RESEARCH ARTICLE

KIF1A-Associated Neurological Disorder (KAND): Spectrum of Movement and Motor Disorders in a Cohort of 51 Patients

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ABSTRACT: Background: *KIF1A*-associated neurological disorder (KAND) encompasses a broad neurodevelopmental and neurodegenerative spectrum in which motor and movement disorders are common but incompletely defined.

Objectives: To systematically characterize motor and movement disorder phenotypes in KAND.

Methods: In this cross-sectional study, 51 individuals with likely-pathogenic or pathogenic *KIF1A* variants underwent standardized neurological assessment using the Spastic Paraplegia Rating Scale (SPRS), SPATAX disability scale, Gross Motor Function Classification System (GMFCS), and Modified Ashworth Scale.

Results: A history of global developmental delay was present in 96.1% and neonatal or infantile hypotonia in 62.7%. Progressive spasticity occurred in 72.5%, predominantly affecting the lower extremities and correlated with age ($\beta = 0.45$, odds ratio [OR] = 1.56, 95% confidence intervals [95% CI] 1.09–2.25, $P = 0.016$). Lower extremity weakness was nearly universal (88.2%) and inversely related with age ($\beta = -0.08$, OR = 0.93, 95% CI 0.86–0.99, $P = 0.032$). Independent walking was achieved by 62.7% at a median age of 24 months, but only 31.4% retained independent ambulation at last evaluation. Movement disorders included motor stereotypies (43.1%), ataxia (19.6%), action tremor (15.6%), and dystonia (3.9%). Cerebellar signs were present in 37.2%. The p.Glu253Lys variant was associated with the most severe phenotype.

Conclusions: KAND encompasses a continuous spectrum of motor and movement disorders that integrates developmental and neurodegenerative features. These findings inform clinical management, genetic counseling, and the design of future clinical trials. © 2026 International Parkinson and Movement Disorder Society.

Key Words: hereditary spastic paraplegia; KIF1A; neurodegeneration; neurodevelopmental disorder; spasticity

KIF1A encodes a neuron-specific kinesin motor protein essential for ATP-dependent anterograde axonal transport of synaptic vesicles, vesicle precursors, and associated cargo along microtubules.[1] Pathogenic variants in *KIF1A* cause a heterogeneous group of neurogenetic conditions collectively termed *KIF1A*-associated neurological disorders (KAND, OMIM 601255), encompassing a wide spectrum of neurodevelopmental and neurodegenerative

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phenotypes, including early-onset hypotonia and weakness, progressive spasticity, global developmental delay/intellectual disability, epilepsy, peripheral and autonomic neuropathy, optic nerve atrophy, microcephaly, and cerebral or cerebellar volume loss.[2] Clinical overlap of KAND with other neurological disorders increases the risk of patients being diagnosed as having cerebral palsy.[3] Although motor and movement disorders are prominent and often disabling, they have not been systematically characterized across the disease spectrum.

In this study, we comprehensively define the spectrum of motor and movement disorders in a cohort of children and young adults with KAND, evaluate genotype–phenotype relationships, and place these findings within the broader context of disease variability.

Methods

Study Design and Participants

This single-center, cross-sectional study (NCT04712812) enrolled individuals with confirmed pathogenic or likely pathogenic *KIF1A* variants (Boston Children's Hospital IRB P00046386). Written informed consent was obtained from all participants or their legal guardians. All individuals underwent comprehensive neurological evaluation by board-certified neurologists using standardized examination protocols. Variant pathogenicity was determined according to American College of Medical Genetics and Genomics (ACMG) criteria.

Clinical Assessments

Motor and functional assessments included the Spastic Paraplegia Rating Scale (SPRS),[4] SPATAX disability stage (SPATAX-DS),[5,6] Gross Motor Function Classification System (GMFCS), and the Modified Ashworth Scale (MAS). The SPRS spasticity subscore was derived from items 7–10. Developmental quotients and attainment of gross motor milestones were systematically documented. Longitudinal motor trajectories were evaluated in a subset of participants with available follow-up data.

Statistical Analysis

Statistical analyses were performed using R (version 4.5.1). Categorical variables are reported as frequencies and percentages. Continuous variables with normal distributions are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are reported as median with interquartile range (IQR) or range. Associations between paired variables were assessed using Spearman correlation coefficients. Age-dependent associations for binary outcomes were assessed using logistic regression with age as a continuous predictor; results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided $P \leq 0.05$ was considered statistically significant.

Results

Participant Characteristics and Molecular Spectrum

Fifty-one individuals with KAND were enrolled, including 26 females (51.0%) and 25 males (49.0%). The median age at clinical assessment was 6.6 years (IQR 4.4–17.1 years; range 0.8–44.0 years), with 42 pediatric participants (82.3%) and 9 adults (17.6%). Genetic analysis identified 29 unique *KIF1A* variants (NM_001244008.2), including 42 classified as pathogenic (82.3%) and 9 as likely pathogenic (17.6%). Three variants initially reported as variants of uncertain significance (c.575 T>G, c.609G>T, c.742G>A) were reclassified according to ACMG criteria (Table S1). Inheritance data were available for 26 families: 22 variants were de novo (84.6%), 4 were inherited (15.4%), and parental mosaicism was suspected in 2 cases. Most variants were missense variants (47/51, 92.2%) and localized to the KIF1A motor domain (Fig. 1). Two families included more than one affected individual.

Global and Motor Development

Global developmental delay was present in 49 of 51 individuals (96.1%), with initial developmental concerns recognized at a median age of 8 months (IQR 6–12 months; range 0–30 months). Loss of previously acquired skills was reported in 13 of 43 individuals (30.2%) and was not systematically associated with intercurrent infections or physiological stressors. Instead, it most often reflected a gradual decline in motor function, particularly worsening spasticity. Speech delay was common (45/51, 88.2%), with nine individuals (17.6%) remaining nonverbal. Dysarthria was present in 14 of 45 individuals (31.1%). Behavioral comorbidities included aggression (13/51, 25.5%) and self-injurious behavior (15/51, 29.4%).

Gross motor milestone acquisition varied widely across the cohort (Fig. 2A). Independent sitting was achieved by 45 of 49 individuals (91.8%) at a median age of 9 months (IQR 6–12 months; range 6–42 months). Crawling occurred in 37 of 42 individuals (88.1%) at a median age of 14 months (IQR 12–18 months; range 7–36 months), and unsupported standing in 28 of 45 (62.2%) at a median age of 23 months (IQR 18–24 months; range 12–30 months). Assisted walking was achieved by 43 of 47 individuals (91.5%) at a median age of 18 months (IQR 14–24 months; range 11–120 months), while independent walking occurred in 32 of 51 individuals (62.7%) at a median age of 24 months (IQR 16–30 months; range 12–60 months). At last evaluation, 16 individuals (31.4%) maintained independent ambulation, 7 (13.7%) walked independently without running ability, 18 (35.3%) required

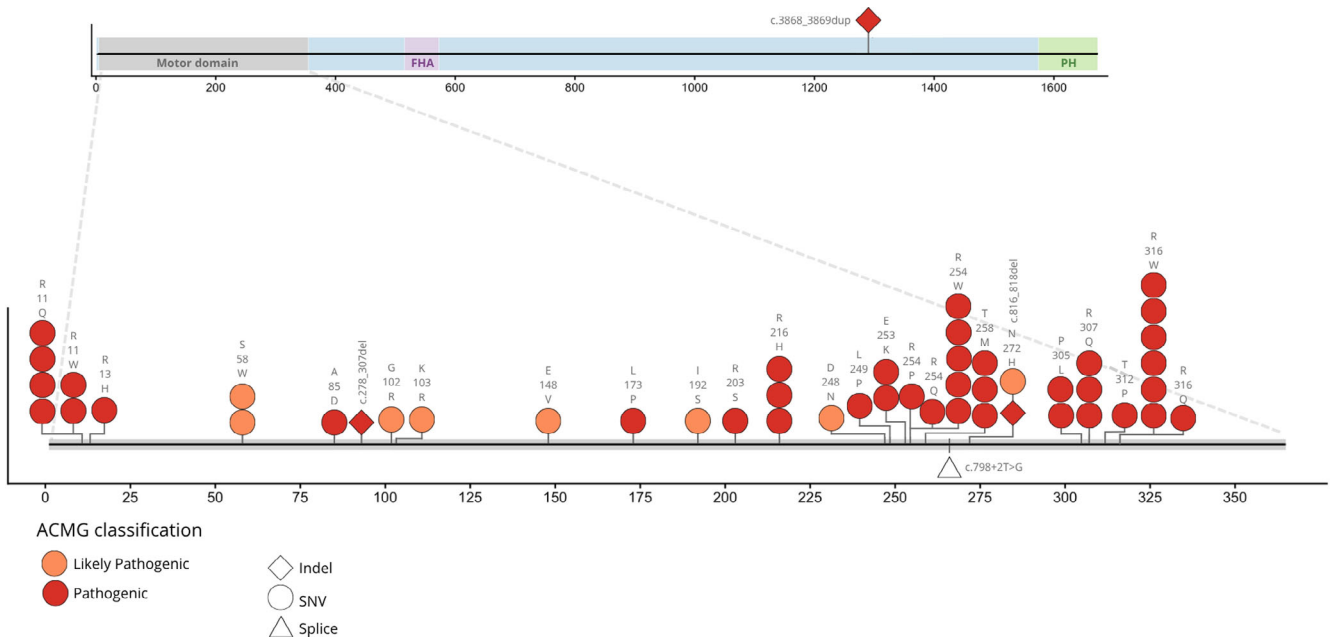


FIG. 1. KIF1A protein schematic and distribution of variants in the study cohort. Schematic representation of the KIF1A protein with variants identified in the cohort. Each symbol denotes a single individual, and variants are color-coded by American College of Medical Genetics and Genomics (ACMG) classification. The upper panel shows the full-length KIF1A protein; the lower panel provides an expanded view of the motor domain. Missense variants are shown as circles; splice-site variants and insertions/deletions (indels) are shown as triangles and diamonds, respectively. Protein domains are annotated according to UniProt (https://www.uniprot.org). [Color figure can be viewed at wileyonlinelibrary.com]

assistance with walking, and 10 (19.6%) were wheelchair dependent.

Spasticity and Motor Function

Neonatal or infantile hypotonia was reported in 32 of 51 individuals (62.7%) and usually moderate to severe, with evolution from hypotonia to lower limb hypertonia in 20 of 51 (39.2%) (Fig. 2B). Lower extremity spasticity was present in 37 of 51 individuals (72.5%) and demonstrated a significant positive association with age ($\beta = 0.45$, OR = 1.56, 95% CI 1.09–2.25, $P = 0.016$; Fig. 2B). Lower extremity weakness was nearly universal (45/51, 88.2%) and inversely correlated with age ($\beta = -0.08$, OR = 0.93, 95% CI 0.86–0.99, $P = 0.032$).

Spasticity severity, quantified using the MAS, showed consistently low scores in the upper limbs (median 0 across all age groups), whereas lower limb involvement was pronounced but varied by muscle group and age, with greatest severity in the gastrocnemius and soleus muscles (Fig. 2C). Overall disease burden assessed using the SPRS demonstrated substantial interindividual variability (median score 22; range 4–43) without correlation with age (Spearman $\rho = -0.0002$, $P = 0.999$; Fig. 2D).

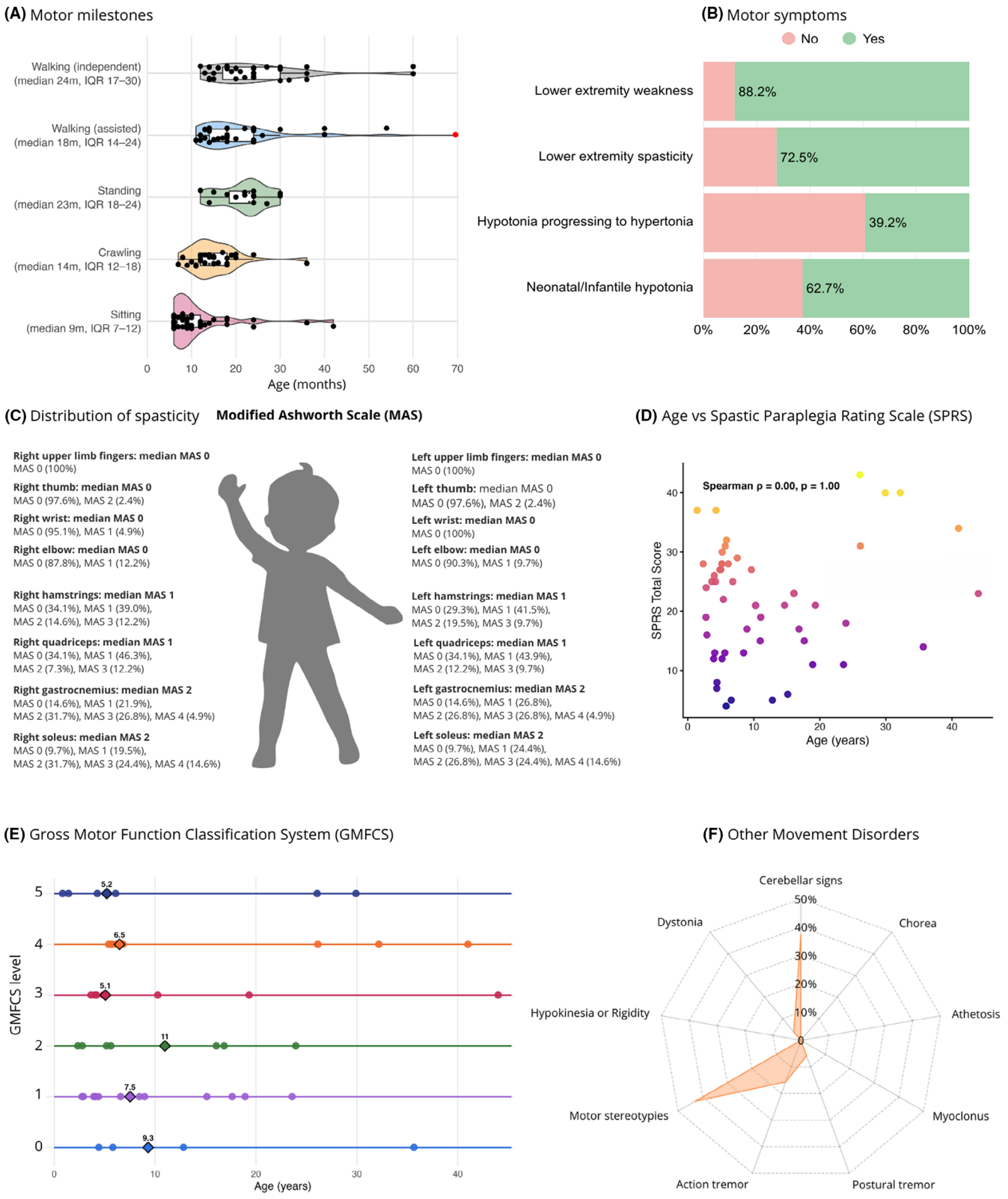
GMFCS scores showed a wide range of functional impairment (Fig. 2E), with a median level of 3. Distribution was as follows: GMFCS level 0 (7.8%), level 1 (25.5%), level 2 (17.6%), level 3 (19.6%), level 4 (15.7%), and level 5 (13.7%). The median SPATAX disability score was 3 (IQR 2–5; range 0–6). Eight individuals (16.3%) remained at stage 0 throughout follow-up. In progression analyses, 89.8% reached stage 1 (first neurological signs on examination) at a median age of 8 months (IQR 6–13). Stage 2 (limited but independent ambulation) was attained by 34.7% at a median age of 18 months (IQR 16–24), and 20.4% progressed to Stage 3 (limited unaided walking) at a median age of 30 months (IQR 29–42). No individual progressed to stage 4 (ambulation with a unilateral aid). Seventeen individuals (34.7%) never achieved independent ambulation and required bilateral support (stage 5; median age 24 months, IQR 20–53), while 11 (22.4%) were wheelchair dependent (stage 6; median age 24 months, IQR 23–222).

Videos 1–4 illustrate the broad motor disability spectrum. Specifically, Video 1 shows cases with early and severe hypotonia and weakness without spasticity; Video 2 demonstrates severe spastic paraparesis with marked functional impairment; Video 3 illustrates cases with spastic paraparesis with mild-to-moderate functional impairment and phenotypic variability; and finally Video 4 demonstrates cases with milder phenotypes and preserved independent ambulation.

Other Motor and Movement Disorders

Additional motor and movement disorders were clinically heterogeneous (Fig. 2F). Motor stereotypies were most common, observed in 22 of 51 individuals

(43.1%), frequently manifesting as hand-flapping or body-rocking behaviors. Cerebellar signs were present in 19 of 51 individuals (37.3%), with ataxia being the most frequent manifestation (10/51, 19.6%). Action tremor was observed in 8 individuals (15.6%), and postural tremor in 3 (5.9%). Other movement disorders



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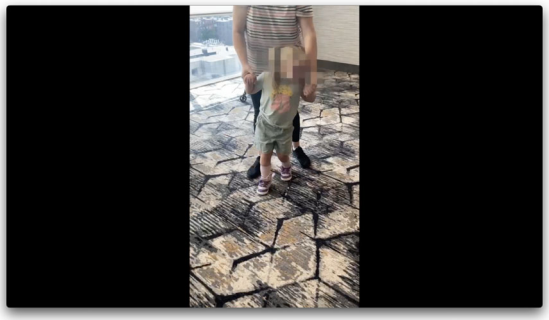


Video 1. Early and severe hypotonia and weakness without spasticity. The patient is a 6-year-old female with *KIF1A*-associated neurological disorder (KAND) (NM_001244008.2:c.920G>A, p.Arg307Gln) with severe lower limb weakness without spasticity, requiring assisted ambulation.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70420

Video 2. Severe spastic paraparesis with marked functional impairment. The first patient is a 4.8-year-old female with *KIF1A*-associated neurological disorder (KAND) (NM_001244008.2:c.946C>T, p.Arg316Trp) with severe lower limb weakness and foot dragging, requiring a walker and parental support for ambulation. The second patient is a 5-year-old male with KAND (NM_001244008.2:c.773C>T, p.Thr258Met) with lower limb spasticity and foot deformity, demonstrating forefoot ambulation with two-handed assistance.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70420

were uncommon, with dystonia identified in 2 individuals (3.9%). Chorea, myoclonus, athetosis, bradykinesia/hypokinesia, and rigidity were not observed.

Other Features

Visual impairment was observed in 31 of 48 individuals (64.6%), and optic nerve atrophy in 28 of 46 (60.9%). Seizures occurred in 16 of 51 individuals (31.4%). Clinical signs consistent with peripheral neuropathy were noted in 21 of 28 assessed individuals (75.0%). Nerve conduction studies were not systemically assessed.

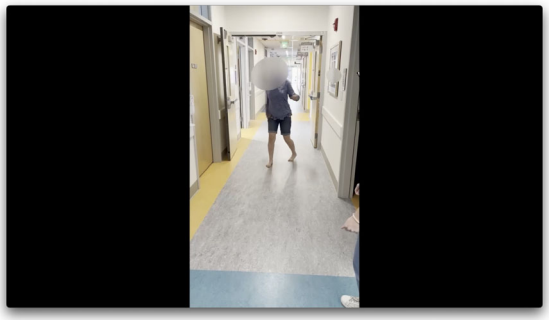
Genotype–Phenotype Correlations

Most individuals in the cohort harbored variants localized to the *KIF1A* motor domain. The substantial genetic heterogeneity, with 29 unique variants across 51 individuals, limited comprehensive genotype–phenotype analyses. One individual carrying a frameshift outside the motor domain (NM_001244008.2:c.3868_3869dup, p.Arg1291Serfs*24) exhibited the mildest phenotype in the cohort, characterized by mild developmental delay, independent ambulation achieved at 20 months, preserved running ability at 4 years of age, and absence of motor regression. In contrast, individuals harboring the p.Glu253Lys variant (NM_001244008.2:c.757G>A) demonstrated the most severe phenotype, including profound hypotonia and weakness (GMFCS level 5), respiratory insufficiency, and feeding difficulties from infancy. One individual in this group additionally exhibited corpus callosum and cingulate gyrus hypogenesis, cerebral and cerebellar atrophy, early-onset dystonia at 5 months of age, and early mortality at 10 months. Additional correlation analyses between in silico pathogenicity prediction scores and clinical severity measures were performed to better characterize potential subtle genotype–phenotype correlations; however, no significant associations were detected (Fig. S1).

Discussion

This cross-sectional study defines the spectrum of motor and movement disorders in KAND,

FIG. 2. Motor development, pyramidal symptoms, movement disorders, and disease severity in *KIF1A*-associated neurological disorder (KAND). (A) Violin plots showing ages at acquisition of gross motor milestones (sitting, crawling, standing, assisted walking, independent walking). Points represent individual participants. Median and interquartile range (IQR) are provided for each milestone. Participants achieving a milestone after 120 months are indicated by a red dot; violin width reflects the density of observations. (B) Prevalence of key motor features in the cohort (n = 51): neonatal/infantile hypotonia, hypotonia progressing to hypertonia, spasticity, and weakness. Bars indicate the proportion present (green) versus absent (pink), with percentages shown. (C) Association of age with spasticity (left) and weakness (right) (n = 51). Each point represents an individual (phenotype present/absent). Solid lines indicate fitted linear models; dotted lines show locally estimated scatterplot smoothing (LOESS) trends for visualization. Age correlated positively with spasticity (Spearman $\rho = 0.53$, $P < 0.001$) but not with weakness (Spearman $\rho = -0.21$, $P = 0.130$). (D) Spastic Paraplegia Rating Scale (SPRS) total score plotted against age (years). Points represent individuals, with color intensity reflecting SPRS total score; the solid line indicates the fitted linear model. No association between age and SPRS total score was observed (Spearman $\rho = 0.00$, $P = 1.00$). (E) Median Modified Ashworth Scale (MAS) scores across bilateral upper- and lower-limb muscle groups, displayed schematically. Values are shown as percentages by MAS category. Upper-limb tone was predominantly normal (median MAS 0), whereas increased tone was more frequent in the lower limbs, particularly gastrocnemius and soleus (median MAS 2). (F) Gross Motor Function Classification System (GMFCS) level plotted against age (years). Points represent individuals, color-coded by GMFCS level; horizontal lines indicate GMFCS categories. Diamonds denote the median age within each GMFCS level. No consistent age-dependent shift in GMFCS level was observed. (G) Radar plot summarizing the proportion of individuals with non-pyramidal movement disorder features (cerebellar signs, chorea, athetosis, myoclonus, postural tremor, action tremor, motor stereotypies, hypokinesia/rigidity, dystonia), expressed as percentages of the total cohort. [Color figure can be viewed at wileyonlinelibrary.com]



Video 3. Spastic paraparesis with mild-to-moderate functional impairment and phenotypic variability. The first patient is a 10-year-old female with *KIF1A*-associated neurological disorder (KAND) (NM_001244008.2:c.173C>G, p.Ser58Trp) with lower limb spasticity (GMFCS II); sibling of the following patient shown, sharing the same pathogenic variant due to parental mosaicism. The second patient is a 35-year-old female with KAND (NM_001244008.2:c.934A>C, p.Thr312Pro) with lower limb spasticity and clinical evidence of peripheral neuropathy. The third patient is a 11-year-old female with KAND (NM_001244008.2:c.760C>T, p.Arg254Trp) with lower limb spasticity and ataxia.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70420

demonstrating near-universal but highly heterogeneous motor involvement spanning pyramidal, cerebellar, peripheral, and behavioral domains, with dystonia observed in a small subset.

Although KAND can present as a relatively pure hereditary spastic paraplegia (HSP) (SPG30),[7-9] it more commonly manifests as a complex childhood-onset disorder with early hypotonia evolving into progressive spasticity, global developmental delay/intellectual disability, optic nerve atrophy, and peripheral neuropathy, often accompanied by epilepsy.[2,10-13] Compared with common autosomal dominant HSPs such as SPG4 and SPG3, individuals in our cohort showed earlier onset, greater functional burden, and a higher prevalence of cerebellar dysfunction, resembling complex spastic paraplegias such as AP-4–associated HSP.[14,15] Given that variants in *KIF1A* disrupt anterograde axonal transport of synaptic vesicles and organelles, the breadth of the KAND phenotype and associated motor disorders is not surprising and may prove even wider than currently recognized. Indeed, parkinsonian features have recently been described in a father–son pair harboring *KIF1A* variants, further expanding the recognized phenotypic spectrum.[16]

Video 4. Mild phenotypes with independent ambulation. The first patient is an 18-year-old female with *KIF1A*-associated neurological disorder (KAND) (NM_001244008.3:c.773C>T, p.Thr258Met) with independent ambulation, lower limb spasticity, pyramidal signs (hyperreflexia, clonus, Babinski sign), and pes cavus. The second patient is a 4.3-year-old female with KAND (NM_001244008.2:c.816_818del, p.Asn272del) with independent, unlimited ambulation, including walking and running (GMFCS 0).
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70420

A biphasic motor trajectory with early and significant hypotonia evolving into lower extremity spasticity emerged as a recognizable signature of KAND, though this pattern is not unique to KAND and may be observed across other childhood-onset neurogenetic disorders, including early-onset and complex forms of HSP. Consistent with this pattern, nearly two-thirds of individuals presented with neonatal or infantile hypotonia, while progressive spasticity became increasingly prominent with age. Spasticity correlated positively with age and predominantly affected the lower extremities in an ascending fashion, consistent with a length-dependent corticospinal axonopathy. In contrast, overall disease burden measured by the SPRS showed marked interindividual variability without clear age dependence, likely reflecting molecular heterogeneity and divergent disease trajectories. The utility of the SPRS in KAND is inherently limited as it is not validated in young children[17,18] and does not account for developmental trajectory or multisystem comorbidities, such as intellectual disability, visual impairment, behavioral dysregulation, and epilepsy typical of KAND, underscoring the need for disease-specific outcome measures. Longitudinal studies stratified by variant domain and functional impact will be required to clarify progression patterns.

Weakness was nearly universal and frequently imposed greater functional limitation than spasticity alone, particularly in younger individuals. Functional disability emerged early, often during critical windows of motor development, and largely reflected failure to achieve age-appropriate milestones rather than frank regression, although skill loss occurred in a subset. This pattern suggests preferential vulnerability of motor functions requiring long axonal projections, refined corticospinal control, and complex neural integration. The 6–18-month developmental window, when concerns were most often first recognized, represents a critical period of motor circuit maturation. While early supportive interventions may optimize function, durable improvement remains limited in the absence of disease-modifying therapy.

Beyond pyramidal dysfunction, KAND commonly exhibited a mixed motor phenotype. Motor stereotypies, ataxia, tremor, and dystonia, were present. Non-

motor features such as visual impairment and cognitive dysfunction further compounded motor disability and independence, while peripheral neuropathy appeared increasingly relevant with age.

Although genetic heterogeneity limited comprehensive genotype–phenotype analyses, pathogenic variants clustered within the kinesin motor domain, particularly regions critical for ATP binding and microtubule interaction. The p.Glu253Lys variant consistently produced the most severe phenotypes in our cohort. This likely reflects its dominant-negative mechanism: the glutamate-to-lysine substitution causes a charge reversal at a highly conserved residue critical for motor domain architecture, severely impairing ATPase activity and microtubule-based motility.[19,20] In vitro assays using heterodimeric motors composed of wild-type and p.Glu253Lys KIF1A have demonstrated that the mutant protein actively interferes with wild-type motor function through dysfunctional heterodimerization, effectively reducing functional motor capacity below 50%.[20] This stands in contrast to simple haploinsufficiency and explains the consistently severe early-onset phenotype observed across multiple unrelated carriers of this variant.[21]

Our findings reinforce growing evidence that KAND is best conceptualized as a continuous phenotypic spectrum rather than discrete clinical subtypes. Extensive overlap across historically defined categories limits the utility of rigid classification schemes. The supplementary video material illustrates this continuum across ages and severity levels and underscores the need for comprehensive, multidisciplinary evaluation of all individuals with KAND. This spectrum-based framework has direct implications for prognosis, genetic counseling, and clinical trial design.

Several limitations warrant consideration: The cross-sectional design precludes inference regarding individual disease trajectories, and peripheral neuropathy was not uniformly assessed by electrophysiology. Genetic heterogeneity further limited variant-specific analyses; moreover, 50/51 patients in our cohort carried mutations in the motor domain, which may have further constrained genotype–phenotype correlation analyses. Furthermore, in the four individuals carrying inherited variants, systematic neurological evaluation of carrier parents was not performed; subtle clinical signs in heterozygous carriers therefore cannot be excluded. Longitudinal follow-up integrating quantitative motor assessments, digital biomarkers, and imaging will be essential to define progression rates and therapeutic windows.

In summary, KAND is characterized by a broad and continuous motor phenotype shaped by early neurodevelopmental disruption and progressive neurodegeneration. Spasticity and weakness emerge as drivers of disability, accompanied by frequent additional movement disorders. By defining age-related patterns, functional consequences, and domain-specific genetic associations, this study provides a clinically grounded framework for patient stratification and outcome measure selection, establishing a foundation for longitudinal natural history studies and emerging therapeutic trials.[22]

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

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