Neurodevelopmental Gene-Related Dystonia-Parkinsonism with Onset in Adults: A Case with *NAA15* Variant

Genomic sequencing and animal-model studies have begun to define a strong neurodevelopmental basis of dystonia.[1] In addition, neurodevelopmental defects are also thought to represent factors contributing to the manifestation of Parkinson's disease (PD) and parkinsonian syndromes.[2-4] Knowledge about single-gene disorders presenting with neurodevelopmental dystonia and/or parkinsonism is still limited, hindering individualized patient care and comprehensive mechanistic understanding.

We have enrolled a male proband demonstrating adult-onset generalized dystonia combined with akinetic-rigid symptoms in our research program aiming to unravel the etiologies of dystonic syndromes.[1] The proband's movement-disorder features started at the age of 46 years, without prior medication intake. He developed dystonic posturing of the lower extremities left>right, and subsequently also posturing of both arms and the trunk with intermittent lateroflexion/camptocormia. These symptoms were followed by manifestation of postural instability, swallowing difficulties, and muscle stiffness. Over time, dystonia became less prominent, whereas slowness of movements and gait dysfunction worsened. Examination at the age of 52 years revealed constant dystonia affecting predominantly the left arm associated with marked parkinsonism (Video S1). During childhood, the proband had experienced gross-motor and speech delays but he had never visited special pediatric services. He showed mild coarse facial features (Video S1) but no evidence of significant cognitive impairment (Montreal Cognitive Assessment [MoCA] score 27/30), autism, or cardiac abnormalities, consistent with the heterogeneous nature of *NAA15*-related disease.[5] There was no family history of neurological disorders. Evaluations including blood biochemistry, metabolic screenings, and genetic testing for spinocerebellar ataxias (SCA 1,2,3,6) and *LRRK2*-associated PD yielded unremarkable results. Chromosomal microarray analysis was unrevealing. Brain imaging could not be performed because the patient did not tolerate the procedure due to abnormal postures. A trial of L-dopa/carbidopa produced improvement with decreased tone, although no sustained response was seen.

By trio whole-exome sequencing,[1] the proband was found to carry a de novo pathogenic nonsense variant in *NAA15*: NM_057175.5:c.382C>T, p.Arg128*. The same variant has previously been identified in two unrelated patients (one published[6] and one from our in-house pediatric cohorts) with classic neurodevelopmental-disease features but no movement disorder. No alternative genetic causes were observed upon in-depth analysis of the exome data (including ExomeDepth-based copy number variation [CNV] assessment), especially no potentially pathogenic variants in established dystonia/parkinsonism-related genes.

NAA15 encodes N-alpha-acetyltransferase-15, an essential component of the N-terminal-acetyltransferase-complex-A mediating the attachment of acetyl-groups to the N-termini of various substrate proteins.[5] N-terminal acetylation has significant impact on protein properties such as folding, complex formation, and activity, and dysfunction of this process has been associated with both neurodevelopmental and neurodegenerative pathological effects including alterations in the stability of α-synuclein.[7] *NAA15*-related disease has been characterized as an infantile-/childhood-onset disorder that presents with variable combinations of milestone delay, intellectual impairment, and dysmorphia.[5] To date, abnormal (limb dystonic) movements have been reported in only a single affected child.[5]

Our case study expands the phenotype of *NAA15*-related disease and serves to enhance awareness of the natural history of this syndrome which can involve adult-onset movement-disorder presentations. Moreover, the findings add *NAA15* to the growing list of genes whose variants can underlie both typical pediatric neurodevelopmental conditions and phenotypes with parkinsonism/dystonia-parkinsonism later in life.[3,4] Notable, yet only recently emerging examples of this group of neurodevelopmental genes include *NR4A2*, *PLXNA1*, *PPP2R5D*, *WARS2*, and *YY1*, which are associated in certain adult cases with dopa-responsive dystonia-parkinsonism, atypical parkinsonian syndromes with dystonia, and parkinsonism resembling PD (Table 1). Further elucidation of this novel class of genetically determined entities is important to gain broader insights into pathogenesis and stratify patients according to etiological subtype and treatment response. We encourage additional collaborative research to improve identification of the spectrum and outcomes of neurodevelopmental gene-linked dystonia-parkinsonism, with the eventual goal of designing more efficient therapies.

Key Words: dystonia, parkinsonism, *NAA15*, neurodevelopmental disorder

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Relevant conflict of interest/financial disclosures: Nothing to report.

Funding agency: MZ receives research support from the German Research Foundation (DFG 458949627; ZE 1213/2-1).

Received: 11 March 2022; **Revised:** 20 May 2022; **Accepted:** 30 May 2022

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29125

TABLE 1 *Recently emerging examples of early-/OR late-onset parkinsonism/dystonia-parkinsonism syndromes associated with variants in neurodevelopmental genes*

Gene	Encoded protein	Features of the associated neurodevelopmental disorder (OMIM)	Parkinsonism/dystonia-parkinsonism phenotypes			
			Reported by (PubMed identifier)	Number of reported patients	Specific presentations	L-dopa response
NAA15	N-alpha-acetyltransferase 15, NatA auxiliary subunit	Developmental delay, intellectual disability, behavioral problems, seizures, dysmorphia (intellectual developmental disorder, autosomal dominant 50, with behavioral abnormalities, 617787)	Present study	1 case	Dystonia-parkinsonism	Yes (partial)
NR4A2	Nuclear receptor subfamily 4, group A, member 2	Developmental delay, intellectual disability, seizures, behavioral problems (N/A)	Wirth et al. (PMID: 31922365)	2 cases	Dystonia-parkinsonism	Yes
PLXNA1	Plexin A1	Developmental delay, intellectual disability, seizures, dysmorphia, midline anomalies, autism (N/A)	O'shea et al. (PMID: 34415653)	1 case	Parkinsonism resembling Parkinson's disease	Yes
PPP2R5D	Protein phosphatase 2, regulatory subunit B (B56), delta	Developmental delay, intellectual disability, seizures, dysmorphia (mental retardation, autosomal dominant 35, 616355)	Kim et al. (PMID: 32743835), Walker et al. (PMID: 33098144), Hetzelt et al. (PMID: 33338668)	5 cases	Parkinsonism resembling Parkinson's disease (4 cases), atypical parkinsonian syndrome (1 case), coexisting dystonia (1 case)	Yes
WARS2	Tryptophanyl-tRNA synthetase 2	Developmental delay, intellectual disability, seizures, infantile motor abnormalities (neurodevelopmental disorder, mitochondrial, with abnormal movements and lactic acidosis, with or without seizures, 617710)	Burke et al. (PMID: 29120065), Virdee et al. (PMID: 31282308), Martinelli et al. (PMID: 32120303), Hübers et al. (PMID: 31970218), Skorvanek et al. (PMID: 34890876)	6 cases	Infantile-onset parkinsonism, parkinsonism resembling Parkinson's disease, dystonia-parkinsonism, complex dystonia	Yes
YY1	Transcription factor YY1	Developmental delay, intellectual disability, behavioral problems, dysmorphia, congenital malformations (Gabriele-de Vries syndrome, 617557)	Indelicato et al. (PMID: 35172867)	1 case	Dystonia-parkinsonism	Not reported

Abbreviation: N/A, not available.

Acknowledgments: We thank the patient and his family for their generous participation and permission to publish this case. Open Access funding enabled and organized by Projekt DEAL.

Data Availability Statement

Data available on request from the authors.

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I. Straka: acquisition of data, clinical examination, analysis and interpretation of data, revision of manuscript for critical intellectual content

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Financial Disclosures

Disclosures (for the preceding 12 months): Nothing to report.