CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Rapid-Onset Dystonia-Parkinsonism Phenotype Consistency for a Novel Variant of *ATP1A3* in Patients Across 3 Global Populations

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Neurol Genet 2021;7:e562. doi:10.1212/NXG.0000000000000562

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Mutations in *ATP1A3*, which encodes the α3 subunit of Na, K-ATPase, produce various neurologic and psychological disorders that are increasingly believed to be on a continuum, from severe infantile presentations to adult-onset movement disorders. We present evidence that a single codon deletion can nonetheless produce a typical syndrome of rapid onset dystonia-parkinsonism (RDP, DYT/PARK-*ATP1A3*, OMIM 128235).[1] The novel heterozygous mutation p.Phe297del (c.889-891delTTC in NM_152296) was identified in 4 patients in 3 different countries with different genetic backgrounds, European, Japanese, and mixed. This supports the idea that there are discrete mutation-related syndromes underlying the continuum of *ATP1A3* phenotypes.

A 19-year-old Japanese man, 44-year-old and 37-year-old Portuguese siblings (older sister and younger brother), and a 29-year-old Brazilian woman were investigated clinically and genetically. Subjects underwent next-generation sequencing panel or Sanger sequencing under research protocols. All 4 cases had typical[1] and mild-to-moderate symptoms of RDP. Details are in table 1. All cases were familial according to family history and/or genetic testing. Rapid onset of oromandibular and upper extremity dystonia occurred in adolescence in 3 patients and at age 25 in 1. There were triggers in 3. Symptoms appeared immediately or over 3 weeks. Three developed mild parkinsonism within a decade. All had mild-to-moderate scores in the Burke-Fahn-Marsden dystonia scale; both the Japanese and Portuguese men work. None suffered from severe psychiatric disorders or intellectual disability. The Japanese man revealed abnormal SPECT, EEG, and memory-guided saccades (e-Methods case 1, figures e-1–5 and table e-1, links.lww.com/NXG/A392, and video 1). The Portuguese woman had normal muscle biopsy and metabolic screening. The Brazilian woman had normal brain tomography.

The presence of consistent symptoms in independent patients with the same recurrent variant is itself strong evidence for pathogenicity. Supporting the pathogenicity of the shared variant, p.Phe297del in *ATP1A3* corresponds to p.Phe305del in *ATP1A2*, which was reported in a case of hemiplegic migraine with symptoms typical of other mutations in that gene (FHM2, OMIM 602481).[2] In all 4 Na, K-ATPase catalytic subunit genes, there are 2 adjacent phenylalanines with the same codons, TTCTTC in *ATP1A1*, *ATP1A2*, and *ATP1A3* and TTTTTT in *ATP1A4*. The deletion of 3 bases is so far the only mutation found at the site. p.Phe297del in *ATP1A3* produced a uniform syndrome on different genetic backgrounds here, suggesting a

*These authors contributed equally to this work. Prof. Sweadner connected these patients and studied the concept of this manuscript. Prof. Kawarai also investigated the gene of case 1.

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by Segawa Institute.

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Table 1 Clinical and Demographic Characteristics of Patients

Profile	Nationality	Japan	Portugal	Portugal	Brazil
	Current age, M/F	19, M	44, F	37, M	29, F
Family history of RDP	Symptomatic DNA verified	Mother (asymptomatic carrier)	Father and 2 other sisters negative; mother died (asymptomatic)	Same family	Maternal grandfather and aunt symptomatic and died; mother (asymptomatic)
Development	Perinatal course	Seizures from day 19 postpartum to 3 mo	Normal	Normal	Listeriosis in first trimester treated with amoxicillin
	Childhood	ADHD-like episode	Normal	Normal	Normal
Clinical course of RDP	Age at onset	16	12	25	15
	Initial symptoms	Acute right arm and oromandibular dystonia with drowsiness	After found unconscious, dysarthria, dysphagia, and dystonia of lower limbs	Dysphonia and oromandibular dystonia	Acute left hand and arm dystonia and oromandibular dystonia
	Trigger	Travel (motion) sickness	Uncertain if syncope/ seizure/bump to the head	None reported, sudden onset	Death of relative
	Progression	5 mo after onset, acute regression with recovery over 1 mo	Anarthria, generalized dystonia with oromandibular involvement, hyperreflexia	2 wk to plateau, then slowly progressive, hyperreflexia	3 wk evolution between onset and plateau of dystonia
	Onset of parkinsonism	16	36	25	None
	Epilepsy	Irregular slow waves in bilateral frontal cortex	Normal EEG	GTCS at 14 after death of relative; medication until 20	None
	Psychosis	None	None	None	None
Severity	BFM dystonia scale[a]	34	58	17.5	24
	Disability scale[b]	7	13	10	5
	Intellectual disability	Mild	None	None	None
	Social state	Painting industry	Lives independently and no regular job	Driver and part time fireman	Lives independently no regular job
Examination	MRI	Normal	Normal	Normal	Normal
	Other	Decreased eye saccade, normal gating of SEP SPECT: hypoperfusion in temporal area, inferior frontal area, hippocampus, and thalamus	Normal muscle biopsy, metabolic screening, and DYT1/6 gene study		Brain tomography normal EMG: Dystonia
Treatment	Medications	Responsive to levodopa, diazepam, and trihexyphenidyl	Responsive to diazepam, trihexyphenidyl, and baclofen and unresponsive to levodopa	Responsive to diazepam and trihexyphenidyl and unresponsive to levodopa	Unresponsive to levodopa

Abbreviations: ADHD = attention-deficit hyperactivity disorder; BFM = Burke-Fahn-Marsden; GTCS = generalized tonic-clonic seizure; RDP = rapid-onset dystonia-parkinsonism.
[a] Scale is 0–120.
[b] Scale is 0–30.

mutation-phenotype relationship. The position in the protein is near the extracellular surface, not close to the ion binding sites or to domains essential for ATP hydrolysis (figure e-6, links.lww.com/NXG/A392). Deleting 1 residue of a helix will change the positions of amino acids around it, and in this case, this has the potential to distort the pathway for K^+ entry and

Na^+ exit at the extracellular surface.[3] The deletion will slightly shorten transmembrane helix M3, which means shifting the short extracellular linker between M3 and M4 inward. There is good reason to predict a functional consequence: movement of the extracellular segment of M4 controls the opening and closing of the ion pathway.[3] The shortening is also likely to affect the orientation of Glu309, which is on M4 approximately opposite Phe297. In one of the most intriguing laboratory studies of *ATP1A3* disease mutations, the secondary mutation p.Glu309Asp was shown to correct the reduced Na^+ affinity of the human mutation p.Asp923Asn, 30 Å distant on the cytoplasmic side of M8.[4] Aspartate is only slightly smaller than glutamate, and the affinity increase was believed to be due to adjustment of the position of M4, which contributes part of the ion binding pocket.[3,5] In this context, p.Phe297del may produce *ATP1A3* and *ATP1A2* neurologic disorders by altered kinetic properties or by inactivation of enzymatic activity.[3,5]

Different *ATP1A3* mutations produce a range of symptoms with considerable overlap,[6] but there seem to be discrete mutation-related syndromes underlying the continuum of phenotypes, and early indications of structure-phenotype relationships.[7] Why mutations of *ATP1A3* produce 1 syndrome and not others is of paramount importance for development of therapies. Factors that can impact phenotype are the level of inactivation (loss of activity or loss of membrane delivery); alteration of neuronal physiology by changing ion affinity, intracellular Na^+, and membrane potential; and whether the protein is stable. Each *ATP1A3* variant will have an intrinsic propensity to each form of damage, resulting in a tendency to produce milder or more severe syndromes. A few mutations, such as p.Asp923Asn, have been shown to produce 2 different syndromes even in the same family, and in such cases, other factors must contribute to symptom differences.

Ethical Standards

The authors hereby declare that the research documented in the submitted study has been carried out in accordance with ethical standards laid down in the 1964 declaration of Helsinki and approved by the Ethics Committee of the Segawa Memorial Neurological Clinic for Children and the institutional review boards of the Tokushima University; Hospital de Clínicas de Porto Alegre; and Hospital de Santo António, Centro Hospitalar Universitário do Porto, Porto, Portugal.

Acknowledgment

The authors thank Prof. Keiko Ikeda, Murayama Medical Center, for useful discussion and collaboration on the early stages of this work.

Study Funding

NIH grant NS058949 to Allison Brashear (K.J.S. and L.J.O.). Health and Labour Science Research Grants for Research on Rare and Intractable Diseases, Clinical Research for Establishment of Evidence Based Guidelines for Hereditary Dystonias and Huntington Disease, Grants-in-Aid from the Research Committee of CNS Degenerative Diseases, the Ministry of Health, Labour and Welfare of Japan (grant to R.K.), and by the Japan Agency for Medical Research and Development for Grants-in-Aid for core hospitals for the Initiative on Rare and Undiagnosed Diseases (to T.K.).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* September 5, 2020. Accepted in final form November 24, 2020.

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Continued

Appendix *(continued)*

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