

RESEARCH ARTICLE

The Movement Disorder Spectrum of *ATP1A3*-Related Disorders: Cross-Sectional Analysis and Video Archive of 88 Patients

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ABSTRACT: Background: *ATP1A3*-related disorders are characterized by genetic heterogeneity and phenotypic pleiotropy, posing significant challenges for classification. Although canonical phenotypes have traditionally guided decision-making, increasing evidence highlights their limitations in capturing the clinical complexity.

Objective: The aims of this study were to characterize movement disorders, paroxysmal features, and genotype-phenotype relationships; to build a curated video archive; and to assess alignment with canonical phenotypes.

Methods: This is an observational study of 88 individuals with pathogenic or likely pathogenic variants in *ATP1A3* who were evaluated in specialized movement disorders programs.

Results: Age at last clinical follow-up ranged from 0.1 to 63 years; 80.7% were pediatric patients. Chronic movement disorders were present in 68 of 88 individuals (75%); most had two or more coexisting phenomenologies. Dystonia was most common (47/88, 53%), followed by spasticity (28/88, 32%) and ataxia (28/92, 32%). Paroxysmal events occurred in 78 of 88 (88%) patients, including dystonic spells (45/78, 58%), abnormal eye movements (37/78, 50%), and hemiplegic episodes (37/78, 47%). Common comorbidities included epilepsy (21/88, 24%), cognitive impairment (41/88, 47%), and neuropsychiatric disorders. Only 22 of 88 (25%) fulfilled criteria for a single canonical phenotype; 28 of 88 (32%) met canonical criteria plus additional features, 18 of 88 (20%) satisfied criteria for

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≥2 canonical phenotypes, and 20 of 88 (23%) fit no canonical category. We identified 43 distinct *ATP1A3* variants; recurrent variants (eg, p.Arg756His, p.Asp801Asn, p.Glu818Lys) showed variable expressivity across categories.

Conclusions: The extensive clinical heterogeneity in *ATP1A3*-related disorders challenges rigid phenotypic classifications. The predominance of patients with overlapping or atypical features supports a shift toward

flexible, symptom-based clinical approaches rather than strict reliance on canonical phenotype recognition. © 2026 International Parkinson and Movement Disorder Society.

Key Words: *ATP1A3*; genotype-phenotype correlation; clinical heterogeneity; alternating hemiplegia of childhood; dystonia

ATP1A3 encodes the $\alpha 3$ subunit of the neuronal sodium-potassium ATPase, a membrane protein essential for maintaining neuronal excitability and synaptic transmission.^{1,2} Disorders that are associated with pathogenic variants in *ATP1A3* comprise a heterogeneous spectrum of neurological conditions, most prominently characterized by movement disorders, paroxysmal neurological episodes, and neurodevelopmental impairment. Epilepsy is a salient feature in a subset of affected individuals, placing *ATP1A3*-related disorders within the broader spectrum of epilepsy-dyskinesia syndromes.³ Notably, *ATP1A3*-related disorders exhibit striking phenotypic pleiotropy, which substantially complicates clinical recognition and diagnostic evaluation.^{4–6} Historically, four core phenotypes have been defined: alternating hemiplegia of childhood (AHC); cerebellar ataxia, areflexia, pes cavus, optic atrophy, sensorineural hearing loss (CAPOS) syndrome⁷; rapid-onset dystonia-parkinsonism (RDP)⁸; and relapsing encephalopathy with cerebellar ataxia (RECA)/fever-induced paroxysmal weakness and encephalopathy (FIPWE)^{9–11} (Supporting Information Table S1). However, additional phenotypes continue to emerge, including developmental and epileptic encephalopathy (DEE),¹² childhood-onset schizophrenia (COS),^{13,14} and D-DEMØ syndrome, which is characterized by dystonia, facial dysmorphism, encephalopathy, severe developmental delay, magnetic resonance imaging (MRI) abnormalities, and no hemiplegia,¹⁵ further expanding the clinical spectrum.

To date, more than 160 variants in *ATP1A3* have been reported, but genotype-phenotype correlations remain incompletely understood.^{5,16,17} Growing evidence questions the utility of rigid phenotypic subdivisions,¹⁸ with canonical entities better conceptualized as anchoring points along a clinical continuum rather than discrete disorders.¹⁹

In this article, we describe 88 patients with *ATP1A3*-related disorders who were evaluated in 12 movement disorder programs. We provide a comprehensive clinical and genetic characterization, supported by a curated video archive, and highlight the extent to which these patients diverge from canonical classifications.

Patients and Methods

Detailed methods are provided in Supporting Information Data S1. This multicenter, cross-sectional study

was conducted under institutional review board approval at participating sites, with written informed consent obtained from all participants or legal guardians. Individuals were eligible if they carried a pathogenic or likely pathogenic *ATP1A3* variant and exhibited at least one chronic or paroxysmal movement disorder; episodic weakness was included as a qualifying feature but was analyzed separately from dystonic episodes. Patients were categorized into four phenotype groups: Canonical, Canonical+, Multiple Canonical, and No Fit, based on alignment with established *ATP1A3*-related syndromes (Supporting Information Table S2). Available video recordings were independently reviewed by blinded movement disorder specialists with consensus adjudication. Descriptive and inferential statistics were applied using appropriate nonparametric and categorical tests, with significance set at $P < 0.05$.

Data Sharing

Anonymized data supporting the findings of this study are available from the corresponding authors on reasonable request.

Results

Demographics and Genetic Features

We collected clinical and genetic data from 88 patients with *ATP1A3*-related disorder across 12 specialized centers (8 pediatric, 4 adult) in North America, Europe, and China, representing diverse ethnic backgrounds. Of these, 85 were not previously reported. The cohort showed a slight female predominance ($n = 47$, 53%). Age at symptom onset ranged from the first days of life to late adolescence (range: 0–21 years; mean: 3.3 years). Age at last clinical follow-up ranged from 0.1 to 63 years (mean: 11.5 years). Of 88 patients, 71 (80.7%) were pediatric (<18 years old). Forty-three distinct pathogenic or likely pathogenic *ATP1A3* variants (NM_152296) were identified, including 19 novel variants. Two variants initially classified as variants of uncertain significance (c.1895A>G, c.388_390delGTG) were reclassified as pathogenic based on phenotypic correlation (Supporting Information Table S3). Demographic

and genetic features are summarized in Table 1 and Figure 1.

Clinical Features

Movement and Motor Disorders

Chronic movement disorders were present in 66 of 88 patients (75%). Most (51/66, 77%) exhibited complex phenotypes with two or more coexisting movement or motor disorders. Dystonia was the most prevalent manifestation (47/88, 53%), followed by spasticity (28/88, 32%), ataxia (28/88, 32%), bradykinesia/hypokinesia (26/88, 30%), and rigidity (22/88, 25%). Eighteen patients (20%) exhibited parkinsonian features, defined in this article as bradykinesia in combination with rigidity; seven of these patients also exhibited tremor, although tremor quality (rest vs. action) was not systematically

assessed. Additional features included chorea (21/88, 24%), tremor (15/88, 17%), myoclonus (10/88, 11%), and stereotypies (10/88, 11%) (Fig. 2). Functional motor assessment showed a median Gross Motor Function Classification System (GMFCS) score of 3 (range: 1–5). GMFCS scores were available for 78 of 88 patients: GMFCS 1 (18/78, 23%), GMFCS 2 (16/78, 20.5%), GMFCS 3 (17/78, 22%), GMFCS 4 (14/78, 18%), and GMFCS 5 (13/78, 16.7%).

Paroxysmal Episodes

Paroxysmal episodes were documented in 78 patients (88%), of these 52% (41/78) were triggered by fever. Dystonic episodes were the most frequent manifestation, occurring in 45/78 patients (58%), followed by abnormal eye movements (39/78, 50%). Hemiplegic episodes were documented in 37 of 78 patients (47%), quadriplegic episodes in 24 of 78 patients (31%), autonomic episodes (encompassing transient abnormalities of sweating, thermoregulation, heart rate and blood pressure, pupillary reactivity, skin color, and gastrointestinal function) in 11 of 78 (14%), apneic episodes in 6 of 78 (7.7%), and paroxysmal kinesigenic dyskinesia in 2 of 78 (2.6%).

Epilepsy

Epilepsy was present in 21 of 88 patients (24%), with 12 of 88 (14%) experiencing status epilepticus. Ten patients met criteria for DEE. Patients required an average of 1.2 antiseizure medications (range 0–7). Seizures were fully controlled in 9 of 21 (43%) and partially controlled in 12 of 21 (57%).

Cognitive and Neuropsychiatric Symptoms

Cognitive impairment was a consistent finding across the cohort, with 41 of 88 patients (47%) presenting with global developmental delay (GDD) and/or intellectual disability. In addition, 26 of 88 patients (29.5%) experienced cognitive decline over time. Formal neuropsychiatric diagnoses further included attention-deficit/hyperactivity disorder (ADHD) (7/88, 8%) and autism spectrum disorder (ASD) (8/88, 9%). Behavioral manifestations covered a broad spectrum, including impulsivity (10/88, 11%), aggressive behavior (8/88, 9%), hyperactivity (7/88, 8%), anxiety (6/88, 7%), depression (4/88, 4.5%), and self-injurious behavior (3/88, 3%).

Additional Neurological Features

Axial hypotonia was common (44/88, 50%), followed by dysarthria (43/88, 49%) and dysphagia (42/88, 48%). Loss of deep tendon reflexes in the lower extremities affected 20 of 88 patients (23%), while pyramidal signs were documented in 17 of 88 (19%). Less frequent manifestations included neuropathy

TABLE 1 Demographic and genetic information

Characteristics	n (%) or mean (range; median)
Sex	
Male	41 (47%)
Female	47 (53%)
Race	
Caucasian	35 (40%)
Asian	39 (44%)
Hispanic	7 (8%)
African	7 (8%)
Age (yr)	
Symptom onset	3.3 (0–21; 1.3)
Movement disorder onset	4.1 (0–21; 2.25)
Molecular diagnosis	8 (0–54; 5)
Last clinical follow-up	11.5 (0.1–63; 8.8)
Inheritance pattern	
De novo	48 (55%)
Inherited	17 (19%)
Unknown	23 (26%)
ATP1A3 variant type	
Missense	81 (92%)
In-frame deletion	2 (2.3%)
In-frame insertion	1 (1.1%)
Splice site	2 (2.3%)
Nonsense (stop gain)	1 (1.1%)
Stop loss	1 (1.1%)

Note: All categorical variables calculated from total cohort (n = 88).

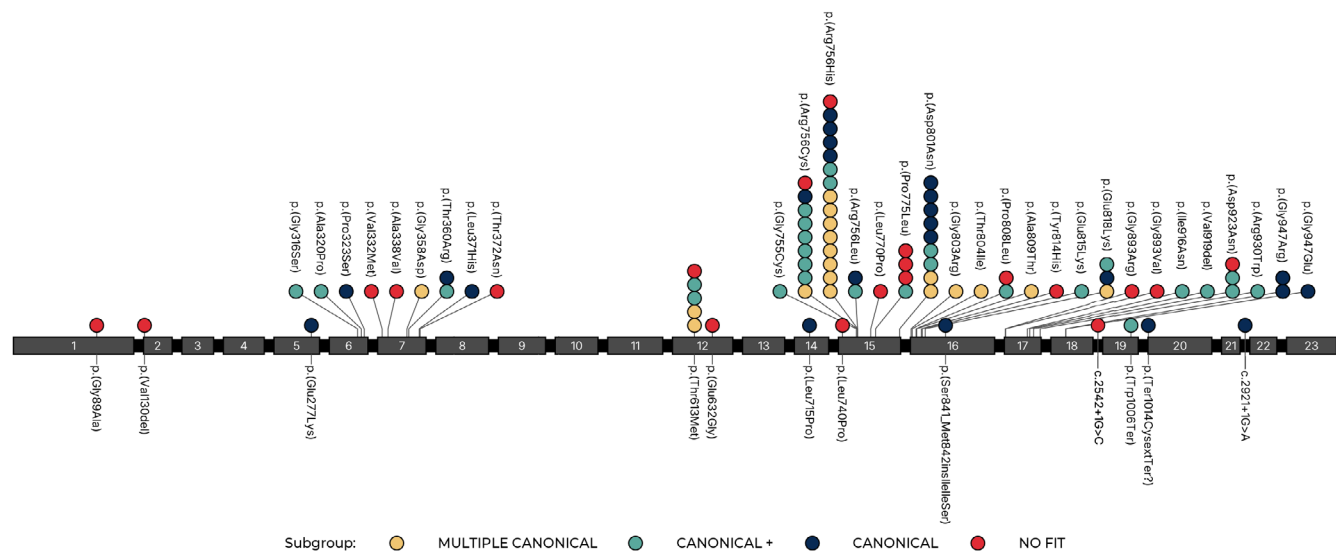


FIG. 1. Distribution of variants across the *ATP1A3* gene in our 88-patient cohort. Schematic of the *ATP1A3* gene structure with 23 exons and 47 distinct variants annotated along the gene. Each dot represents an individual patient, with dots color-coded according to clinical phenotype: Canonical+, Multiple Canonical, and No Fit. Phenotypic heterogeneity is evident, because patients harboring identical variants may present with different clinical phenotypes, indicated by differently colored dots at the same variant position. [Color figure can be viewed at wileyonlinelibrary.com]

(5/88, 6%), pes cavus (5/88, 6%), hearing loss (3/88, 3%), and optic nerve atrophy (2/88, 2%).

Neuroimaging

Brain MRI studies were available in 78 patients, with abnormal findings reported in 34 of 78 (44%). Cerebral atrophy represented the most common finding, with mild global atrophy in 7 of 78 cases (9%) and moderate global atrophy in 5 of 78 cases (6%). Hippocampal sclerosis was documented in 5 of 78 patients (6%) who all presented with epilepsy, and cerebellar atrophy was found in 4 of 78 (5%). Other findings included polymicrogyria (2/78, 2.5%), focal cortical dysplasia (1/78, 1.3%), ventriculomegaly (2/78, 2.5%), and nonspecific periventricular white matter signal changes (2/78, 2.5%).

Flunarizine Treatment

Flunarizine was administered to 39 of 88 patients (44%), all of whom had paroxysmal symptoms, most in the context of AHC. Twenty-eight patients (28/39, 72%) reported partial or complete benefit, nine (9/39, 23%) had no response, and two (2/39, 5%) discontinued treatment because of negative side effects. Only one patient with isolated chronic movement disorder received a trial of flunarizine, without benefit.

Phenotypic Classification

Among the 88 patients, only 22 (25%) fulfilled criteria for a single canonical phenotype, whereas 66 (75%) had overlapping or atypical features. We categorized patients into four groups as detailed in Table 2. A video archive (Videos 1–32) illustrating the

spectrum of movement disorders is summarized in Supporting Information Table S4.

Canonical

Of the 22 patients who fulfilled diagnostic criteria for well-defined *ATP1A3*-associated phenotype, AHC represented the largest subgroup (12/22, 54.5%), characterized by paroxysmal episodes of hemiplegia alternating between sides and/or quadriplegia. These were often accompanied by dystonic episodes occurring independently or simultaneously with hemiplegic attacks, paroxysmal abnormal eye movements, particularly nystagmus, and were also associated with developmental delay or intellectual disability (Videos 1–6). The most frequent reported variants were p.Asp801Asn ($n = 5$) and p.Gly947Arg ($n = 3$). Three patients (13.6%) presented with RDP, featuring acute onset of dystonia and parkinsonism (Video 8), each harboring different genetic variants. Six patients (27.3%) had RECA/FIPWE, manifesting with fever-triggered episodic weakness (Video 9) and encephalopathy, predominantly carrying p.Arg756His or p.Arg756Cys variants. One patient presented with CAPOS syndrome, associated with the characteristic p.Glu818Lys variant.

Canonical +

Twenty-eight patients (28/88, 32%) fulfilled diagnostic criteria for a recognized phenotype but exhibited additional clinical features not typically associated with their primary classification. This group demonstrated the greatest phenotypic diversity, with 9 of 28 patients presenting with RDP + (32.1%), 8 of 28 AHC+ (28.6%), 8 of 28 RECA/FIPWE+ (28.6%), 2 of 28 CAPOS+ (7.1%), and 1 of

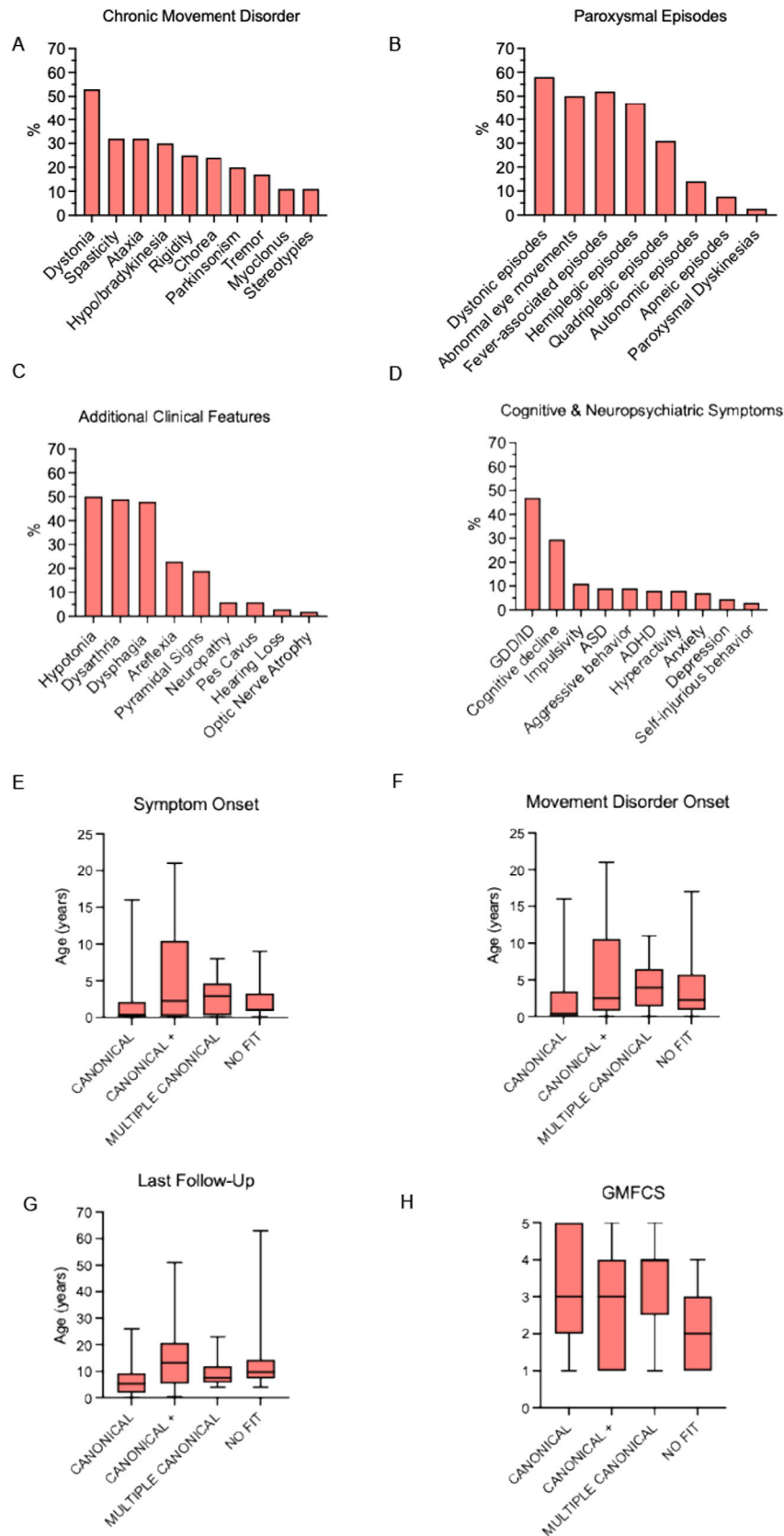


FIG. 2. (A–D) Summary of the prevalence of chronic movement disorders, paroxysmal symptoms and episodes, cognitive and neuropsychiatric manifestations, and additional clinical features. Data are presented as percentages of the entire cohort. **(E–H)** Boxplots showing age at symptom onset, age at movement disorder onset, age at last neurology follow-up, and Gross Motor Function Classification System (GMFCS) scores across phenotypic subgroups (Canonical, Canonical+, Multiple Canonical, and No Fit). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Patient classification into four groups based on adherence to established ATP1A3-related phenotypes

Group	Description	Phenotype	n	Percentage (within group)	Percentage (total cohort N = 88)
Canonical (n = 22; 25%)	Patients who met established diagnostic criteria for well-defined ATP1A3-related phenotypes	AHC	12	54.5%	13.6%
		RECA/FIPWE	6	27.3%	6.8%
		RDP	3	13.6%	3.4%
		CAPOS	1	4.5%	1.1%
Canonical+ (n = 28; 32%)	Patients who met diagnostic criteria for one established ATP1A3-related phenotype but with additional clinical features not typically associated with their primary classification	RDP+	9	32.1%	10.2%
		AHC+	8	28.6%	9%
		RECA/FIPWE+	8	28.6%	9%
		CAPOS+	2	7.1%	2.2%
		DEE+	1	3.6%	1.1%
Multiple Canonical (n = 18; 20%)	Patients who simultaneously met diagnostic criteria for two or more established ATP1A3-related phenotypes	RECA/FIPWE + RDP	9	50%	10.2%
		AHC + DEE	4	22.2%	4.5%
		RDP + DEE	1	5.56%	1.1%
		RDP + AHC	1	5.56%	1.1%
		RECA/FIPWE + AHC	1	5.56%	1.1%
		CAPOS + RECA/FIPWE	1	5.56%	1.1%
No Fit (n = 20; 23%)	Patients who did not satisfy diagnostic criteria for any established ATP1A3-related phenotype	Isolated hemiplegic episodes	5	25%	5.7%
		Mixed movement disorders	15	75%	17%

Abbreviations: AHC, alternating hemiplegia of childhood; RECA/FIPWE, relapsing encephalopathy with cerebellar ataxia/fever-induced paroxysmal weakness and encephalopathy; RDP, rapid-onset dystonia-parkinsonism; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss; DEE, developmental epileptic encephalopathy.

28 DEE+ (3.6%). Additional features varied considerably, often representing cross-phenotypic manifestations, for example, hemiplegic episodes in patients with RDP (Video 17), severe chronic dystonia in patients with AHC, and parkinsonian symptoms in patients with RECA/FIPWE. Fever-related episodes were also documented in individual RDP (Video 14) and patients with AHC. Notably, some patients with AHC developed severe refractory epilepsy. Complex motor disorder combinations were also exemplified by RDP+ cases that presented with myoclonus, spasticity, and motor stereotypies.

Multiple Canonical

Eighteen patients (18/88, 20%) met criteria for multiple established phenotypes. The most frequent combination was RECA/FIPWE + RDP (9/18, 50%),

followed by AHC + DEE (4/18, 22.2%). Other combinations included CAPOS + RECA/FIPWE and AHC + CAPOS. The RECA/FIPWE + RDP combination (Video 21) was predominantly associated with the p-Arg756His variant (7/9 patients, 78%). The AHC + DEE combination occurred in patients who had severe epileptic encephalopathy from birth while also meeting AHC diagnostic criteria. Notably, one of these patients had bilateral polymicrogyria. Two of these patients carried the classic AHC variant p.Asp801Asn. Some patients demonstrated particularly complex presentations transcending dual classifications. One patient simultaneously met criteria for RECA/FIPWE and AHC while additionally presenting with myoclonus and dystonia and pes cavus (Videos 22 and 23). Another patient fulfilled diagnostic criteria for both AHC and CAPOS with concomitant myoclonus and dystonia (Video 24).

Patient 65

7 year old female with AHC (canonical)
ATP1A3: c.2840G>A; p.Gly947Glu

Video 1. 7-year-old girl with paroxysmal episodes characterized by right arm monoplegia.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 91

2 year old Female with AHC (canonical)
ATP1A3: c.2839G>C ; p.Gly947Arg

Video 4. 2-year-old girl with paroxysmal episodes characterized by cervical dystonia and spontaneous horizontal nystagmus.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 59

6 month old female with AHC (canonical)
ATP1A3: c.2144T>C; p.Leu715Pro

Video 2. 6-month-old girl with paroxysmal episodes characterized by of generalized weakness.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 2

1 year old Female with AHC (canonical)
ATP1A3: c.1079C>G; p.Thr360Arg

Video 5. 1-year-old girl with paroxysmal episodes of generalized weakness and horizontal nystagmus.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 3

8 month old Male with AHC (canonical)
ATP1A3: c.1112T>A; p.Leu371His

Video 3. 8-month-old boy with paroxysmal episodes characterized by generalized dystonia and abnormal rapid horizontal eye movements.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 91

2 year old Female with AHC (canonical)
ATP1A3: c.2839G>C ; p.Gly947Arg

Video 6. 2-year-old girl with paroxysmal episodes characterized by hemiplegia.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

No Fit Category

Twenty patients (20/88, 23%) did not satisfy diagnostic criteria for any established phenotype. The most common presentation involved isolated episodes of

hemiplegia (5/20, 25%). These patients exhibited hemiplegic episodes but lacked sufficient additional criteria such as early onset before 18 months, different paroxysmal episodes, or abnormal neurological development



Video 7. 5-year-old boy with broad-based ataxic gait. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>



Video 8. 8-year-old girl, wheelchair-dependent, with generalized dystonia exacerbated by voluntary movement. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>



Video 9. 10-month-old boy with fever-induced paroxysmal episodes characterized by encephalopathy, generalized weakness, intermittent right lower-limb dystonia, and right upper-limb tremor. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

required for AHC diagnosis. Other presentations included complex movement disorders characterized by dystonia, myoclonus, chorea, and abnormal eye movements that did not cluster into recognizable patterns, as well as milder presentations with isolated focal dystonia or atypical combinations such as mild ataxia with stereotypies (Video 29). Some patients presented with less common manifestations, including isolated jaw dystonia, paroxysmal dyskinesia, or predominant spasticity (Video 30). Additional representative videos are summarized in Supporting Information Table S4.

Comparative Analyses

Age at symptom onset showed trends toward earlier onset in the canonical group (mean 2.22 years) compared with canonical+ patients (4.98 years), although not statistically significant ($P = 0.07$). Movement disorder onset showed significant differences between groups ($H = 8.09$, $P = 0.04$), with canonical patients exhibiting earliest onset (mean: 2.43 years) compared with canonical+ patients (mean: 5.39 years). Age at last neurological follow-up showed canonical patients being significantly younger at 6.9 years compared with other groups ($P = 0.01$). Canonical+ patients had the oldest mean age at follow-up of 14.6 years. GMFCS scores differed significantly across molecular subgroups [Kruskal-Wallis $H(3) = 8.39$, $P = 0.04$], with the multiple canonical group showing the most severe motor impairment (median 4, IQR: 3–4) and the No Fit group demonstrating the best motor function (median 2, IQR: 1–3). Post hoc pairwise comparison confirmed a

Patient 9

4 year old Female with RECA/FIPWE (canonical)
ATP1A3: c.2267G>T; p.Arg756Leu

Video 10. 4-year-old girl with significant truncal and gait ataxia.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 67

21 year old Male with AHC+ (canonical+)
ATP1A3: c.2401G>A; p.Asp801Asn

Video 13. 21-year-old man, wheelchair-dependent, with severe generalized dystonia.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 4

10 month old Male with AHC+ (canonical+)
ATP1A3: c.2423C>T; p.Pro808Leu

Video 11. 4-month-old boy with paroxysmal episodes characterized by downbeat nystagmus.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 11

11 year old Female with RDP+ (canonical+)
ATP1A3: c.1838C>T; p.Thr613Met

Video 14. 11-year-old girl, wheelchair-dependent, with generalized dystonia.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 4

10 month old Male with AHC+ (canonical+)
ATP1A3: c.2423C>T; p.Pro808Leu

Video 12. 4-month-old boy with paroxysmal episodes of dystonic arm posturing, persistent tonic downgaze, and lateral nystagmus.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 54

50 year old Male with RDP+ (canonical+)
ATP1A3: c.2788C>T; p.Arg930Trp

Video 15. 50-year-old man with dystonia of the upper extremities, most prominent with posturing and action, and parkinsonism with decrement on rapid alternating movements and bradykinesia.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

significant difference between these two groups (adjusted $P = 0.03$).

Given that AHC represented the predominant canonical phenotype in our cohort, we performed a targeted comparison between canonical AHC patients ($n = 12$)

and those presenting with AHC+ and AHC + DEE phenotypes ($n = 12$). This comparison indicated that AHC+ patients demonstrated significantly higher rates

Patient 61

30 year old Male with RDP+ (canonical+)
ATP1A3: c.3017G>A; p.Trp1006Ter

Video 16. 30-year-old man with dystonic posturing of the upper limbs, exacerbated by posture, and subtle shoulder and upper-limb myoclonus.

Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 63

19 year old Male with RDP+ (canonical+)
ATP1A3: c.1838C>T; p.Thr613Met

Video 17. 19-year-old man with generalized dystonia and marked posturing of the left upper limb, trunk, and neck. Exam is also notable for dystonic tongue tremor.

Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 66

20 year old Male with RECA/FIPWE+ (canonical+)
ATP1A3: c.2267G>T; p.Arg756Leu

Video 18. 20-year-old man with generalized myoclonus exacerbated by voluntary movement, most prominent in the trunk, shoulders, and upper limbs.

Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

of chronic movement disorders compared with canonical AHC patients (66.7% vs. 25%, $\chi^2 = 4.20$, $P = 0.04$). However, both groups showed comparable

Patient 95

16 year old Male with CAPOS+ (canonical+)
ATP1A3: c.2747T>A; p.Ile916Asn

Video 19. 16-year-old boy with dystonic hand posturing, dysmetria, and intention tremor on finger-to-nose testing.

Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 95

16 year old Male with CAPOS+ (canonical+)
ATP1A3: c.2747T>A; p.Ile916Asn

Video 20. 16-year-old boy with ataxic gait, en bloc turning, and decreased arm swing.

Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 57

29 year old Male with RDP + (canonical +)
ATP1A3: c.2266C>T; p.Arg756Cys

Video 21. 29-year-old man, wheelchair-dependent, with severe generalized dystonia including facial involvement and severe dysarthria, exacerbated by voluntary movement or posture.

Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

GMFCS scores (Mann–Whitney U test, $P = 0.88$), and response rates to flunarizine therapy showed no significant difference ($P = 0.38$).

Patient 62

18 year old Male with RECA/FIPWE + AHC (multiple canonical)
ATP1A3: c.1838C>T; p.Thr613Met

Video 22. 18-year-old man with paroxysmal episodes of generalized weakness and a high-amplitude, low-frequency hand tremor. Severe anarthria was also noted on exam.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 97

3 year old Male with AHC+EIEE (multiple canonical)
ATP1A3: c.2425G>A; p.Ala809Thr

Video 25. 3-year-old boy with generalized dystonia and prominent dystonic tremors of the upper extremities.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 62

18 year old Male with RECA/FIPWE + AHC (multiple canonical)
ATP1A3: c.1838C>T; p.Thr613Met

Video 23. 18-year-old man with dystonia tremor when holding a posture and inducible hand myoclonus.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 69

4 year old Male with AHC+EIEE+PMG (multiple canonical)
ATP1A3: c.2401G>A; p.Asp801Asn

Video 26. 4-year-old boy with dystonic tremor during paroxysmal episodes.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 64

23 year old Female with AHC+CAPOS (multiple canonical)
ATP1A3: c.1073G>A; p.Gly358Asp

Video 24. 23-year-old woman with segmental myoclonus involving bilateral arms and shoulders.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 69

4 year old Male with AHC+EIEE+PMG (multiple canonical)
ATP1A3: c.2401G>A; p.Asp801Asn

Video 27. 4-year-old boy with persistent posturing of all extremities consistent with generalized dystonia.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Genotype–Phenotype Correlations

Our cohort encompassed 43 distinct pathogenic variants, with p.Arg756His (15/88, 17%), p.Asp801Asn (9/88, 10%), and p.Arg756Cys (8/88, 9%) representing

the most frequent variants (Fig. 1; Supporting Information Table S5). The variant p.Arg756His demonstrated marked phenotypic heterogeneity, ranging from canonical RECA/FIPWE presentations (n = 3)

Patient 60

60 year old Female with Isolated generalized dystonia (no fit)
ATP1A3: c.2309T>C; p.Leu770Pro

Video 28. 60-year-old woman with generalized dystonia, predominantly affecting the upper limbs, worse with action or posture. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 92

16 year old Female with Mixed Movement Disorder (no fit)
ATP1A3: c.2219T>C; p.Leu740Pro

Video 31. 16-year-old girl with generalized dystonia, prominent action-induced limb dystonia, and evidence of a marked sensory trick. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 68

7 year old Female with Mild Dystonia and Mild Ataxia (no fit)
ATP1A3: c.1895A>G; p.Glu632Gly

Video 29. 7-year-old girl with mild dystonic posturing of bilateral ankles. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 92

16 year old Female with Mixed Movement Disorder (no fit)
ATP1A3: c.2219T>C; p.Leu740Pro

Video 32. 16-year-old girl with asymmetric dystonic gait and prominent left-sided upper- and lower-limb dystonia, with evidence of a sensory trick. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

Patient 71

12 year old Male with Spasticity (no fit)
ATP1A3: c.2324C>T; p.Pro775Leu

Video 30. 12-year-old boy with spastic paraparesis and no extrapyramidal features. On exam, patient ambulates with posterior walker for longer distances. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mds.70227>

to complex multiphenotypic combinations. The majority of patients ($n = 7$) exhibited multiple canonical features (RECA/FIPWE + RDP), while RECA/

FIPWE+ ($n = 2$) patients presented with parkinsonian features and complex movement disorders. Individual cases also presented as canonical RDP or as No Fit with complex movement disorders. The AHC-associated variant p.Asp801Asn ($n = 9$) showed consistent AHC-spectrum presentations: five patients presented canonical AHC, while four demonstrated expanded phenotypes (AHC+ or AHC + DEE). All patients harboring p.Glu818Lys ($n = 3$) exhibited CAPOS-related features: one canonical CAPOS and two CAPOS+ presentations with additional bradykinesia or concurrent RECA/FIPWE features. The variant p.Arg756Cys ($n = 8$) exhibited one canonical RECA/FIPWE case, four RECA/FIPWE+ cases, two RDP+ cases, and one No Fit case with isolated paroxysmal dyskinesias and quadriplegic episodes. Patients carrying p.Thr613Met ($n = 5$) showed variable clinical presentations: two RDP+, one RECA/FIPWE+RDP combination, one RECA/FIPWE+AHC, and one No Fit with isolated hemiplegic episodes.

Paroxysmal Episodes Versus Chronic Movement Disorders

To further explore clinical patterns, we stratified patients into two groups: those with exclusively paroxysmal episodes (22/88, 25%) and those with chronic movement disorders either alone (10/88) or combined with paroxysmal episodes (56/88), analyzed together as a single chronic group (66/88, 75%). Key differences emerged between these groups: patients with paroxysmal-only presentations demonstrated significantly earlier disease onset at 1.14 years (median: 0.29, range: 0–7.3) compared with 4.07 years (median: 2.0, range: 0–21) in the chronic group ($P = 0.001$). At last neurological evaluation, patients with chronic movement disorders were significantly older, with a mean age of 13.43 years (median: 11.55, range: 0.3–63) compared with 5.93 years (median: 5.7, range: 0.1–16.2) in the paroxysmal-only group ($P < 0.001$). Despite this, functional motor impairment was comparable between groups. GMFCS showed no significant difference between groups, with median scores of 2.5 (IRQ:2–5) in the paroxysmal-only group versus 3.0 (IRQ:2–4) in the chronic group (Mann–Whitney U test, $P = 0.88$). Patients with chronic movement disorders showed significantly higher rates of dysarthria and areflexia ($P < 0.05$). Comprehensive comparisons of all neurodevelopmental, neuropsychiatric, and additional clinical features are presented in Supporting Information Table S6.

Discussion

ATP1A3-related disorder epitomizes phenotypic pleiotropy within the broader group of epilepsy-dyskinesia syndromes. Traditional phenotype labels such as AHC, RDP, and CAPOS have long guided diagnosis, but they capture only part of the spectrum, and robust genotype–phenotype correlations remain elusive.^{5,20} In this multicenter study of 88 patients, we characterize the breadth of movement and paroxysmal features and highlight the frequent overlap across canonical boundaries.

Chronic movement disorders were the predominant manifestation, underscoring their clinical burden.²¹ Most patients exhibited complex motor phenotypes with two or more coexisting disorders, most commonly dystonia, which spanned classic RDP-like forms to atypical variants such as isolated jaw dystonia. Beyond dystonia, myoclonus and stereotypies were notable yet likely underrecognized. Myoclonus extended beyond its prior association with RDP²² and CAPOS²³ to include RECA/FIPWE and isolated cases. Paroxysmal exercise-induced dyskinesia (PED), recently emphasized by LeDoux,²⁴ was also observed and is clinically important given its potential treatment considerations. One patient carried the p.Asp923Asn variant, previously

linked to PED,²⁵ while another harbored p.Arg756Cys, typically associated with RECA/FIPWE.²⁶ Spasticity, present in more than one-third of cases, deserves greater attention than it has received in prior reports.²⁷

Epilepsy was identified in 24% of patients, predominantly in AHC, with generally favorable treatment responses. The lower frequency compared with earlier reports^{28,29} likely reflects our inclusion criteria emphasizing movement disorders. Except in cases associated with polymicrogyria, the mechanisms of epileptogenesis in *ATP1A3*-related disorder remain incompletely defined,^{30,31} warranting dedicated study.

In our cohort, 72% of patients treated with flunarizine for paroxysmal symptoms reported partial or complete benefit. These findings support consideration of flunarizine therapy in all patients with pathogenic variants in *ATP1A3* presenting with paroxysmal episodes, irrespective of their specific phenotypic classification.

Traditional categorical classifications have guided clinical practice, but accumulating data demonstrate significant limitations in their ability to encompass the full clinical spectrum. Historically, AHC, RDP, and CAPOS dominated the literature, supported by structured diagnostic frameworks such as the Aicardi criteria^{8,32,33} and the 2014 International Task Force guidelines.³⁴ However, the utility of these rigid phenotypic subdivisions has been increasingly questioned in recent years, as evidenced by the progressive expansion of the phenotypic spectrum and the creation of numerous additional diagnostic categories, including D-DEMØ, COS, DEE, adult rapid-onset cerebellar ataxia,^{35,36} adult rapid-onset ataxia (ARA),³⁷ primarily neurodevelopmental phenotypes (ADHD, ASD, and GDD), and PED.¹⁸ This evolution has been accompanied by the progressive broadening of initial diagnostic criteria^{38,39} and the description of “classical” and “atypical” AHC phenotypes.⁴⁰

The systematic classification presented in this article highlights these limitations. Canonical+ patients met criteria for a traditional phenotype but displayed additional features that transcended boundaries, for example, RDP patients with hemiplegic episodes or AHC patients with chronic dystonia and bradykinesia. Patients with multiple canonical phenotypes presented with some of the most complex and severe symptoms. Overlap of RECA/FIPWE and RDP, most often with p.Arg756His, was common and associated with the highest GMFCS scores, reflecting more extensive neurological involvement. The No Fit group was particularly instructive, comprising patients with clear pathogenic variants but atypical or incomplete presentations. This group included isolated hemiplegic episodes, unusual movement disorder constellations, and novel features. As others have argued,^{5,19} such incomplete phenotypes suggest that canonical categories are best viewed as classifications of convenience rather than discrete syndromes.

Age-related patterns provided further insight. Canonical patients had the earliest onset of motor symptoms, whereas Canonical+ and No Fit groups were older at last follow-up. Patients with only paroxysmal presentations showed significantly earlier onset than those with chronic movement disorders. Whether these differences reflect disease progression from paroxysmal to chronic stages, or distinct clinical trajectories, remains unresolved.^{29,41,42} Notably, GMFCS level was similar across groups, suggesting comparable motor burden. In subgroup analyses, AHC+ patients showed higher rates of chronic movement disorders compared with classical AHC, although motor severity and flunarizine response were similar. These findings, although limited by sample size, underscore the value of differentiating between canonical and expanded phenotypes.

Our cohort demonstrated marked genotypic variability alongside broad phenotypic expression, with 47 distinct variants identified. Associations between recurrent variants and clinical features aligned partly with prior literature.^{5,38} The most reported associations include p.Asp801Asn and p.Glu815Lys for AHC, p.Thr613Met and p.Ile758Ser for RDP, p.Arg756His and p.Arg756Cys for RECA/FIPWE, and p.Glu818Lys for CAPOS.^{17,43,44} Although some variants in our cohort maintained relatively strong adherence to their established phenotypic associations, such as p.Asp801Asn and p.Glu818Lys, others demonstrated significant variability. Particularly, the p.Arg756His variant, traditionally

associated with RECA/FIPWE, showed remarkable phenotypic diversity. Most patients presented with expanded phenotypes combining RECA/FIPWE + RDP, while one patient unexpectedly presented with canonical RDP. Additional cases showed evolving parkinsonian features or complex movement disorders, suggesting that this variant may also be particularly associated with prominent movement disorder phenotypes. In a recent report, the variant p.Pro775Leu was associated with spasticity and intellectual disability, falling outside standard *ATP1A3*-related disorder phenotypes.⁴⁵ Similarly, our three patients with this variant were all classified as noncanonical; however, only one presented with this specific symptom combination, whereas the other two had dystonia as their primary manifestation. Notably, among the 19 novel variants identified in our cohort, all were observed in single patients, apart from p.Thr373Arg that was found in two patients, both presenting with AHC-related features (AHC and AHC+).

Our study has several limitations. First, referral to specialized movement disorder centers likely introduced ascertainment bias, potentially overestimating the prevalence of chronic movement disorders relative to paroxysmal-only presentations. Second, data collection relied on retrospective surveys, and although standardized forms were used, variable detail and completeness across sites may have affected consistency, particularly for neuropsychiatric and developmental features, which

Chronic Movement / Motor Disorder	Paroxysmal Episodes	Additional Symptoms
<input type="checkbox"/> Dystonia (Yellow, Green, Red)	<input type="checkbox"/> Hemiplegic episodes (Yellow)	<input type="checkbox"/> Global developmental delay (Yellow)
<input type="checkbox"/> Ataxia (Yellow, Blue, Red)	<input type="checkbox"/> Quadriplegic episodes (Yellow)	<input type="checkbox"/> Cognitive impairment (Yellow, Green, Blue, Red)
<input type="checkbox"/> Hypo/bradykinesia (Green)	<input type="checkbox"/> Dystonic episodes (Yellow)	<input type="checkbox"/> Neuropsychiatric symptoms
<input type="checkbox"/> Rigidity (Green)	<input type="checkbox"/> Other episodes of weakness (Blue, Red)	<input type="checkbox"/> Dysphagia (Green)
<input type="checkbox"/> Tremor (Green)	<input type="checkbox"/> Abnormal eye movements (Yellow, Blue, Red)	<input type="checkbox"/> Dysarthria (Yellow, Green, Red)
<input type="checkbox"/> Chorea / Athetosis (Yellow, Red)	<input type="checkbox"/> Autonomic episodes (Yellow)	<input type="checkbox"/> Hypotonia (Yellow, Blue, Red)
<input type="checkbox"/> Myoclonus	<input type="checkbox"/> Apneic episodes	<input type="checkbox"/> Pes cavus (Blue)
<input type="checkbox"/> Stereotypies	<input type="checkbox"/> Fever related episodic symptoms (Blue, Red)	<input type="checkbox"/> Areflexia (Blue)
<input type="checkbox"/> Spasticity	<input type="checkbox"/> Seizures (Yellow)	<input type="checkbox"/> Hearing loss (Blue)

Age at Onset:	Other Symptoms:	ATP1A3 Variant:
<input type="checkbox"/> < 18 months (Yellow)	<input type="text"/>	<input type="text"/>
<input type="checkbox"/> 6 months - 4 years (Blue)		
<input type="checkbox"/> 8 months - 10 years (Red)		
<input type="checkbox"/> 18 months - 60+ years (Green)		

■ AHC
 ■ RDP
 ■ CAPOS
 ■ RECA/FIPWE

FIG. 3. Clinical symptom checklist for *ATP1A3*-related disorders with color-coded phenotype associations. Each symptom is annotated with colored indicators denoting its typical association with established *ATP1A3*-related phenotypes, including alternating hemiplegia of childhood (AHC), rapid-onset dystonia-parkinsonism (RDP), cerebellar ataxia, areflexia, pes cavus, optic atrophy, sensorineural hearing loss (CAPOS) syndrome, and recurrent encephalopathy with cerebellar ataxia and fever-induced paroxysmal weakness/epilepsy (RECA/FIPWE). [Color figure can be viewed at wileyonlinelibrary.com]]

are major contributors to disease burden. Third, the survey prioritized core movement disorder phenomenology; systematic data on additional therapeutic interventions (including oxygen therapy, cannabidiol, ketogenic diet), flunarizine dosing regimens, and cardiac/autonomic symptoms were not collected across all centers. Fourth, although video review enhanced phenotypic classification, availability was incomplete, and subtle manifestations may have been underrecognized. Fifth, genetic interpretation reflected current standards, but classification of variants, particularly novel singletons, remains provisional and may evolve with future evidence. Finally, statistical power for subgroup comparisons was limited by small sample sizes, restricting the ability to detect genotype–phenotype associations beyond the most recurrent variants.

Taking all data into consideration, we do not propose our four-group classification in clinical practice, because it adds complexity without clear diagnostic utility. Instead, our findings support a symptom-based framework that captures each patient’s unique constellation of chronic movement disorders, paroxysmal events, and associated features, as suggested by Vezyroglou et al.⁵ Such an approach could guide individualized care more effectively than rigid adherence to canonical categories. To operationalize this approach, we developed a structured symptom checklist (Fig. 3) that systematically documents key clinical features across three domains: chronic movement disorders, paroxysmal episodes, and additional symptoms. The checklist includes color-coded indicators that map individual symptoms to their typical canonical phenotype associations (AHC, RDP, CAPOS, RECA/FIPWE), allowing clinicians to identify characteristic features, phenotypic overlap, and presentations that do not fit classical categories.

Given the high prevalence and burden of chronic movement disorders, systematic assessment across the full spectrum, including dystonia, spasticity, rigidity, myoclonus, chorea, stereotypies, and paroxysmal dyskinesias, is essential. One of the most valuable contributions of this study is the creation of a comprehensive video archive (Videos 1–32), which provides a visual atlas of *ATP1A3*-related movement disorders. This resource captures subtle, overlapping, and atypical features that are difficult to convey in text, serving both clinical and educational purposes. ■

Conclusions

ATP1A3-related disorder exemplifies the complexity of epilepsy-dyskinesia syndromes and highlights the limitations of prescriptive phenotypic classifications, which should be viewed as recognizable patterns along a clinical continuum rather than discrete entities. Our systematic analysis shows that most patients present

with overlapping or atypical constellations of symptoms, supporting a shift toward viewing these disorders along a clinical continuum. The prominence of chronic movement disorders, the variability of genotype–phenotype relationships, and the substantial proportion of patients who do not fit canonical categories all underscore the need for flexible, symptom-based approaches to clinical characterization. In this context, *ATP1A3*-related disorders emerge as a paradigm of clinical heterogeneity and phenotypic pleiotropy, providing a model for how rare genetic syndromes may be more effectively understood, diagnosed, and managed when approached through the lens of spectrum-based frameworks.

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K.B.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

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

C.D.: 1A, 1B, 1C, 3B.

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Data Availability Statement

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

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Supporting Data

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