RESEARCH ARTICLE

# Spectrum of Movement Disorders in Early-Onset Hereditary Spastic Paraplegia: A Study of 428 Cases

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**ABSTRACT: Background:** Movement disorders occur in early-onset hereditary spastic paraplegia (HSP), but their prevalence, genotype associations, and clinical impact are not well defined.

**Objectives:** To delineate the spectrum and frequency of movement disorders across childhood-onset HSP genotypes and assess associations with clinician- and caregiver-reported outcomes.

**Methods:** We performed a cross-sectional analysis of 428 children and young adults with molecularly confirmed HSP enrolled in a multicenter natural history study. Standardized clinical phenotyping and video examinations were reviewed. Movement and motor disorders (dystonia, ataxia, parkinsonism, tremor, choreoathetosis) were identified using predefined criteria. Associations with SPATAX-EUROSPA disability stage (SPATAX), Spastic Paraplegia Rating Scale (SPRS; total and spasticity subscore), Modified Ashworth Scale, and Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) quality-of-life scores were analyzed with nonparametric tests and multivariable linear models adjusted for age and sex.

**Results:** Movement disorders were present in 27.6% (118/428) of participants; 22.8% of these had ≥2 movement disorders. Dystonia (16.4%) and ataxia (10.0%) predominated. Distinct genotype-specific patterns were observed: dystonia in SPG4, SPG3A, and AP-4-HSP; parkinsonism in SPG11; and ataxia in SPG15, SPG76, SPG7, SPG5a, and SPG46. Presence of any movement disorder correlated with greater disability and motor burden and lower quality of life. In adjusted models, dystonia and parkinsonism were associated with higher SPATAX and SPRS scores, whereas ataxia and tremor correlated with lower scores; dystonia showed the largest decrement in CPCHILD.

**Conclusions:** Movement disorders are common, genotype-specific, and clinically impactful features of childhood-onset HSP. Routine screening and genotype-tailored management of movement disorders, especially dystonia, may improve functional outcomes and quality of life. © 2025 International Parkinson and Movement Disorder Society.

**Key Words:** ataxia; childhood-onset movement disorders; dystonia; hereditary spastic paraplegia; parkinsonism

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Hereditary spastic paraplegia (HSP) encompasses a clinically heterogeneous group of over 90 neurogenetic disorders characterized by progressive lower limb spasticity and weakness. HSP is broadly categorized into *pure* forms, limited to pyramidal tract dysfunction, and *complex* forms, which present with additional neurological features.[1,2]

While spasticity remains the hallmark of HSP, both clinical experience and emerging evidence suggests that other motor and movement disorders, including dystonia, tremor, parkinsonism, and ataxia, contribute to disease burden in certain genotypes.[3-5] However, the prevalence, spectrum, and clinical relevance of these extrapyramidal features remain poorly defined, largely due to limited systematic evaluation.

This gap is particularly relevant in childhood-onset complex HSP, where extrapyramidal features are common, and may even precede the development of spasticity and influence both prognosis and therapeutic decision-making.[6] In this cross-sectional study we aimed to: (1) delineate the spectrum of movement disorders in a large cohort of children and young adults with HSP; (2) identify genotype-specific associations; and (3) examine the impact of these features on motor function and quality of life using validated clinician- and patient-reported outcome measures.

# Methods

## Study Design and Participants

Between May 28, 2018 and August 30, 2024, patients with genetically confirmed HSP were enrolled in the Registry and Natural History Study for Early-Onset Hereditary Spastic Paraplegia (NCT04712812), approved by the Boston Children's Hospital Institutional Review Board (IRB-P00033016). Written informed consent was obtained. A second cohort of predominantly adult patients was recruited through UNICAMP, Brazil under local ethics committee approval (CAAE 83241318.3.1001.5404).

This cross-sectional observational study included patients who met the following criteria: (A) a molecularly confirmed diagnosis of HSP; (B) a standardized clinical evaluation, including neurological examination and at least one clinician-reported outcome measure (CROM); and (C) an age at symptom onset between 0 and 30 years, consistent with early-onset HSP. Patients were excluded if they had: (A) uncertain or incomplete molecular diagnoses; (B) insufficient clinical data precluding reliable classification of movement disorders; or (C) concomitant neurological diseases unrelated to HSP. The primary analysis focused on childhood- and young adult–onset cases (ages 0–30 years). To assess age-related distribution patterns, we incorporated a second, predominantly adult cohort from UNICAMP (ages 11–73 years), enabling cross-sectional projection of clinical features across a wider age spectrum.

Patients with molecular subtypes typically associated with pure HSP (eg, SPG3A, SPG4) were included. Cases presenting additional neurological features such as dystonia, ataxia, choreoathetosis, tremor, or parkinsonism were categorized as complex HSP.

CROMs included the Spastic Paraplegia Rating Scale (SPRS),[7] the SPATAX-EUROSPA disability stage (SPATAX), and the Modified Ashworth Scale (MAS). A spasticity subscore was derived from SPRS items 7–10, reflecting lower limb tone and strength. All CROMs, motor findings, and movement disorder classifications were performed by trained movement disorder specialists. Raters were not blinded to genotype. Video recordings were obtained in selected cases to document and illustrate relevant phenotypes.

Patient-reported outcome measures (PROMs) included the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD),[8] a validated tool assessing health-related quality of life in pediatric populations with neurodisabilities.

Demographic, clinical, and molecular data were extracted from standardized case report forms and centralized in a REDCap (Research Electronic Data Capture) database. Cross-sectional analyses were based on each patient's most recent clinical evaluation. To avoid unstable estimates, only HSP subtypes with at least three patients were included in genotype-specific analyses.

Movement disorders were defined using simplified clinical criteria. Parkinsonism required at least two of the following symptoms: rigidity, bradykinesia/hypokinesia, resting tremor, postural instability. Choreoathetosis was scored if either chorea or athetosis was observed. Tremor encompassed postural, resting, or action tremor.

## Statistical Analysis

All analyses were performed using R (version 4.3.1); detailed methods are provided in the Supplementary Material.

## Data Sharing

Data are provided in the Supplementary Material (Tables S1–S3), and additional data are available from the corresponding author upon reasonable request.

# Results

## Demographic and Molecular Characteristics

The cohort included 428 individuals with genetically confirmed HSP across 14 subtypes. Median age at last clinical evaluation was 9 years (range 0.7–30, IQR 9.9). The most frequently represented subtypes were adaptor protein complex 4 (AP-4)-related HSP (SPG47, SPG50,

SPG51, and SPG52) accounting for 61.4% (263/428) of the cohort, followed by SPG4 (17.8%, 76/428), SPG15 (5.6%, 24/428), SPG3A (5.1%, 22/428), and SPG11 (3.7%, 16/428). This distribution reflects both broader subtype prevalence and the center's specific research focus in AP-4-associated and other early-onset forms of HSP.

To validate age-dependent analyses, an independent cohort of 71 patients (range 11–73 years, median 39, IQR 17) was included (Table S1).

## Spectrum of Extrapyramidal Movement Disorders with HSP

Overall, 27.6% (118/428) of patients exhibited at least one movement disorder, with four HSP subtypes accounting for the majority of cases (Fig. 1A). The prevalence of movement disorders varied widely by genotype (Fig. 1B). For example, 24.3% of individuals with AP4-related HSP presented with movement disorders, whereas the frequency was substantially higher in SPG15, with 66.7% of patients exhibiting at least one extrapyramidal feature.

Among all patients with movement disorders, 77.1% (91/118) presented with a single phenomenology, 18.6% (22/118) with two, and 4.24% (5/118) with three distinct movement disorders (Fig. 1C). Across the entire cohort, the most prevalent movement and motor disorders were dystonia, ataxia, parkinsonism, and tremor (Fig. 1D). Representative cases are illustrated in Videos 1–4.

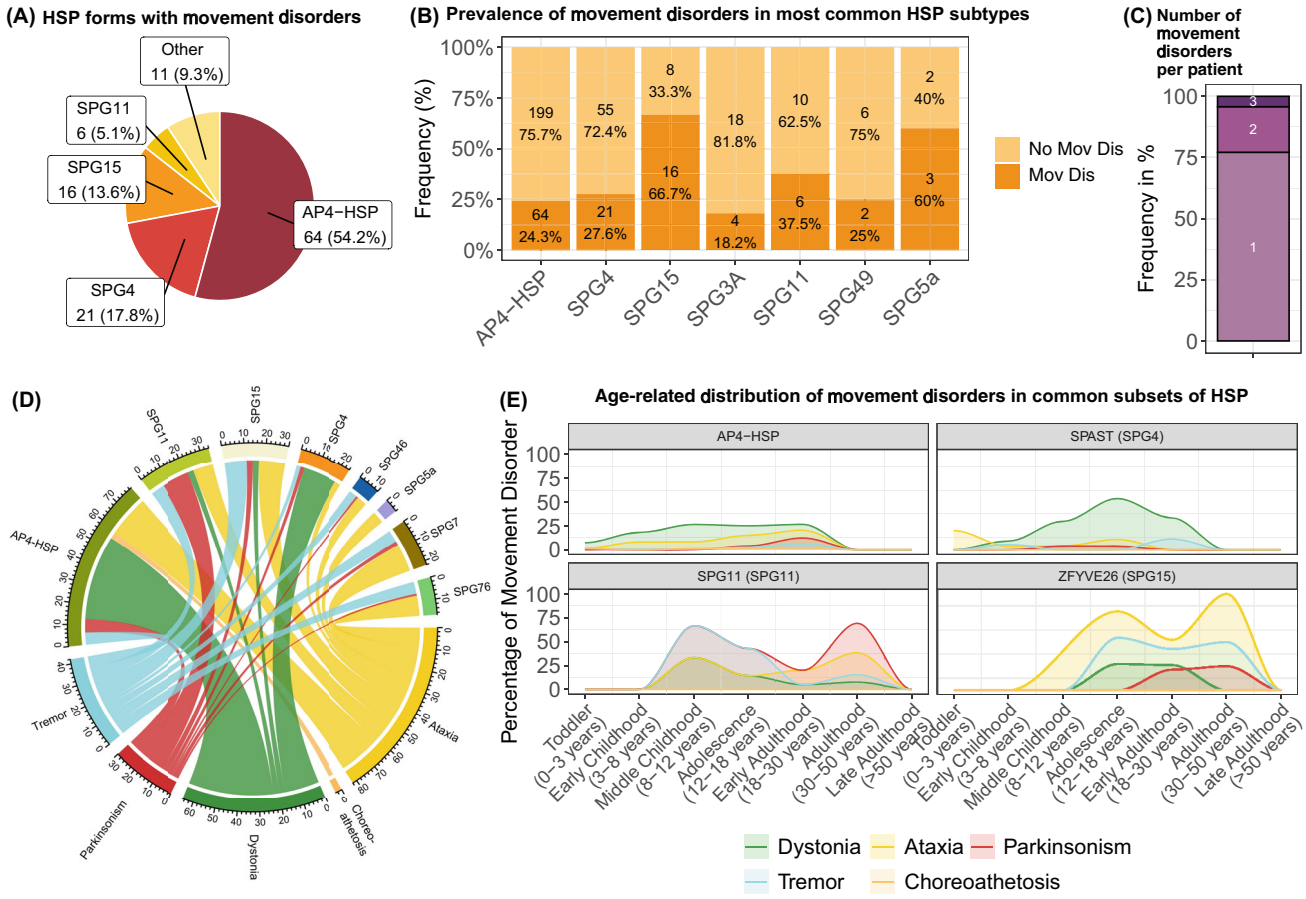



**FIG. 1.** Spectrum of movement disorders across hereditary spastic paraplegia (HSP) subtypes and genotype–phenotype correlations. Overview of the study cohort, illustrating genetic distribution, demographic features, and the occurrence of movement disorders. (A) Distribution of the most common movement/motor disorders across the cohort, with four HSP subtypes accounting for the majority of cases. (B) Prevalence of movement disorders among the most frequent HSP subtypes with extrapyramidal involvement, demonstrating wide variability by genotype. (C) Distribution of movement disorder burden per patient, showing that approximately one-quarter presented with two or more movement disorders, underscoring the clinical complexity in childhood-onset HSP. (D) Chord diagram illustrating associations between HSP subtypes and movement disorders. Each ribbon corresponds to the absolute number of patients per gene–symptom pair. (E) Age-stratified analysis of movement disorder prevalence in four genotypes with sufficient sample size (n > 14): AP4-related HSP, *SPAST* (SPG4), *SPG11* (SPG11), and *ZFYVE26* (SPG15). In AP4-related HSP, dystonia was the predominant early-onset feature and persisted into adulthood, while ataxia, tremor, and parkinsonism emerged later, particularly during adolescence. In SPAST-HSP, movement disorders were rare in early childhood, but dystonia increased with age, suggesting phenotypic progression. In SPG11-HSP, tremor and parkinsonism were most frequent in childhood and adolescence, with ataxia emerging in adulthood. In *ZFYVE26*-HSP, ataxia showed a bimodal distribution, tremor was persistent from mid-childhood, dystonia peaked in early adulthood, and parkinsonism gradually appeared in later decades. [Color figure can be viewed at wileyonlinelibrary.com]


**Video 1.** A 15-month-old female with AP-4-associated hereditary spastic paraplegia (HSP) exhibiting generalized dystonia characterized by sustained bilateral dystonic posturing of the arms, hand fisting, and paroxysmal extension of bilateral lower limbs with inward foot turning. [Color figure can be viewed at wileyonlinelibrary.com]
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70141

**Video 2.** Preschool-aged female with AP-4-associated hereditary spastic paraplegia (HSP) demonstrating gait ataxia characterized by a wide-based stance, inability to maintain a trajectory, and mild dragging of the left foot. [Color figure can be viewed at wileyonlinelibrary.com]
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70141

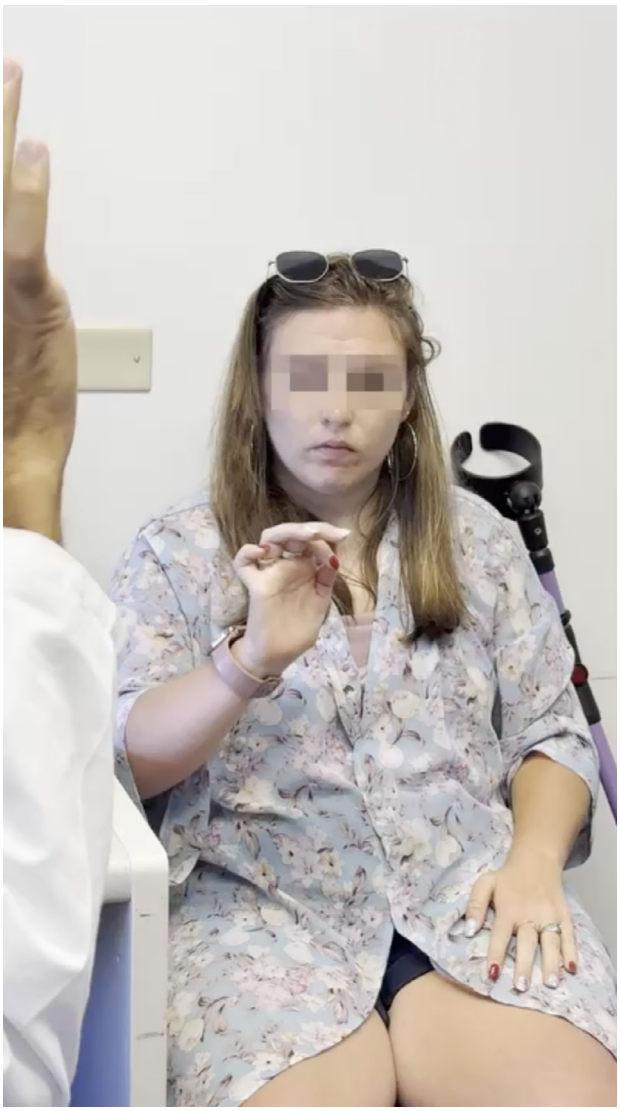
## HSP Subgroups Show Distinct Patterns of Extrapyramidal Movement Disorders

Distinct movement disorder profiles were observed across HSP subtypes. Ataxia was present in all HSP subtypes with movement disorders except SPG3A, and frequently represented among patients with SPG15 (15/21, 71.43%), SPG11 (10/27, 37.04%), and AP4-related HSP (21/83, 25.30%), and relatively underrepresented in SPG4 (3/21, 14.29%). Ataxia was a ubiquitous finding in individuals with SPG7, SPG5a, SPG46, and SPG76 in whom any movement/motor disorder was observed (Fig. 1D).

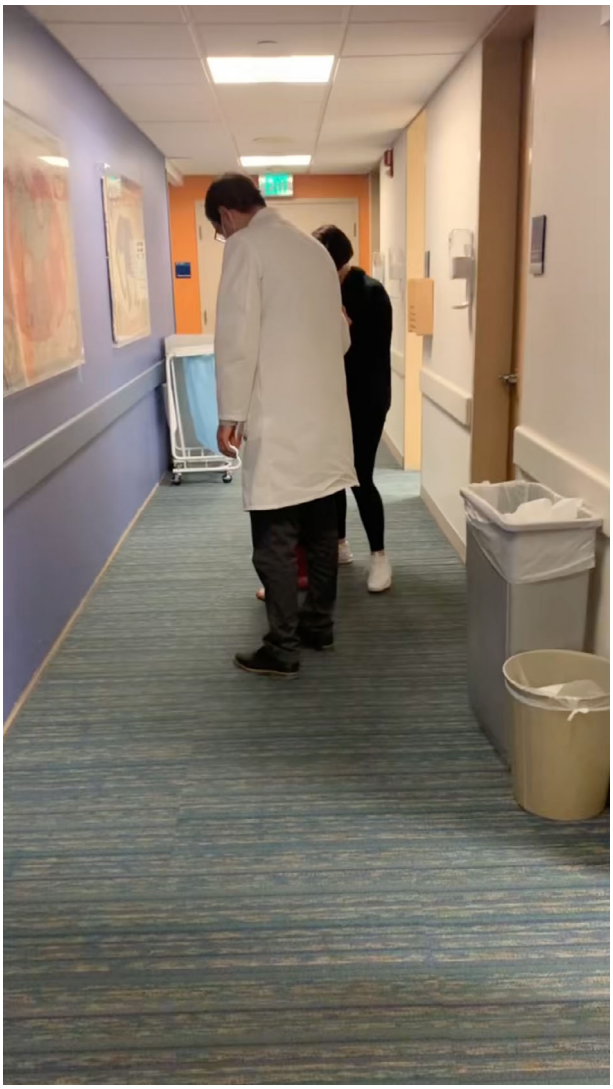
Dystonia emerged as the predominant movement disorder in several subtypes, including SPG4 (17/21, 80.95%), SPG3A (4/5, 80.00%), and AP4-related HSP (42/83, 50.60%). It was less frequently observed in SPG15 (3/21, 14.29%) and SPG11 (3/27, 11.11%) and not represented at all in SPG76, SPG5a, SPG46, and SPG7 (Fig. 1D).

Parkinsonism was most prevalent in individuals with SPG11 (14/27, 51.85%), while being less commonly diagnosed in other HSP subgroups such as SPG46 (1/5, 20.00%), SPG15 (3/21, 14.29%), SPG7 (2/14, 14.29%), SPG4 (2/21, 9.52%), AP4-HSP (7/83, 8.43%), and SPG76 (1/13, 7.69%) (Fig. 1D).

Tremor was most frequently diagnosed in patients with SPG46 (4/5, 80.00%), SPG15 (11/21, 52.38%), SPG76 (6/13, 46.15%), and SPG7 (6/14, 42.86%). Furthermore, we observed that a quarter of SPG11 (7/27,



**Video 3.** Young adult female with SPG11 demonstrating parkinsonian features including bradykinesia shown during rapid hand open-close movements, without clear amplitude decrement, and marked hypomimia. [Color figure can be viewed at wileyonlinelibrary.com]
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70141



**Video 4.** Adolescent male with SPG15 showing parkinsonism characterized by bradykinesia on gait assessment, shuffling steps, and evidence of postural instability. [Color figure can be viewed at wileyonlinelibrary.com]
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70141

25.93%) patients were diagnosed with tremor and only a few SPG4 (2/21, 9.52%) and AP4-HSP (6/83, 7.23%) patients.

Choreoathetosis was only present in very few AP4-HSP patients (3/83, 3.61%) and not documented in any other HSP represented in our cohort.

## Age-Related Distribution of Movement Disorders in HSP Subtypes

To evaluate the age-dependent distribution of movement disorder phenomenologies, we conducted a cross-sectional analysis of their prevalence across age groups, focusing on four genetically defined subgroups with sufficient representation: AP4-related HSP, SPG4, SPG11, and SPG15.

In AP4-related HSP, dystonia was the most frequent movement disorder across all age groups, with frequency increasing from toddler age to middle childhood (Fig. 1E). In contrast, ataxia showed low prevalence before age 12 years and the highest in early adulthood. Tremor and parkinsonism were overall rare but tended to be documented more frequent in early adulthood. Taken together, cross-sectional data suggest that movement disorders are more often observed in older age groups, consistent with later disease stages.

In SPG4, a more diffuse pattern of movement disorders was observed, with dystonia being the most frequently documented movement disorder in adolescence

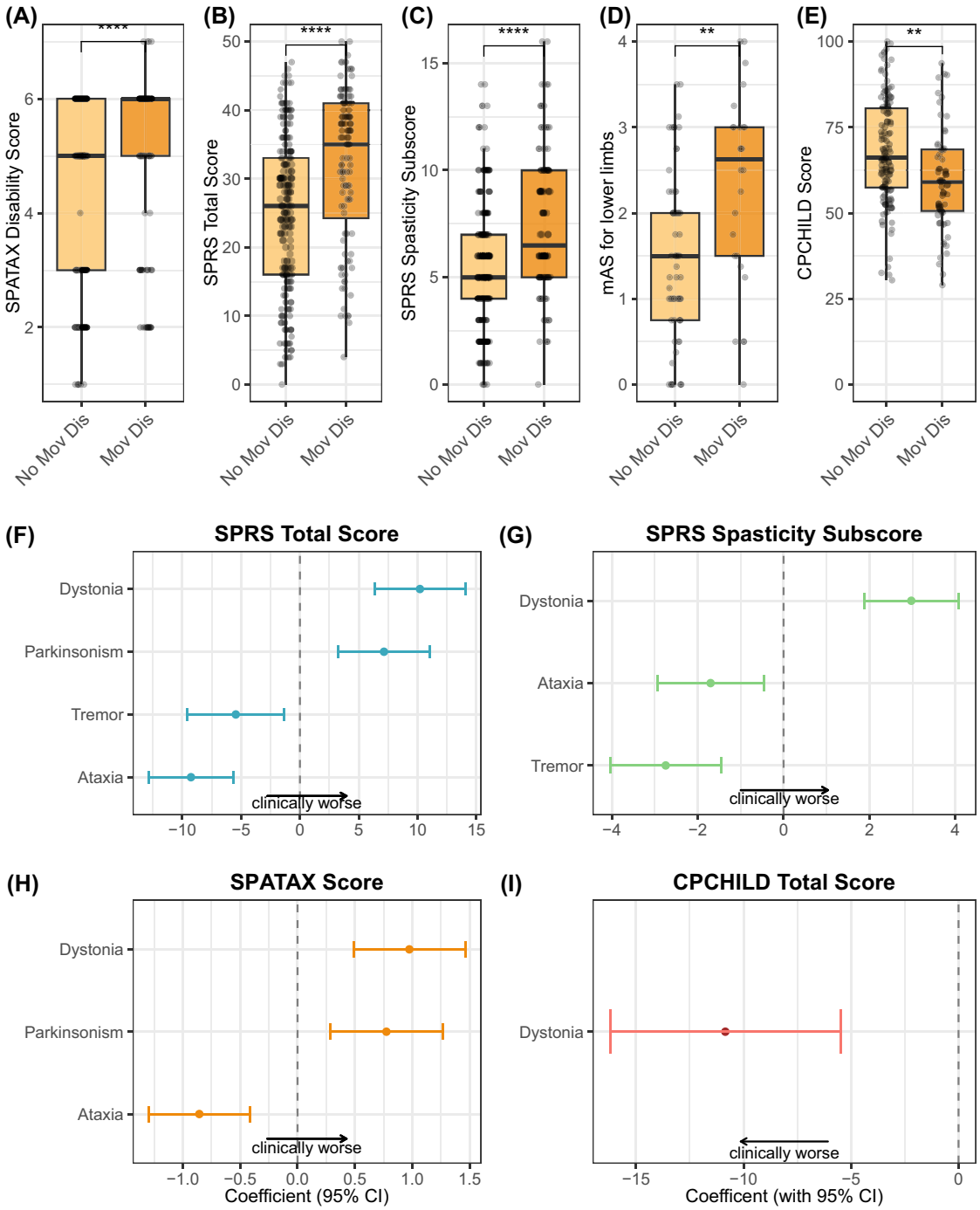



**FIG. 2.** Effect of movement disorders on clinical rating and patient-reported outcome measures. (A–E) Comparison of clinical rating outcome measures (CROMs) and patient-reported outcome measures (PROMs) between patients with and without movement disorders, analyzed using the Wilcoxon rank-sum test. Across all measures, patients with movement disorders demonstrated worse outcomes. Mov Dis, movement disorder. (A) SPATAX-EUROSPA disability stage (SPATAX) total score was higher in patients with movement disorders (median 6 vs. 5, $P = 0.000027$, $r = 0.24$), indicating more severe gait impairment. (B) Spastic Paraplegia Rating Scale (SPRS) total score (median 33 vs. 26, $P = 2.93 \times 10^{-7}$, $r = 0.29$) and (C) SPRS spasticity subscore (median 6 vs. 5, $P = 3.69 \times 10^{-7}$, $r = 0.29$) were significantly elevated, reflecting greater motor burden. (D) Modified Ashworth Scale (MAS) scores for the lower limbs were higher in patients with movement disorders (median 2.25 vs. 1.5, $P = 0.0016$, $r = 0.32$). (E) Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) scores, reflecting health-related quality of life, were lower in the movement disorder group (median 59.0 vs. 66.5, $P = 0.00103$, $r = 0.25$), indicating greater impact on daily care and participation. (F–I) Multivariable linear regression models adjusted for age and sex evaluating associations between specific movement disorders and outcome measures. Results are shown as regression coefficients ($\beta$) with 95% confidence intervals. Only significant associations ($P_{adj} < 0.05$) are displayed. (F) SPRS total scores were increased in patients with dystonia ($\beta = 10.2$, $P_{adj} < 0.00001$) and parkinsonism ($\beta = 7.14$, $P_{adj} = 0.00128$), but decreased with ataxia ($\beta = -9.26$, $P_{adj} < 0.00001$) and tremor ($\beta = -5.45$, $P_{adj} = 0.02443$). (G) SPRS spasticity subscores were positively associated with dystonia ($\beta = 2.97$, $P < 0.00001$) and negatively with tremor ($\beta = -2.74$, $P_{adj} = 0.0003$) and ataxia ($\beta = -1.7$, $P_{adj} = 0.024$). (H) SPATAX scores were elevated in dystonia ($\beta = 0.97$, $P_{adj} = 0.00092$) and parkinsonism ($\beta = 0.77$, $P_{adj} = 0.0067$) but reduced in ataxia ($\beta = -0.86$, $P_{adj} = 0.00092$). (I) Dystonia was independently associated with a reduction in CPCHILD scores ($\beta = -10.84$, $P_{adj} = 0.00096$), highlighting its adverse effect on quality of life. Full regression details are provided in Tables S2 and S3. [Color figure can be viewed at wileyonlinelibrary.com]

and adulthood. This goes along with our previously reported findings that dystonia is the leading movement disorder in SPG4 (Fig. 1D), while other movement disorders are less common and therefore limit the interpretability of the evolution of movement disorders in SPG4.

In SPG11, tremor and parkinsonism were the most frequent movement disorder in middle childhood and adolescence. In older patients, tremor prevalence was lower while frequency of ataxia was higher (Fig. 1E).

In SPG15, ataxia was the most frequently documented motor disorder across all available age groups. Tremor emerged as the second most frequent movement disorder in middle childhood and across the lifespan. This correlates well with our previously reported findings. Dystonia was most common during adolescence and early adulthood, albeit only being documented in around a quarter of patients. Parkinsonism was also only documented in around a quarter of SPG15 patients, but was predominantly seen in early adulthood and adulthood, supporting the expected later onset of parkinsonism. These cross-sectional patterns are consistent with progressive multisystem involvement in SPG15,[9] although confirmation in longer longitudinal studies is needed.

### Extrapyramidal Movement Disorders Correlate with Functional Outcomes

To assess the impact of movement disorders on motor function and quality of life in childhood-onset HSP, we analyzed CROM and CPCHILD scores in the pediatric cohort. SPATAX scores were available for 316 patients (73.8%) and ranged from 1 to 7 (median 5, IQR 3), reflecting moderate to severe motor impairment. Patients with movement disorders had significantly higher SPATAX scores (median 6 vs. 5, $P = 2.7 \times 10^{-}5$, $r = 0.24$), indicating greater disability (Fig. 2A). SPRS scores (308 patients, 71.9%) ranged from 0 to 50 (median 29, IQR 20). Patients with movement disorders showed higher scores (median 33 vs. 26, $P = 2.93 \times 10^{-7}$, $r = 0.29$), suggesting a moderate association with functional severity (Fig. 2B). The SPRS spasticity subscore (items 7–10) was available for 309 patients and also revealed higher values in patients with movement disorders (median 6 vs. 5, $P = 3.69 \times 10^{-7}$, $r = 0.29$) (Fig. 2C). MAS scores were reported in 97 patients (22.6%) and showed significantly greater tone abnormalities in those with movement disorders (median 2.25 vs. 1.5, $P = 0.0016$, $r = 0.32$) (Fig. 2D). CPCHILD scores, available in 174 patients (40.6%), reflected moderate impairment (median 63.1, IQR 22.8). Presence of a movement disorder was associated with lower quality-of-life scores (median 59.0 vs. 66.5, $P = 0.001$, $r = 0.25$) (Fig. 2E).

In multivariable linear regression models adjusted for age and sex, dystonia ($\beta = 0.97$, $P_{adj} = 0.00092$) and parkinsonism ($\beta = 0.77$, $P_{adj} = 0.0067$) were significantly associated with higher SPATAX scores, reflecting greater disability (Fig. 2H). In contrast, ataxia was associated with lower SPATAX scores ($\beta = -0.86$, $P_{adj} = 0.00092$) (Fig. 2H).

Dystonia ($\beta = 10.2$, $P_{adj} < 0.00001$) and parkinsonism ($\beta = 7.14$, $P_{adj} = 0.001$) also correlated with higher total SPRS scores, while ataxia ($\beta = -9.26$, $P_{adj} < 0.00001$) and tremor ($\beta = -5.45$, $P_{adj} = 0.024$) correlated with lower scores (Fig. 2F). Dystonia was further associated with increased spasticity ($\beta = 2.97$, $P_{adj} < 0.00001$), whereas tremor and ataxia were linked to reduced spasticity scores (tremor: $\beta = -2.74$, $P_{adj} = 0.0003$; ataxia: $\beta = -1.7$, $P_{adj} = 0.024$) (Fig. 2G). Age was independently associated with higher spasticity scores ($\beta = 0.15$ per year, $P_{adj} = 0.003$), but sex was not a significant factor. Patients with neuropathy demonstrated significantly higher SPATAX disability levels (median 6 vs. 5, $P = 0.0004$, $r = 0.43$), SPRS (median 36 vs. 23, $P = 0.0003$, $r = 0.43$), and SPRS spasticity subscores (median 7 vs. 5, $P = 0.043$, $r = 0.24$), while differences in MAS and CPCHILD scores were not significant (median 1.5 vs. 1.75, $P = 0.56$, $r = 0.1$ and median 63.2 vs. 80.5, $P = 0.447$, $r = 0.16$). Fisher's exact test did not identify a significant association between neuropathy and movement disorders ($P = 0.22$, OR = 1.89, 95% CI 0.67–5.20).

Among all movement disorders, dystonia had the most pronounced impact on quality of life, associated with an average 10.9-point reduction in CPCHILD score ($\beta = -10.84$, $P_{adj} = 0.00096$) (Fig. 1). Other movement disorders did not show significant associations in adjusted models.

## Discussion

While prior studies have examined genotype–phenotype correlations in HSP, only a few have explicitly addressed movement and motor disorders outside of a meta-analytic framework.[3,10] This cross-sectional study provides the most comprehensive genotype-resolved characterization of movement disorders in early-onset HSP to date, encompassing 428 patients across 14 molecularly confirmed subtypes. Collectively, the findings expand the pyramidal-centric view of HSP by establishing extrapyramidal dysfunction as a frequent and clinically important feature in multiple genotypes.

Approximately one-third of patients exhibited at least one movement disorder, most commonly dystonia or ataxia. Distinct genotype-specific associations were evident: dystonia predominated in SPG4, SPG3A, and

AP4-HSP; parkinsonism was most frequent in SPG11; and ataxia was a hallmark of SPG15, SPG76, SPG7, SPG5a, and SPG46. These distributions suggest differential vulnerability of extrapyramidal circuits, potentially reflecting genotype-specific effects on basal ganglia-cerebellar-corticospinal networks rather than isolated corticospinal tract involvement. Such associations may refine diagnostic algorithms and inform targeted surveillance and therapeutic strategies, particularly as disease-modifying treatments emerge.[11-17]

Beyond diagnostic implications, the presence of movement disorders was associated with higher SPATAX, SPRS, SPRS spasticity, and MAS scores, suggesting greater overall motor disability. However, as the severity of movement disorders was not quantified separately (ie, through specific clinical rating scales), these associations should be interpreted cautiously. Dystonia and parkinsonism showed associations with increased burden, independent of age or sex. Nonetheless, it remains possible that these findings partly reflect the natural disease progression of genotypes commonly associated with these manifestations, such as SPG11 and SPG4. Ataxia and tremor were paradoxically associated with lower functional scores. Given that spasticity is a major contributor to disability in HSP, the relative contribution of movement disorders versus spasticity to these functional measures cannot be clearly differentiated in this cohort. While existing CROMs like the SPRS capture complex phenotypes,[7] these results support the need for outcome measures and interventions tailored to symptom-specific presentations in both clinical practice and trial design.

Quality-of-life analyses further indicated a substantial burden associated with movement disorders, particularly dystonia, which was associated with significantly lower CPCHILD health-related quality-of-life scores independent of age and sex. This highlights the broader toll of extrapyramidal features beyond motor function on daily care, autonomy, and psychosocial well-being. Dystonia emerged as a clinically relevant symptom across functional and quality-of-life metrics, warranting early recognition and consideration of supportive and interventional strategies.

Age-stratified analyses revealed genotype-specific temporal patterns of movement disorders. In AP4-HSP, dystonia was present from early childhood, whereas ataxia, tremor, and parkinsonism were more frequently reported in early adulthood, consistent with the progressive evolution of AP4-HSP from a neurodevelopmental toward a neurodegenerative disorder.[18,19] In SPG4, dystonia emerged later, suggesting a distinct developmental trajectory. SPG11 and SPG15 exhibited more complex age-related profiles, with parkinsonism predominating in SPG11 and ataxia in SPG15. Taken together with the finding that most patients exhibited only one movement disorder at a time, the coexistence of spasticity with a specific movement disorder may direct diagnostic consideration toward specific genotypes.[4,9] Consistent with a prior meta-analysis[3] reporting later age at onset in HSP patients with movement disorders, our data also indicate that movement disorders appear more frequently in older age groups, consistent with a progressive emergence, though confirmation in longitudinal studies is needed. Recognizing such temporal dynamics may improve prognostic counseling, guide monitoring strategies, and help define optimal observation windows for natural history and therapeutic studies.[20]

Despite the strengths of this large, deeply phenotyped cohort, several limitations warrant consideration, and our findings must be interpreted with caution. Smaller sample sizes in several rarer subtypes, including SPG46, SPG76, and SPG5a, constrained statistical power, reduced estimate reliability, and limited detection of subtle genotype-specific effects. Observed associations in these groups should therefore be considered hypothesis-generating and require confirmation in larger cohorts. The cross-sectional design precludes within-patient longitudinal analysis, which may overestimate the frequency of later-onset movement disorders while underrepresenting early or transient manifestations. Overrepresentation of AP-4-related HSP, while enabling detailed subgroup analyses, introduces ascertainment bias that limits generalizability to other subtypes. Finally, relevant covariates such as treatment history, comorbidities such as neuropathy, and socioeconomic context were not systematically captured, and the absence of quantitative motor, neuroimaging, or electrophysiological data further limited mechanistic interpretation.

A further limitation is the lack of specific rating scales for the assessment of dystonia, ataxia, tremor, choreoathetosis, and parkinsonism. The use of dedicated scales could provide more granular and comparable data. Future prospective studies should incorporate such standardized instruments to enhance the precision and reproducibility of movement disorder phenotyping in HSP.

In summary, movement disorders are prevalent, phenotypically diverse, and clinically impactful features of childhood-onset HSP, with dystonia emerging as particularly burdensome across functional and quality-of-life domains. Future work should prioritize longitudinal, genotype-specific natural history studies, the development of sensitive outcome measures, and integration of quantitative motor and neuroimaging biomarkers to better delineate mechanisms. Such efforts will be essential for advancing symptom-specific interventions and optimizing patient-centered outcomes as targeted therapies for HSP continue to emerge.

**Author Roles:** (1) Research Project: A. Conception; B. Organization; C. Execution; (2) Statistical Analysis: A. Design; B. Execution; C. Review

and Critique; (3) Manuscript: A. Writing of the First Draft; B. Review and Critique.
D.R.: 1B, 1C, 2A, 2B, 2C, 3A, 3B.
J.E.A.: 1B, 1C, 2A, 2B, 2C, 3A, 3B.
K.Y.: 1B, 1C, 3B.
V.Q.: 1B, 1C, 3B.
L.S.: 1B, 1C, 3B.
K.B.: 1B, 1C, 3B.
Z.Z.: 1C, 3B.
H.A.P.A.: 1C, 3B.
J.R.: 1C, 3B.
N.B.: 1C, 3B.
S.C.: 1C, 3B.
A.T.: 1C, 3B.
M.K.: 1B, 1C, 3B.
F.M.S.: 1B, 1C, 3B.
C.G.-S.: 1B, 1C, 3B.
M.C.F.J.: 1B, 1C, 3B.
D.E.-F.: 1A, 1B, 2C, 3A, 3B.

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## Data Availability Statement

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

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