic analysis highlights the fascinating spectrum of movement disorder phenotypes in common EDS. Additional illustrative examples of frequently observed movement disorder presentations include the common occurrence of paroxysmal tonic upgaze in *CACNA1A*-related disease (Supplementary Videos 10 and 11), the frequent presentation of generalized dystonia in *MECP2*-related Rett syndrome (Supplementary Video 12), the combination of motor stereotypies and generalized chorea in *FOXG1*-related disorder (Supplementary Video 13), and paroxysmal dystonia in UBA5-related disorder (Supplementary Video 14).

In addition to these well-recognized associations, we identified novel or less common movement disorder phenotypes linked to specific genetic etiologies. Paroxysmal non-kinesigenic dyskinesia with upper limb dystonia and chorea was observed in *PRRT2*-related disease (Supplementary Video 15), while generalized chorea was noted in *CDKL5*-related disorder (Supplementary Video 16). Prominent hand stereotypies were frequently seen in *GNAO1*-related disorder (Supplementary Video 17), and paroxysmal generalized dystonia was identified in *GRIN2B*-related disorder (Supplementary Video 18). Stereotypies and generalized myoclonus were present in *KCNA2*-related disease (Supplementary Video 19), whereas parkinsonism was observed in an adult individual with *KCNQ2*-related disorder (Supplementary Video 20). Additionally, generalized chorea was found in *SCN8A*-related disease (Supplementary Video 21). Our analysis also

documented numerous cases of complex, mixed movement disorders, further underscoring the diversity and phenotypic complexity of movement disorder presentations in EDS. For example, the co-occurrence of spasticity and ataxia was frequently observed in *SPTAN1*-related disorder (Supplementary Videos 22 and 23).

Epilepsy

A formal epilepsy diagnosis was rendered in 66.8% (n=401) of patients, with 37.2% (n=150) meeting criteria for developmental and epileptic encephalopathy (DEE) [35]. Specific epilepsy syndromes were identified in some cases, including infantile spasms (n=56), Early Infantile Developmental and Epileptic Encephalopathy (EIDEE, previously referred to as Ohtahara syndrome) (n=7), Lennox-Gastaut syndrome (n=14), and Dravet syndrome (n=11). Infantile spasms were most frequently associated with *CDKL5* variants, affecting 76.7% (23/30) of these patients. As expected, Dravet syndrome was exclusively observed in patients with *SCN1A* variants.

Generalized motor seizures were the most common leading seizure type (53.1%, n=187), followed by focal seizures with impaired awareness (21.6%, n=76) and generalized non-motor seizures (17.3%, n=61). Seizure onset remained unclear in 3.7% (n=13) of patients. Specific genes were significantly associated with distinct seizure types (Figure 3A). For instance, *CDKL5* variants were strongly linked to generalized motor seizures (OR=17.7, 95%-CI=4.4–156.1, p_{adj}=3.4e-6), while patients with *SLC2A1* (OR=3.8, 95%-CI=1.5–9.1, p_{adj}=6.2e-3) or *CACNA1A* (OR=10.5, 95%-CI=2.6–50.6, p_{adj}=5.0e-3) variants were more likely to experience generalized non-motor seizures.

No significant overall associations were observed between seizure types and movement disorder phenomenologies (Figure 3B). However, generalized non-motor seizures tended to be more common in patients with ataxia (OR=2.0, 95%-CI=1.1–3.7, p=1.1e-2, p_{adj}=0.29) aligning with the finding of ataxia being a prominent symptom in both *SLC2A1*- and *CACNA1A*-related conditions where this seizure type is prevalent.

Seizure control varied widely across affected genes (Figure 3C). Of the 65.2% (n=397) of patients for whom seizure control data were available, 42.1% (n=167) achieved complete control, 43.8% (n=174) had partial control, and 14.1% (n=56) experienced no seizure control. Among the most frequently affected genes, complete seizure control was reported in 40% (24/60) of patients with *MECP2* variants, 54.6% (12/22) of those with *ATP1A3* variants, and 90.9% (10/11) of patients with *PRRT2* variants. In contrast, *CDKL5* variants were associated with the highest proportion of uncontrolled medically-refractory epilepsy (43.3%, 13/30).

Temporal Patterns of Epilepsy and Movement Disorder Onset

Overall, movement disorders tended to have a more variable age of onset and were recognized after seizure-onset. Patients were most frequently diagnosed with epilepsy during the first year of life (1–12 months, 32.9%, n=131) and with a movement disorder typically between ages 1–3 years (36.2%, n=197). However, the age range and sequence of symptom onset varied considerably across different genetic etiologies (Figure 4). For several affected genes, including *CDKL5*, *GNAO1*, *PRRT2*, *WDR45*, and *SLC2A1*, seizures were noted before the manifestation of movement disorders. Notably, while seizure onset often clustered in the neonatal (e.g., *CDKL5*) or infantile period (e.g., *PRRT2*), the emergence of movement disorders was more temporally dispersed. For other genes, seizure and movement disorder onset coincided (e.g., *ATP1A3*, *STXBP1*, *FOXG1*), or the movement disorder preceded the onset of seizures (e.g., *MECP2*, *CACNA1A*).

Movement Disorders by Age Group

An exploratory analysis examined the distribution of movement disorders across age groups for the 12 most commonly affected genes, utilizing retrospective longitudinal data of a relatively large number of available cases (Figure 5). This analysis provides a preliminary view of the progression of movement disorder phenomenologies over time and highlights broader trends. A recurring pattern emerged: Hyperkinetic movement disorders predominated during infancy and childhood, while hypokinetic disorders and other motor disorders, such as parkinsonism and spasticity, became more frequent in later stages of childhood and early adulthood. This trend was particularly

evident in patients with *FOXG1*, *SLC2A1*, and *WDR45* variants. Similar patterns were observed for the second leading movement disorders (Figure S12). For instance, spasticity was the most frequent second movement disorder in adulthood for patients with *MECP2* and *GNAO1* variants.

Developmental trajectories vary across affected genes

Developmental outcomes in patients with EDS often deviate from typical pediatric trajectories, yet systematic data - particularly regarding motor development - remain limited for many genetic etiologies. To better characterize developmental patterns, we examined the frequency and severity of neurodevelopmental delay in patients under five years old, intellectual disability (ID) in those over five years, and achievement of motor milestones (Figure 6A–C). Overall, 86.9% (518/596) of patients were reported to have global developmental delay, with mild (27.4%, n=163), moderate (28.4%, n=169), and severe (31.2%, n=186) developmental delays occurring at similar frequencies (Figure 6A). Developmental delays affected multiple domains including motor development, with motor delay noted in 80.5% (484/601) of patients and speech delay reported for 82.6% (495/599). 43.5% (237/545) of patients older than 24 months and 38.5% (151/392) of patients older than 6 years were non-verbal.

The prevalence and severity of developmental delay varied considerably by gene (Figure 6A). For example, most patients with *PRRT2* variants (86.8%, 33/38) showed no developmental delay, whereas 75.6% (34/45) of patients with *ATP1A3* variants had a predominantly mild (55.9%, 19/34) global developmental delay. Conversely, severe global developmental delay was highly prevalent among patients with *ARX* (100%, 7/7), *FOXG1* (65.0%, 13/20), *STXBP1* (63.2%, 12/19), and *GNAO1* (52.5%, 21/40) variants.

These trends were also reflected in the assessment of gross motor development, as assessed by major motor milestones including head control, unsupported sitting and walking (Figure 6C). 83.9% (481/573) of individuals over the age of 6 months had achieved head control and 77.8% (442/568) over 10 months had achieved unsupported sitting. Among patients older than 18 months

(n=564), 62.1% (344/554) had achieved unsupported walking, with a median age at achievement of 36.0 months (95%-CI=29.0–48.0; n=293) and high variability across genes. Most patients with *PRRT2* (78.4%, 29/37) and *ATP1A3* (82.9%, 34/41) variants, for example, achieved independent walking at a normal or slightly delayed median age (*PRRT2*: 13 months [95%-CI=12–23], n=22; *ATP1A3*: 19 months [95%-CI=15–28], n=29). In contrast, only 40.0% (14/35) of patients with *GNAO1*, 17.9% (5/28) with *CDKL5*, and 10.0% (2/20) with *FOXG1* variants ever achieved this milestone. Trends observed for developmental delays were mirrored in the prevalence and severity of ID in patients over five years old. ID was reported in 80.4% (311/387) of these patients, reflecting severity patterns consistent with the findings for developmental delay (Figure 6B).

Motor function is severely impaired in EDS and depends on affected gene

Many EDS are associated with significant functional motor impairment. To evaluate this, we assessed gross motor function using the Gross Motor Function Classification System (GMFCS) at the last follow-up. We analyzed the age at which the use of walking aids or full-time wheelchair-dependence was first reported (Figure 6D–F).

Detailed retrospective data on the age of walking aid and wheelchair usage were available for 40.6% (247/609) and 40.1% (244/609) of patients, respectively. Among those requiring a walking aid, most became dependent between the ages of 1–3 years (56.7%, 76/134) or during early childhood (4–7 years, 23.9%, 32/134) (Figure 6D). Similarly, in non-ambulatory patients, wheelchair dependence typically occurred between the ages of 1–3 years (48.3%, 73/151) or 4–7 years (27.2%, 41/151), reflecting that this subset of children with EDS never achieved the ability to walk independently (Figure 6E).

To gain a more granular understanding of motor impairment progression, we performed a time-to-event analysis based on patient age and GMFCS score at the last follow-up (Figure 6F). GMFCS data were available for 97.9% (596/609) of patients, with 78.7% (469/596) exhibiting at least some

degree of motor impairment (GMFCS≥1) by a median age of 11.2 years (95% CI=9.8–12.4, n=450). Among these, 44.6% (266/596) developed severe motor impairment requiring permanent use of a walking aid or wheelchair (GMFCS≥3) at a median age of 16.6 years (95% CI=15.0–18.4, n=259). A total of 22.2% (132/596) progressed to GMFCS level 5, characterized by profound limitations in voluntary movement control (including difficulty maintaining head and neck posture); by the age of 35.8 years (95% CI=27.4–NA, n=129) 49.0% of patients at risk had progressed to level 5.

Motor impairment progression was highly dependent on genetic etiology (Figure S14). For example, most patients with *PRRT2* variants (92.1%, 35/38) did not exhibit permanent gross motor impairment (GMFCS=0). In contrast, patients with *MECP2* variants showed a higher prevalence of motor impairment: 95.5% (84/88) had at least mild impairment (GMFCS ≥ 1) by a median age of 11.8 years (95%-CI: 8.8–13.8, n=78), and 61.4% (54/88) progressed to severe impairment (GMFCS≥3) by a median age of 13.8 years (95%-CI=11.9–21.7, n=52). The most severely impaired patients, reaching GMFCS level 5 in the majority of cases were predominantly carriers of *FOXG1* (65.0%, 13/20; median age: 7.8 years [95%-CI=6.3–NA]), *CDKL5* (53.3%, 16/30; median age: 8.5 years [95%-CI=5.0–NA]), and *GNAO1* (52.6%, 20/38; median age: 13.8 years [95%-CI=11.3–NA]) variants.

Genetic etiologies are associated with distinct phenotypic signatures

To identify clinical findings significantly associated with specific genetic etiologies and highlight distinct phenotypic signatures, we performed a comparative phenotypic enrichment analysis (Figure 7). While some findings were, as expected, pathognomonic for certain genes in the context of EDS - such as Dravet syndrome for *SCN1A* (OR=Inf, 95%-CI=307.8–Inf, p_{adj}=3.1e-18) or iron deposition (OR=107.9, 95%-CI=17.2–1,163.9, p_{adj}=2.2e-6) on brain imaging for *WDR45* - this analysis revealed unique and nuanced phenotypic profiles for most of the frequently affected genes.

For instance, patients with *FOXG1* variants were significantly more likely having microcephaly (OR=37.3, 95%-CI=8.7–337.0, p_{adj}=8.8e-9), being gastrostomy tube-dependent (OR=8.2, 95%-CI=3.0–25.0, p_{adj}=3.2e-4), being non-verbal (OR=7.4, 95%-CI=2.1–39.6, p_{adj}=5.5e-3), and having severe NDD (OR=4.3, 95%-CI=1.6–13.0, p_{adj}=1.6e-2) as well as reaching GMFCS level 5 (OR =7.1, 95%-CI=2.6–21.5, p_{adj}=9.3e-4) and less likely to achieve unsupported sitting (OR=0.25, 95%-CI=0.1–0.7, p_{adj}=3.8e-2), reflecting the profound developmental, intellectual, and motor impairments frequently seen in these patients. Similarly, patients with *CDKL5* variants were severely affected in both the motor and developmental domains, but *CDKL5* variants were also enriched for severe epilepsy-related features such as DEE (OR=59.9, 95%-CI=9.7–2,444.4, p_{adj}=1.2e-10), medically-refractory epilepsy (OR=10.7, 95%-CI=3.2–55.9, p_{adj}=3.6e-5), infantile spasms (OR=31.2, 95%-CI=11.9–92.6, p_{adj}=9.6e-14), and generalized motor seizures (OR=18.4, 95%-CI=4.5–161.4, p_{adj}=3.1e-6). *GNAO1* variants exhibited a phenotype dominated by severe dystonia, including status dystonicus (OR=9.7, 95%-CI=2.2–40.5, p_{adj}=2.3e-2), permanent dystonia (OR=9.5, 95%-CI=4.4–21.5, p_{adj}=1.6e-10), cervical dystonia (OR=7.0, 95%-CI=2.0–28.1, p_{adj}=1.6e-2), and dysarthria (OR=6.8, 95%-CI=2.1–25.8, p_{adj}=7.8e-3). *MECP2* variants, in addition to motor stereotypies and global developmental delay and regression, prominently featured neuropsychiatric findings consistent with autism spectrum disorder as well as gastrointestinal symptoms. Finally, *PRRT2* variants, as expected, were strongly associated with paroxysmal kinesigenic dyskinesia (OR=93.4, 95%-CI=37.1–253.7, p_{adj}=1.3e-26) and an overall milder clinical course for both motor and epilepsy features, evidenced by a lower likelihood of having delayed motor development (OR=0.02, 95%-CI=0.005–0.06, p_{adj}=9.4e-28) and higher likelihood for complete seizure control (OR=14.5, 95%-CI=2.0–633.8, p_{adj}=6.1e-3).

In summary, this analysis highlights distinct clinical signatures for most of the frequently affected EDS genes, enabling more targeted surveillance and symptomatic treatment of clinical manifestations, anticipatory guidance, and providing a basis for designing longitudinal natural history studies.

Comparative Assessment of Pharmacotherapeutic Treatment Effectiveness

Previous studies have examined the use of antiseizure medications (ASM) in EDS, often focusing on prescription frequencies [36-44]. However, no comprehensive evaluation of treatment responses - particularly for movement disorders - has been reported to date. To address this gap, we assessed which medications patients used for both seizures and movement disorders, categorizing treatment outcomes into nine distinct response categories.

A total of 47 different medications were reported. The most commonly used ASM across all genetic etiologies were levetiracetam (35.1%, 214/609), valproate (31.8%, 194/609), clobazam (21.2%, 129/609), and topiramate (17.7%, 108/609). For movement disorder targeted symptomatic treatment, diazepam (12.2%, 74/609), baclofen (11.2%, 68/609), and clonidine (11.0%, 67/609) were most frequently used. To better understand potential genotype-specific therapeutic effects, we analyzed gene–medication combinations (Figure S14) and gene-cluster medication combinations in a one-versus-remainder approach (Figure S15).

For example, seizures in patients with *CDKL5* variants showed a favorable response to cannabidiol (OR=4.2, 95%-CI=1.3–13.3, p_{adj}=9.2e-3), while patients with *PRRT2* variants responded well to valproate (OR=26.0, 95%-CI=2.2–1,418.6, p_{adj}=2.7e-3). For movement disorders, permanent improvements were reported with botulinum toxin in *MECP2* variants (OR=181.4, 95%-CI=22.5–7,965.8, p_{adj}=9.4e-11), carbamazepine in *PRRT2* (OR=6.1, 95%-CI=1.6–29.9, p_{adj}=2.4e-3), acetazolamide in *CACNA1A* (OR=5.1, 95%-CI=1.1–24.6, p_{adj}=2.8e-2), gabapentin in *ATP1A3* (OR=23.9, 95%-CI=2.2–1,216.6, p_{adj}=2.4e-3), and trihexyphenidyl in *GNAO1* variants (OR=8.4, 95%-CI=1.5–41.4, p_{adj}=7.1e-3).

Of great clinical importance, conversely, some medications showed limited efficacy or even worsened symptoms in certain contexts. Levodopa was more likely to have no benefit in patients with *GNAO1* (OR=8.9, 95%-CI=1.4–65.7, p_{adj}=9.5e-3) or *MECP2* variants (OR=25.7, 95%-

CI=1.3–1,548.1, p_{adj}=1.6e-2). Additionally, worsening of movement disorders was associated with amantadine in patients with *ATP1A3* variants (OR=Inf, 95%-CI=4.6–Inf, p_{adj}=1.6e-3), as well as perampanel (OR=Inf, 95%-CI=1.9–Inf, p_{adj}=8.5e-3), and trihexyphenidyl in cases with *ARX* variants (OR=23.2, 95%-CI=1.0–1,568.0, p_{adj}=2.4e-2).

We also evaluated the use of non-pharmacological interventions, namely DBS, which was reported in 24 cases (Figure S16). DBS was most commonly used in patients with *GNAO1* variants (54.2%, 13/24), with electrodes almost exclusively placed in the internal globus pallidus (95.8%, 23/24) across genetic etiologies. Clinician-reported clinical improvement was observed in 75.0% (18/24) of all patients treated with DBS including two thirds (76.9%, 10/13) of those with *GNAO1* variants. In contrast, however, DBS showed no benefit in the three patients with *ATP1A3* variants.

Discussion

The EDS comprise a diverse and evolving group of predominantly childhood-onset monogenic disorders commonly encountered in movement disorder and epilepsy clinics worldwide. This study places special emphasis on accurately characterizing the spectrum of movement disorders in EDS, addressing a critical gap in the literature where many conditions have been primarily described from an epilepsy-centric perspective.

Leveraging the collaborative network of the International Parkinson and Movement Disorders – Pediatric Movement Disorders Special Interest Group, this study defined a list of 105 monogenic disorders commonly presenting with both epilepsy and movement disorders. Data collection utilized a standardized clinician-reported survey, supplemented by reviews of medical records and, where available, videos of neurological examinations. The survey was specifically designed to capture data relevant to EDS while remaining sensitive to a broader range of clinical manifestations, including those outside the established phenotypic spectrum. Contributions came from clinicians self-identifying as movement disorder specialists (fellowship-trained) or pediatric neurologists with substantial expertise in diagnosing and managing movement disorders.

This collaborative effort resulted a comprehensive cross-sectional analyses of movement disorders, epileptic seizures, associated comorbidities, and treatment responses. An intriguing initial finding was that, among the 105 predefined genes, cases were only identified for variants in 74 genes. This observation may reflect: 1) The ultra-rare nature of certain EDS, which potentially escape detection even in a dataset drawn from over 30 centers worldwide, including large tertiary care programs; 2) the recent identification of some conditions, which may not yet be fully represented in clinical practice yet; 3) the tendency for some EDS to be rapidly diagnosed due to their prominent epilepsy manifestations, with subsequent referral to movement disorder specialists (from which we recruited predominantly) being less routine; 4) diagnostic gaps in accessing genetic testing as some diagnostic approaches (single gene testing, gene panels) might be insufficient to establish a diagnosis, particularly in cases with a potentially broader or atypical phenotypic spectrum than currently described in the literature. Overall, 12 genes accounted for two thirds of the cohort, underscoring their relative prevalence in specialized movement disorder clinics worldwide. Using available data on gene prevalence in developmental and epileptic encephalopathies [45] as a reference, we find considerable overlap between the most commonly implicated genes and those observed in our EDS cohort, though notable differences also emerge. For example, ion channelopathies such as *SCN1A* and *KCNQ2* are typically associated with epilepsy-predominant phenotypes and are less commonly linked to prominent movement disorders. The genetic testing modalities employed in this study highlight the increasing accessibility of exome and genome sequencing across diverse healthcare settings, but multigene panels remain commonly used at some centers. As the clinical and genetic spectrum of EDS continues to expand, including insights from this study, it is essential to acknowledge the limitations of multigene panels in capturing the full complexity of this group of disorders. To address this, broader testing approaches should be prioritized to ensure more comprehensive diagnostic capabilities.

A second notable observation is that, while all patients included in the study, based on the required inclusion criteria, presented with a movement disorder, only 66.8% also had comorbid epilepsy. While some of these cases may reflect a potential later manifestation of epilepsy, this likely

accounts for only a small subset, as seizures in most EDS typically manifest early and are often the initial symptom. Instead, this finding suggests that certain EDS may occasionally present with movement disorders as the main or sole manifestation, highlighting the phenotypic pleiotropy commonly observed in many monogenic movement disorders. Clinically, these cases often fall on the milder end of the severity spectrum for a given EDS, as the presence of epilepsy is frequently associated with more severe neurodevelopmental and behavioral challenges, as well as greater motor impairment. This observation may be helpful for family counseling and anticipatory guidance in clinical care, though it warrants confirmation through longitudinal studies.

A third important observation is that the movement disorder spectrum in EDS extends beyond what is classically defined as 'dyskinesia' to all major hyper- and hypokinetic movement disorders, and thus the term EDS may warrant reconsideration. To better characterize the motor disorder spectrum observed in EDS, we asked participants to rank both the leading and second most prominent movement disorders while also recording the full range of phenomenologies present. This approach revealed that most EDS cases present with mixed movement disorders, where multiple phenomenologies coexist in the same patient. This finding highlights the complexity of movement disorders in EDS and emphasizes the need for comprehensive clinical evaluation and care. In clinical practice, it is often useful to identify the leading phenomenology, defined as the most clinically prominent and functionally impairing disorder, and to design treatment plans and goals centered around it. Simultaneously, clinicians should explore synergistic treatments that address multiple comorbid movement disorders. For example, medications or DBS can often be optimized to target both dystonia and chorea, which represent the most common combination of movement disorders identified in the cohort.

While our analysis begins to elucidate the movement disorder signatures associated with the most common EDS, it also uncovers several novel associations. These findings are valuable not only for refining genetic testing approaches and optimizing care for specific EDS but also for suggesting previously unexplored shared disease mechanisms and possibly the re-classification of variants of uncertain significance. For instance, the late-onset manifestation of levodopa-responsive parkinsonism in individuals with *KCNQ2* variants indicates that channelopathies may impair

dopamine-driven circuits. Such novel associations have significant implications for clinical care and quality of life, underscoring the need for further investigation. Larger, prospective cohort studies focusing on individual rare forms of EDS are essential to validate these observations and translate them into improved management strategies.

Along the same theme, our molecule pathway analysis provides a systems-level view of EDS-associated gene relationships, offering a functional classification framework that extends beyond traditional, manually curated pathway annotations. By utilizing an unbiased clustering approach, we identified potential mechanistic overlaps between EDS subtypes, revealing shared molecular networks that underlie distinct clinical presentations. These findings highlight key biological pathways that could serve as therapeutic targets. Additionally, this comprehensive classification framework offers a predictive tool for phenotypic spectrum assignment of newly discovered EDS genes, aiding in genotype-phenotype correlations.

Data on motor disability in EDS reveal high rates of dependence on walking aids and wheelchairs, highlighting the severity of motor impairment in many cases. We suspect that movement disorders impose a substantial disease burden, particularly in patients whose seizures have been adequately managed or suppressed. In the cohort, 15 patients had a documented history of status dystonicus requiring inpatient-level care. This is likely an underestimation due to the study's retrospective design, potentially varying definitions of status dystonicus, and differences in treatment thresholds. This variability is further reflected by the overall low number of patients for whom any data on the history of status dystonicus was reported (203/609). For example, frequent hyperkinetic crises observed in individuals with *GNAO1* mutations would meet the most recent criteria for status dystonicus [46,47], but this may not have been applied universally. Recently published standardized practice guidelines for the management of status dystonicus in the pediatric population will help address these inconsistencies [46]. However, these guidelines will need to be adapted for patients with EDS, as their preexisting medication burdens often necessitate a tailored approach to ensure effective and safe management. Movement disorders may also significantly affect other critical domains, such as sleep, swallowing function, and self-injurious behaviors, the latter particularly

in cases involving severe stereotypies. Given these broad impacts, the role of movement disorders in determining overall health-related quality of life warrants further investigation in future studies.

Focusing on the 12 most common EDS in the cohort (*ATP1A3, CACNA1A, CDKL5, FOXG1, GNAO1, MECP2, PRRT2, SCN1A, SCN8A, SCL2A1, STXBP1, WDR45*), we analyzed the temporal patterns of movement disorder and seizure onset, as well as the evolution of specific movement disorder phenomenologies. Our findings indicate that, in the majority of conditions, seizures manifest either before or simultaneously with movement disorders, although subtle movement disorders may precede seizure onset in some cases. Hyperkinetic movement disorders, such as dystonia, chorea, and stereotypies, generally appear early in the disease course, while ataxia and parkinsonism tend to emerge later. For example, in *MECP2*-associated Rett syndrome and *WDR45*-associated BPAN, stereotypies manifest in early childhood, whereas dystonia and parkinsonism become more prominent during the second decade of life. Most EDS, however, exhibit a mixed and overlapping spectrum of movement disorders, with multiple phenomenologies often coexisting within the same age groups. These findings must be interpreted with caution due to the cross-sectional nature of the dataset, which limits our ability to capture longitudinal symptom changes. This limitation is particularly evident in conditions associated with *CACNA1A* and *ATP1A3*, which exhibit diverse spectrum of clinical manifestations, each with a characteristic age of onset.

Genotype-phenotype correlations have been described for several genes included in this study. For instance, in *SLC2A1*, movement disorders are less frequently associated with missense mutations [48]; in *FOXG1*, deletions are more commonly linked to epilepsy and a higher seizure burden compared to missense mutations [49]; and in *CDKL5*, specific variants - such as missense mutations in the Arg178 hotspot - are associated with lower developmental scores and increased clinical severity [50]. While our analysis did not explicitly stratify cases by genotype-phenotype relationships, the broad phenotypic spectrum captured in our study highlights the need for longitudinal, prospective investigations to refine these associations. A better understanding of genotype-phenotype correlations is essential for genetic counseling and may have important implications for clinical care and therapeutic decision-making.

The relatively high number of cases, particularly for the 12 most common genes, enabled an unbiased approach to identifying less common but highly specific disease manifestations, as well as differential responses to symptomatic treatments. While this approach has several limitations, including a non-standardized treatment approach, it allowed for the identification of novel associations. One of the most critical findings was that certain anti-seizure medications worsened movement disorders in specific EDS cases and should therefore be used with caution. These observations underscore the importance of individualized treatment strategies and careful medication selection in managing EDS as well as a multidisciplinary approach in disease-managing.

While our results provide important insights, several limitations must be also acknowledged. First, as a survey-based study, the data are subject to potential reporting bias, particularly in terms of the interpretation and categorization of movement disorders by individual clinicians. Second, although the multicenter nature of the study reduces bias toward specific conditions, the dataset may still reflect a slight overrepresentation of certain disorders due to the continued predominance of a few high-contributing sites in data collection. Third, the quality of data may vary across participating centers, reflecting differences in clinical expertise, diagnostic tools, and documentation practices. However, this variability also highlights the real-world applicability of the findings, as they represent diverse clinical practices across multiple geographic regions and health-care settings. Addressing these limitations in future studies, such as by implementing standardized data collection protocols or leveraging prospective longitudinal designs, will help refine and expand upon the conclusions drawn here.

In summary, this study offers a systematic analysis of EDS, revealing critical insights into their clinical and molecular spectrum. It underscores the need for interdisciplinary collaboration to improve diagnostic accuracy and treatment strategies. These findings lay the groundwork for future longitudinal studies and molecular investigations that may further refine the care of patients with EDS and inform broader research on monogenic movement disorders.

Data availability

Anonymized data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 Overview of Patient Demographics, Genetic and Functional Characteristics, and Survival Analysis. (**A**) Geographic distribution of the study population, showing the majority of individuals from North America, particularly the USA, with additional representation from South America, Europe, Asia, and Australia. (**B**) Distribution of the affected genes within the cohort, highlighting the top ten most frequently mutated genes. Remaining genes are grouped and displayed as an aggregate category. (**C**) UMAP embedding of combined Gene Ontology (GO) and Protein-Protein Interaction (PPI) adjacency data, illustrating functional gene clusters. Clusters are labeled with their top enriched biological process GO terms, revealing functional relationships among the affected genes. (**D**) Sex distribution among patients with the most frequently affected genes, showing sex-specific prevalence patterns. (**E**) Kaplan-Meier survival curves stratified by the 12 most frequently affected genes and the overall cohort (Cumulative). The 95% confidence

interval for the cumulative cohort is shown as a shaded ribbon. Censoring was applied at the last follow-up for individuals not reported as deceased. (**F**) Inheritance patterns among patients with the most frequently affected genes.

Figure 2 Spectrum and Characteristics of Movement Disorder Phenomenologies. (**A**) Distribution of the predominant or leading (left) and second-leading (right) movement disorder phenomenologies among patients with the 12 most frequently affected genes, displayed as absolute counts. (**B**) Associations between leading and second leading movement disorder phenomenologies across the cohort. (**C**) Associations between reported movement disorder phenomenology (both leading and second leading) and typical pattern of occurrence across the cohort. (B & C) Significant associations ($p_{adj}<0.05$) are indicated by black circles around dots.

Figure 3 Seizure Spectrum, Control, and Associations with Movement Disorders. (**A**) Distribution of the most common seizure types among patients with the 12 most frequently affected genes, shown as absolute counts. This panel highlights the prevalence of specific seizure phenotypes within the cohort. (**B**) Associations between seizure types and movement disorder phenomenologies across the cohort. No significant associations were identified, suggesting independent phenotypic manifestations. (**C**) Seizure control status among patients with the most frequently affected genes. Bar opacity reflects the absolute number of patients for each gene (log2-transformed for clarity). The first bar (Cumulative) represents the entire cohort, with transparency set to zero for contrast, illustrating the overall distribution of seizure control outcomes.

Figure 4 Age at Diagnosis for Epilepsy and Movement Disorder. Age at diagnosis of epilepsy and movement disorder among patients with the 12 most frequently affected genes. Dot size represents the percentage of patients with both epilepsy and movement disorder reported, illustrating the co-occurrence and temporal relationship between the two neurological conditions.

Figure 5 Temporal Distribution of Movement Disorder Phenomenologies. Cross-sectional analysis showing the distribution of the leading movement disorder phenomenologies over time

among patients with the 12 most frequently affected genes. This temporal distribution highlights the dynamic progression and age-dependent patterns of movement disorders in different EDS.

Figure 6 Developmental and Functional Motor Impairment. (**A**) Severity of developmental delay among patients with the most frequently affected genes, illustrating the spectrum of developmental challenges within the cohort. (**B**) Severity of intellectual disability among patients with the most frequently affected genes, highlighting the cognitive impact associated with these genetic variants. (**C**) Cumulative event curves for time to achieve independent walking across the cohort, stratified by gene for the twelve most frequently affected genes and the entire cohort (Cumulative). The 95% confidence interval for the cumulative cohort is shown as a shaded ribbon, with median times to event marked by dashed lines. Data were censored at the last follow-up for individuals not reported to have achieved independent walking. (**D**) Age at walking aid dependence among patients with the most frequently affected genes, reflecting progressive motor impairment. (**E**) Age at wheelchair dependence among patients with the most frequently affected genes. (**F**) Cumulative event curves for time to reach GMFCS levels across the cohort, with 95% confidence intervals shown as shaded ribbons and median times to event indicated by dashed lines. Time-to-event data were censored at the last follow-up for individuals not reported to have reached the respective level. (A-B & D-E) Bar opacity reflects the absolute number of patients for each gene (log_2-transformed for clarity); the first bar (Cumulative) represents the entire cohort, with transparency set to zero for contrast.

Figure 7 Phenotypic Enrichment Analysis Stratified by Affected Gene. One-versus-rest enrichment analysis for categorical clinical findings among patients with the 12 most frequently affected genes. Colored dots represent significantly enriched (positive enrichment) or underrepresented (negative enrichment) clinical findings. Labels indicate findings that are significantly enriched in each gene, revealing gene-specific phenotypic patterns and highlighting distinctive clinical manifestations associated with each genetic variant.

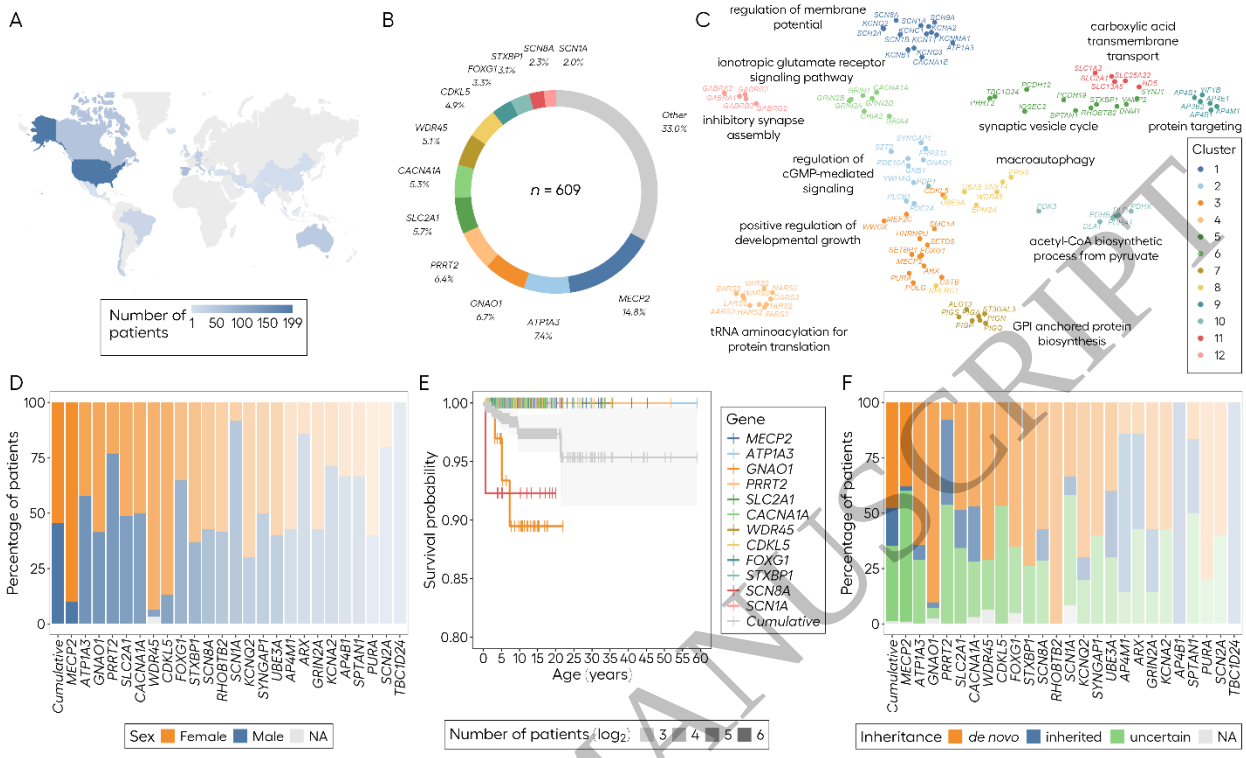

Figure 1
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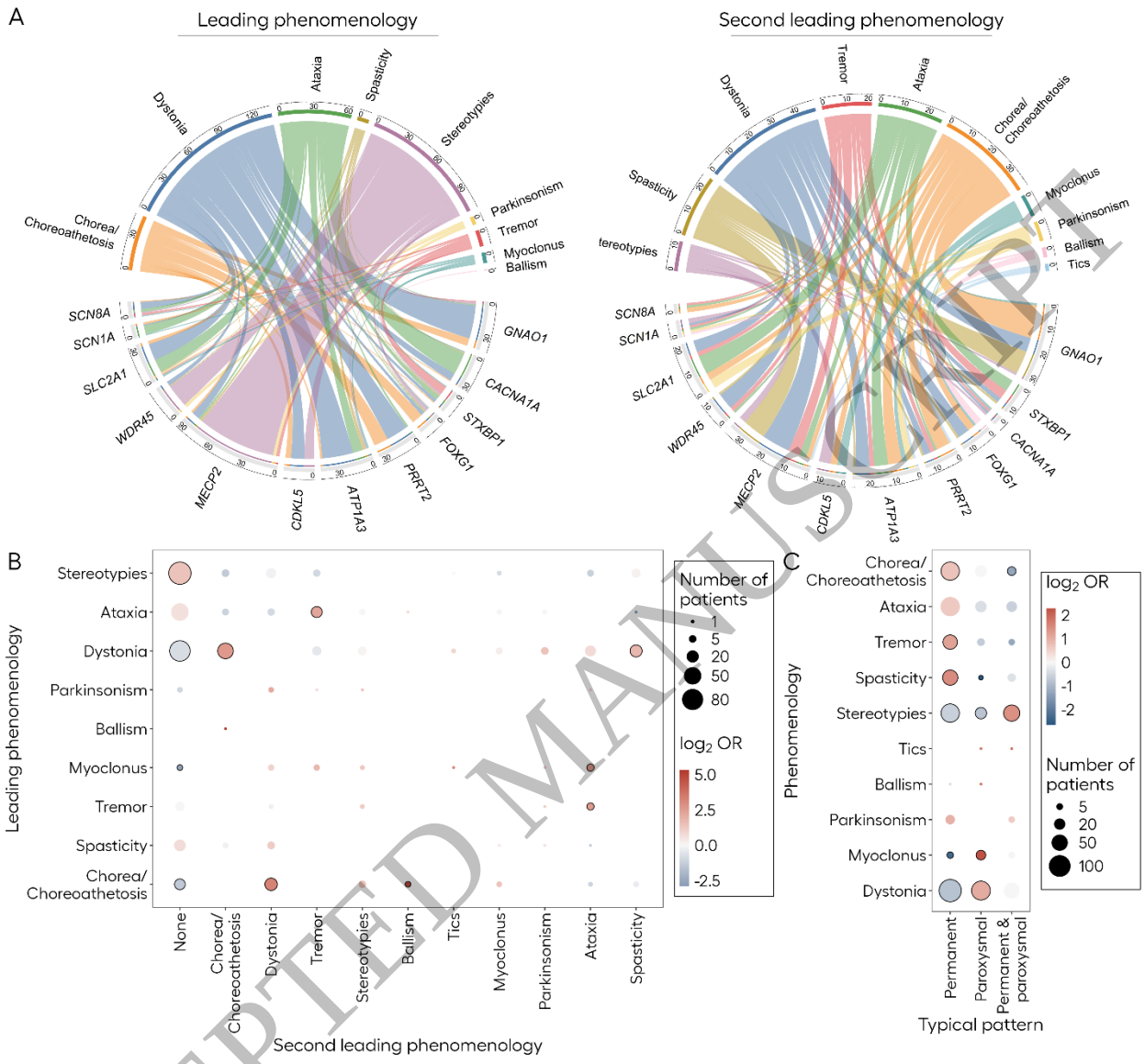

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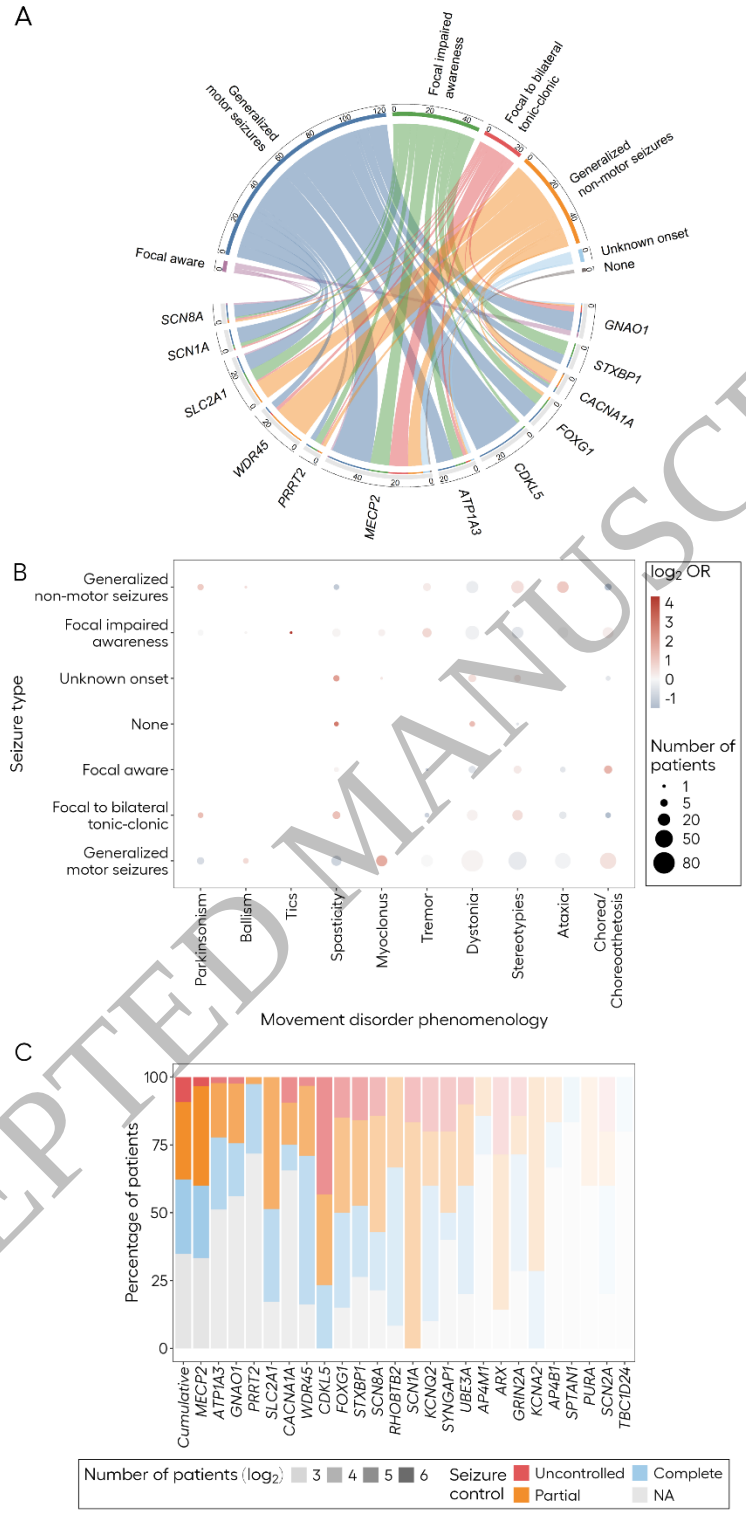

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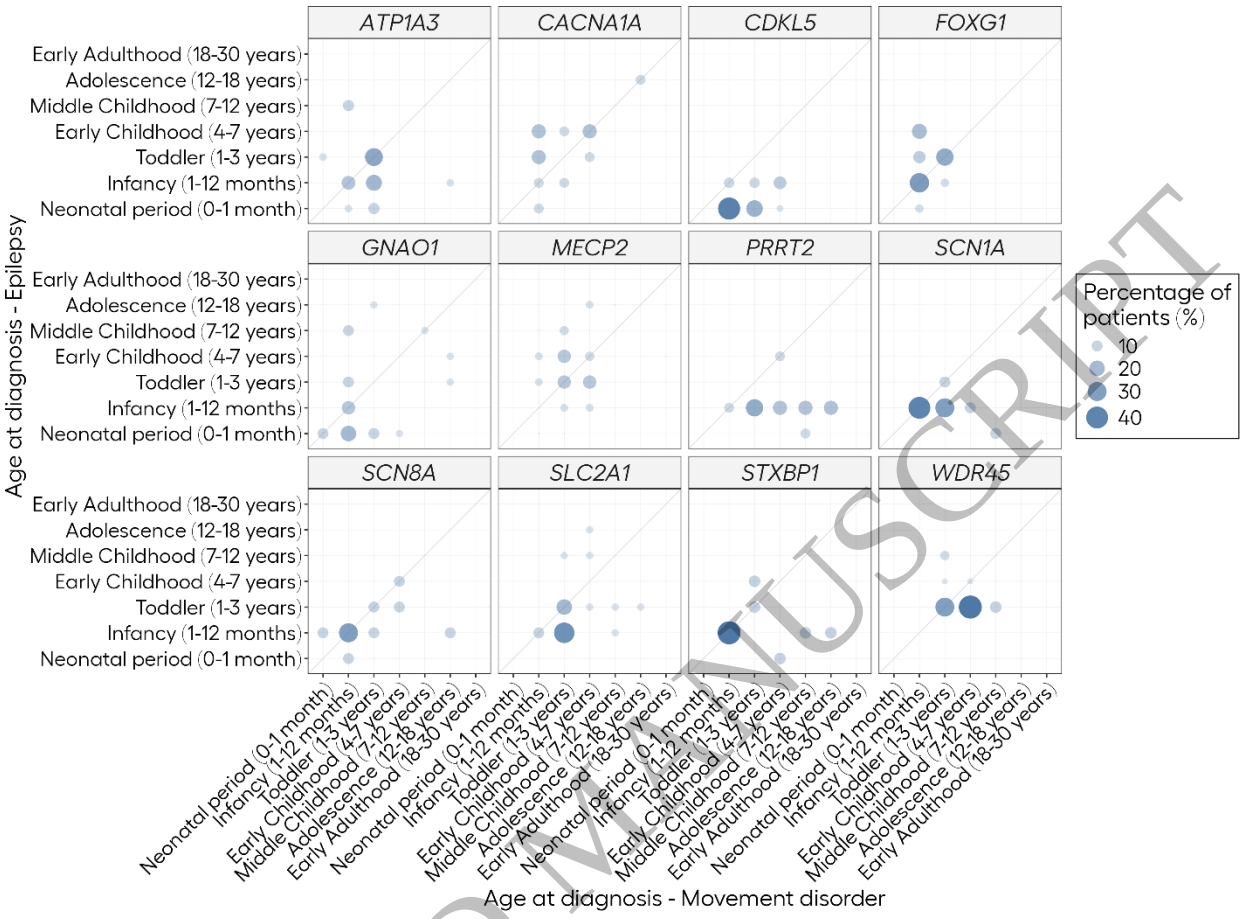

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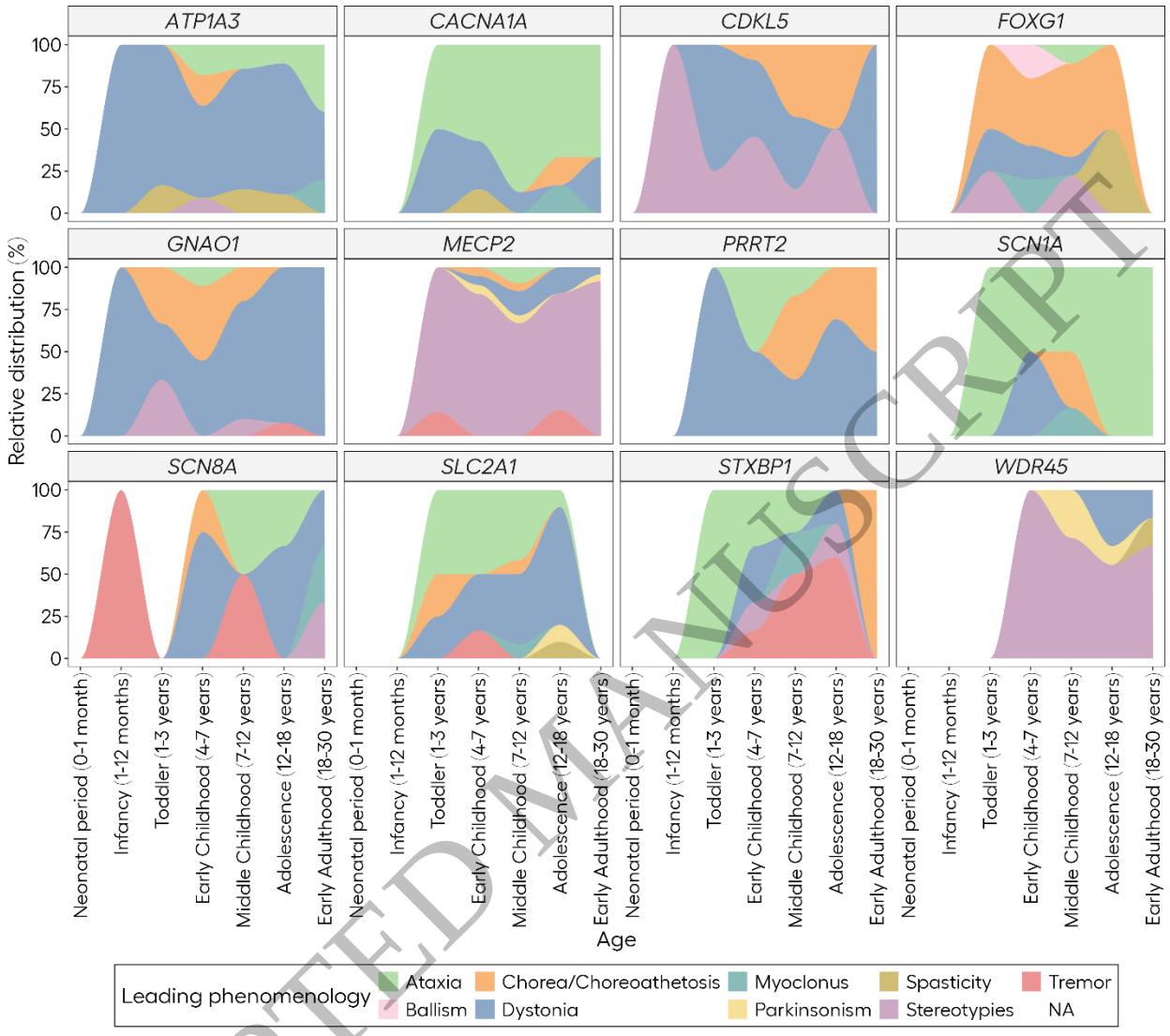

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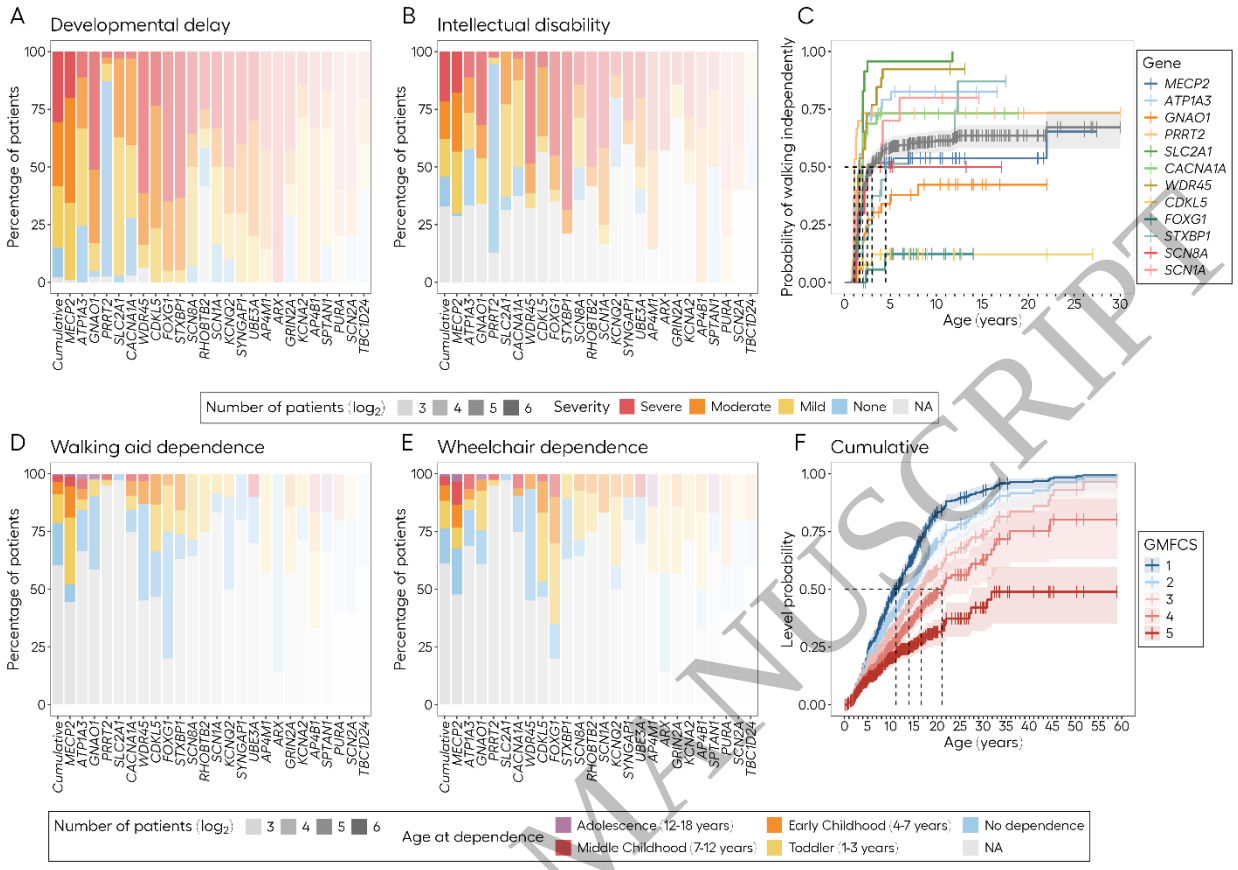

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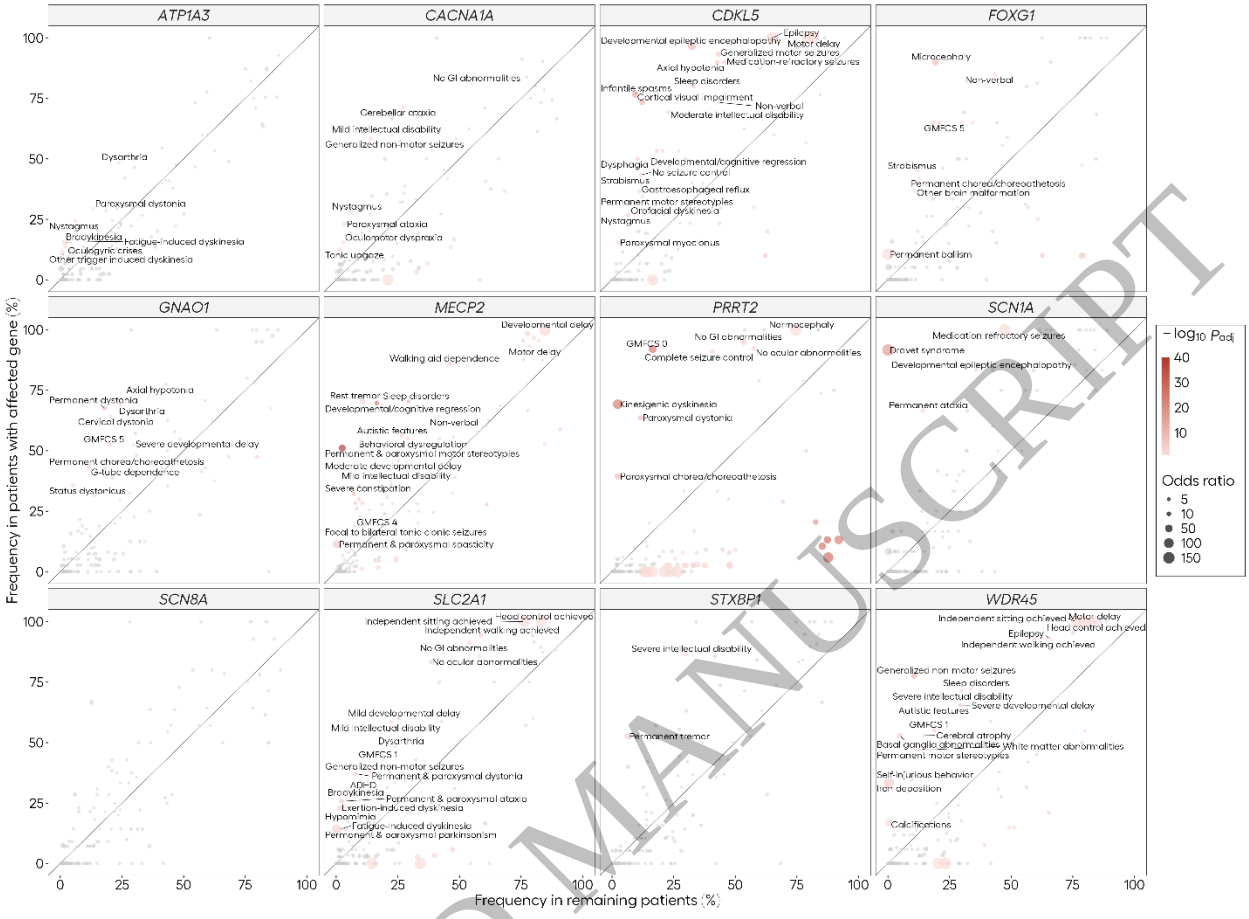

Figure 7
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