LETTER: NEW OBSERVATION

Expanding the Motor Phenotype and Molecular Spectrum of *NAA15*-Related Disorder: Two Cases of Isolated Childhood-Onset Gait Dystonia

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Heterozygous truncating variants in *NAA15*, encoding the auxiliary subunit of the N-terminal acetyltransferase A (NatA) complex, cause an autosomal-dominant neurodevelopmental disorder (OMIM #617787) characterized by intellectual disability, autism spectrum disorder, and variable congenital anomalies.[1] A movement disorder spectrum is emerging that ranges from adult-onset dystonia-parkinsonism[2] to childhood-onset lower-limb dystonia[3,4] and cortical myoclonus with paroxysmal dyskinesia.[5] All previously reported patients have carried truncating variants predicted to undergo nonsense-mediated decay (NMD), consistent with a haploinsufficiency mechanism.[1-5]

We describe two unrelated girls (current ages 5 and 6 years) with childhood-onset, action-induced gait dystonia caused by *de novo* non-truncating *NAA15* variants. Clinical, genetic, and treatment details are summarized in Table 1 and File S1; representative examination findings are shown in Videos S1 and S2.

Patient 1 developed right-leg dragging and frequent falls at 4 years of age. Examination demonstrated action-induced right-leg dystonia with thigh internal rotation, knee flexion, and intermittent equinovarus posturing that was reproducibly triggered by ambulation and worsened with distance, following a relapsing–remitting course exacerbated by febrile illness. Trio exome sequencing identified a *de novo* heterozygous in-frame deletion in *NAA15* (NM_057175.3:c.283_285del; p.Lys95del). Patient 2 developed action-induced bilateral lower-limb dystonia at 4.5 years of age, evolving from left-leg posturing during running to a bilateral high-stepping gait, with partial spontaneous improvement over the subsequent 12 months. Trio exome sequencing identified a *de novo* heterozygous missense variant (NM_057175.5:c.301A>G; p.Lys101Glu). Both variants are absent from gnomAD v4.1, situated in exon 4 within the NAA10-binding region of *NAA15*, and have supportive *in silico* predictions of pathogenicity (CADD≥26; AlphaMissense≥0.91). Sequential trials of oxcarbazepine, levodopa, clonazepam, and trihexyphenidyl produced no benefit in Patient 1, and trihexyphenidyl was discontinued in Patient 2 because of gait worsening and constipation. Neuroimaging, cerebrospinal fluid studies, and metabolic workup were unremarkable, with mild associated neurodevelopmental features (attention-deficit/hyperactivity disorder; transient speech delay).

The five previously reported patients with *NAA15*-associated movement disorders all carried truncating variants expected to undergo NMD and produce haploinsufficiency (Table 1).[1-5] The variants identified here are not predicted to trigger NMD and likely yield full-length protein with altered function, raising the possibility of mechanisms beyond haploinsufficiency, such as hypomorphism, altered NatA complex assembly, or dominant-negative interference. Both lie within the N-terminal tetratricopeptide-repeat region that mediates NAA10 binding, immediately adjacent to the

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TABLE 1 *Published cases of DYT-NAA15*

Parameter	Cheng et al.[1] (PMID: 29656860)	Straka et al.[2] (PMID 35730864)	Yubero et al.[4] (PMID: 36221186)	Danti et al.[3] (PMID: 38380600)	Freri et al.[5] (PMID: 38643413)	Case 1	Case 2
Genotype	c.228_232delCTTGA; p.Asp76Glufs*20	c.382C>T; p.Arg128*	c.2282C>G; p.Ser761*	c.1645C>T; p.Arg549Ter	c.1492dup; p.Met498Asnfs*3	c.283_285del; p.Lys95del	c.301A>G; p.Lys101Glu
Inheritance	De novo	De novo	Maternal	De novo	De novo	De novo	De novo
Age at last follow-up (years)	8	52	13	13	10	6	5
Sex	Male	Male	Female	Female	Female	Female	Female
Developmental delay	Mild	Mild	Mild	Mild	Mild	Normal	Normal
Facial dysmorphism	Yes	Coarse facial features	Yes	No	No	No	No
Age at movement disorder onset (years)	3	46	3	2.5	12	4	4.5
Movement disorder	Left leg paroxysmal dystonia	Dystonia-parkinsonism	Bilateral lower-limb dystonia	Right leg gait dystonia	Cortical myoclonus; paroxysmal dyskinesias	Paroxysmal gait-induced leg gait-dystonia	Paroxysmal gait-induced leg gait-dystonia
Medications trialed	None	L-dopa (partial response)	L-dopa (no response); trihexyphenidyl 10 mg/day (good response)	L-dopa (partial response); trihexyphenidyl (good response)	None	Oxcarbazepine (no response); L-dopa (no response); trihexyphenidyl (poorly tolerated/ ineffective); clonazepam (no response)	Trihexyphenidyl (ineffective)
Outcome	Spontaneous remission by 5 years	Generalized dystonia (predominantly left arm); parkinsonism	Mild torsion dystonia in both feet, stable for ~10 years	Remission after trihexyphenidyl; off treatment since 9 years	–	Persistent right leg gait dystonia	Mildly improved spontaneously but still with gait-induced leg gait-dystonia
Other clinical features	ASD; attention issues	–	ADHD; astigmatism; hyperopia; recurrent bronchitis; atopic dermatitis	ADHD; anxiety; OCD	Specific learning disorder	ADHD	–

Abbreviations: L-dopa, levodopa; –, not reported; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive–compulsive disorder. Variants are reported using Human Genome Variation Society (HGVS) nomenclature relative to NM_057175 (NAA15).

recurrent truncating variants previously reported in exon 3.[1] The clinical picture closely resembles the pediatric cases of Yubero et al.[4] and Danti et al.,[3] supporting a recognizable phenotypic signature. Functional studies and additional cases are required to confirm variant-level pathogenicity. In contrast to the prior cases, both of whom derived good-to-excellent benefit from trihexyphenidyl,[3,4] both of our patients experienced either no benefit or adverse effects.

Under the International Parkinson and Movement Disorder Society nomenclature framework,[6,7] *NAA15* now meets the evidence threshold for designation as a monogenic dystonia, with consistent phenotypes reported across independent cohorts. We suggest that *NAA15* be considered for formal designation as DYT-*NAA15*, provisionally placed within the "dystonia presenting with developmental delay" subcategory,[6] pending further case aggregation and functional confirmation. ■

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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.

References

1. Cheng H, Dharmadhikari AV, Varland S. Truncating variants in NAA15 are associated with variable levels of intellectual disability, autism spectrum disorder, and congenital anomalies. Am J Hum Genet 2018;102(5):985–994.
2. Straka I, Švantnerová J, Minár M, Stanková S, Zech M. Neurodevelopmental gene-related dystonia-parkinsonism with onset in adults: a case with NAA15 variant. Mov Disord 2022;37(9):1955–1957.
3. Danti FR, Keller Sarmiento IJ, Moloney PB. Childhood-onset lower limb focal dystonia due to a NAA15 variant: a case report. Mov Disord 2024;39(4):747–749.
4. Yubero D, Martorell L, Nunes T, Lyon GJ, Ortigoza-Escobar JD. Neurodevelopmental gene-related dystonia: a pediatric case with NAA15 variant. Mov Disord 2022;37(11):2320–2321.
5. Freri E, Canafoglia L, Ciaccio C. Cortical myoclonus and complex paroxysmal dyskinesias in a patient with NAA15 variant. Mov Disord 2024;39(7):1238–1240.
6. Lange LM, Gonzalez-Latapi P, Rajalingam R. Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society Task Force — an update. Mov Disord 2022;37(5):905–935.
7. Marras C, Lang A, van de Warrenburg BP. Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society Task Force. Mov Disord 2016;31(4):436–457.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.