

Case Reports

Intermediate Phenotypes of *ATPIA3* Mutations: Phenotype–Genotype Correlations

Pichet Termsarasab^{1*}, Amy C. Yang² & Steven J. Frucht¹

¹ Movement Disorder Division, Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, ² Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

Background: *ATPIA3*-related disorders include rapid-onset dystonia–parkinsonism (RDP or DYT12), alternating hemiplegia of childhood (AHC), and CAPOS syndrome (Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss).

Case Report: We report two cases with intermediate forms between RDP and AHC. Patient 1 initially presented with the AHC phenotype, but the RDP phenotype emerged at age 14 years. The second patient presented with levodopa-responsive paroxysmal oculogyria, a finding never before reported in *ATPIA3*-related disorders. Genetic testing confirmed heterozygous changes in the *ATPIA3* gene in both patients, one of them novel.

Discussion: Intermediate phenotypes of RDP and AHC support the concept that these two disorders are part of a spectrum. We add our cases to the phenotype–genotype correlations of *ATPIA3*-related disorders.

Keywords: *ATPIA3*, rapid-onset dystonia–parkinsonism, dystonia, parkinsonism

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*To whom correspondence should be addressed. E-mail: pichetterm@gmail.com

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Introduction

Historically, heterozygous *ATPIA3* mutations were initially described in rapid-onset dystonia–parkinsonism (RDP or DYT12) (MIM 128235).¹ Advances in genetic techniques led to the subsequent discovery that abnormalities in the same gene were responsible for some forms of alternating hemiplegia of childhood (AHC) (MIM 614820),² and also the CAPOS syndrome (Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy and Sensorineural hearing loss) (MIM 601338).³ Although clinical features of RDP and AHC differ, on rare occasions patients have been reported with clinical features overlapping between the two,^{4,5} suggesting that RDP and AHC are disorders in the same spectrum^{4,6,7} rather than just allelic disorders as initially envisioned.⁸

In this paper, we present two unusual patients with *ATPIA3*-related disorders with clinical features overlapping between RDP and AHC.

Our first patient carried a novel missense variant previously unknown in intermediate phenotypes or any *ATPIA3*-related disorders. Our second patient carried a known deleterious mutation and possessed an unusual phenotype never before reported in the intermediate form. These two unique patients illustrate the expanding phenotypic spectrum of *ATPIA3*-related disorders.

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Case report

Patient 1

A 24-year-old female without family history of neurologic illness presented for evaluation of global developmental delay from early childhood and monthly alternating hemiplegic episodes lasting minutes to hours since her early teens. She usually recovered from these



Video 1. The first patient's office examination demonstrates a prominent risor grin, drooling and marked dysarthria. Asymmetric dystonia of the left arm and hand led to flexion posturing of the elbow, prominent wrist and finger flexion, and ulnar deviation of her wrist. A rostrocaudal gradient of dystonia is evident, with preservation of walking.

episodes after sleeping, but at age 14 she developed a severe episode that was not terminated by sleep. A diagnosis of "AHC" was made at this time, and a hospital evaluation for epilepsy was negative. Since that event, she developed continuous and unremitting posturing and functional impairment of the left arm, dysarthria, and lower cranial dystonia with marked drooling.

On examination a prominent risus sardonicus, marked dysarthria, and prominent drooling were evident (Video 1). Ocular motor examination was normal, and asymmetric dystonic posturing of the arms was present accompanied by parkinsonism. A rostrocaudal gradient of her dystonia was noted with only very mild involvement in her legs. Deep tendon reflexes were 3+ throughout.

Sanger sequencing of exons 1–23 in the *ATPIA3* gene at a commercial laboratory revealed a novel heterozygous missense variant (NM_152296.4: c.2851G>A; NP_689509.1: p.E951K) in exon 21. This variant is not found in large publically available cohorts.^{9–11} *In silico*, this variant is predicted to be damaging by SIFT (Sorting Intolerant From Tolerant) and probably damaging by PolyPhen-2 (with a score of 0.998).^{12,13} The position is highly conserved across multiple vertebrate species (from humans to zebrafish; Genomic Evolutionary Rate Profiling [GERP] score 2.91).¹⁴ Though not reported, this variant was also seen once in another patient with AHC in a research cohort in Utah (T. Newcomb, personal communication, June 12, 2015). Based on the new American College of Medical Genetics and Genomics standards and guidelines for interpretation of sequence variants, this variant is classified as likely to be pathogenic.¹⁵ Her parents elected not to pursue testing since they were asymptomatic. Botulinum toxin injection to the left arm provided temporary relief of dystonia.

Patient 2

A 10-year-old female presented to our office with her parents after being adopted from China 8 months prior. Information on her early development was limited. At age 1 year she was brought to an orphanage with obvious global developmental delay. When her adoptive mother met her in China, she was malnourished, immobile,



Video 2. Patient number 2 is shown in three segments. segment 1.

A home video demonstrates an oculogyric episode, with eyes elevated upward with intermittent lateral deviation, accompanied by head tilt to the left and jaw deviation to the right. She was uncomfortable but did not lose consciousness. This episode lasted almost 1 minute, after which she partially recovered and looked exhausted. About 20 seconds afterwards, she developed oculogyria with upward eye deviation again. **Segment 2.** The second home video segment shows her in a stroller. She developed dystonic posturing of her neck with tilting to the left and lateral rotation to the right, accompanied by dystonic posturing of her hands and jaw opening. She recovered before her mother transferred her to a cushion. **Segment 3.** This video segment shows her during her initial office evaluation, already treated with levodopa. Her speech was mildly soft and indistinct with no ocular motor abnormalities. Mild symmetric dystonic posturing of both hands with intermittent choreiform movements of her fingers was present. There was no parkinsonism or dysmetria. She walked well with good arm swing.

mute, drooling, and unable to use her arms to feed herself but she could sit and walk. She seemed alert however, and after a few visits recognized her adoptive mother. She had experienced frequent episodes since childhood that had been labeled epileptiform (Video 2). Review of the video showed clear oculogyria with upward and lateral deviation of both eyes, accompanied by neck posturing. After her first evaluation in the United States, her referring neurologist started her on levodopa 200 mg/day, and the episodes dramatically improved, along with improved motor performance.

Examination in the office revealed a cooperative young girl with mildly soft and indistinct speech. Ocular motor examination was normal. There was symmetric mild dystonic posturing of both hands, with slow choreiform movements of her fingers, mild incoordination of the hands and no overt parkinsonism. She walked well with good arm swing. Deep tendon reflexes were 1+ throughout.

Owing to the dramatic response to levodopa and presence of oculogyria, our differential diagnosis included levodopa-responsive forms of aromatic L-amino acid decarboxylase (AADC)¹⁶ and tyrosine hydroxylase (TH) deficiency. Surprisingly, whole exome sequencing (and confirmed using the Sanger method) at a commercial laboratory revealed a known pathogenic heterozygous mutation (NM_152296.4: c.2401G>A; NP_689509.1: p.D801N) in exon 17 of the *ATPIA3* gene.^{17–19} There were no mutations found in the *DDC* or *GCHI* genes. Coverage for these two loci was at 100% and at least 10× (N. Alexander, personal communication, August 8, 2015). Since the *TH* gene was not well covered by whole exome sequencing, separate *TH*

Table 1. Clinical Features of Our Patients with Intermediate Forms of Alternating Hemiplegia of Childhood and Rapid-onset Dystonia–Parkinsonism

Clinical Feature	Patient 1	Patient 2
Developmental delay	+	+
Drooling	+ ¹	+
Paroxysmal alternating hemiplegia	+	
Paroxysmal oculogyria		+ ¹
Hypotonia		+
Recovery of the episode with sleep	+	
Asymmetric dystonia	+ ¹	
Mild bilateral hand dystonia		+ ¹
Rostrocaudal gradient of dystonia	+ ¹	
Speech involvement	+ ¹	+ ¹ (mild)
Stabilization of the symptoms over time	+	

Clinical features of each patient were classified according to whether they were more compatible with alternating hemiplegia (in pink) vs. rapid-onset dystonia–parkinsonism (in green). “+” sign indicates the presence of the features in each patient.

¹Features that are seen in the videos.

gene sequencing was performed at the same commercial laboratory using the Sanger method, which included all exons, flanking splice regions, and the cyclic adenosine monophosphate (cAMP) response element spanning c-74 to c-67 in the promoter region. *TH* deletion/duplication analysis was also performed via a dense exonic comparative genomic array. These methods did not detect any mutations, deletions, or duplications in the *TH* gene. Test method details for whole exome sequencing, *TH* sequencing, and deletion/duplication analysis can be found at the commercial laboratory’s website (www.genedx.com). Cerebrospinal fluid studies were not available.

Discussion

We present two unusual patients with missense changes in the *ATPIA3* gene whose clinical features overlapped between AHC and RDP. In classic AHC, patients experience symptom onset before 18 months of age, consisting of paroxysmal alternating hemiplegia events, developmental delay, and drooling. The classic RDP phenotype is often milder than AHC, with the main feature of rapid-onset parkinsonism over minutes to weeks, and stabilization of symptoms with minimal progression after a month. A rostrocaudal gradient of symptoms, asymmetric involvement, and prominent bulbar involvement including dysarthria and/or dysphagia is characteristic.

Our two patients’ clinical histories and examination overlapped between these two disorders (Table 1). In fact, Patient 1 started with an AHC phenotype, and her RDP phenotype emerged at age 14 years. Sasaki et al.⁵ reported and reviewed cases in the literature with intermediate phenotype between AHC and RDP,^{4,20} all of which (six patients) had D923N mutations in the *ATPIA3* gene. Rosewich et al.⁶ later reported two patients with intermediate phenotype and the novel mutations I810F and W382R. The missense variant in our first patient, E951K, has never been reported in *ATPIA3*-related disorders,

including the intermediate phenotype between AHC and RDP. The mutation in Patient 2, D801N, is one of the most common mutations reported with the classic AHC phenotype,²¹ but has never been reported in the intermediate form of AHC and RDP. Although almost all reported genetic derangements in *ATPIA3*-related disorders are *de novo*,²² parental genetic testing was not available in either of our patients. Phenotype–genotype correlations in *ATPIA3*-related disorders are summarized in Table 2.

The *ATPIA3* gene encodes the $\alpha 3$ -subunit of the enzyme Na^+/K^+ ATPase. This enzyme functions to pump three molecules of Na^+ out and two molecules of K^+ into the cell to maintain the electrochemical gradient at the plasma membrane prior to depolarization. Both the E951K and D801N variants are located in the transmembrane regions of the ATP1A3 protein, which is also a cation-transporting ATPase region near the C-terminus. In previous studies, it was found that mutations causing AHC phenotypes tend to affect the transmembrane regions or functional domains compared to those causing RDP phenotypes,⁶ although this association cannot be applied in all cases.

Interestingly, Patient 2 presented with paroxysmal oculogyria dramatically responsive to levodopa, a phenomenon never reported before in AHC or RDP. AHC patients can have episodic ocular motor abnormalities, reported in up to 93% in one study,²³ including nystagmus and intermittent esotropia or exotropia. In 1993, Dobyns et al.²⁴ reported two out of 12 RDP patients with persistent (not paroxysmal) oculogyric crisis at the onset, lasting days or weeks. Genetic testing of the *ATPIA3* gene was not available at that time, but subsequently one of them was found to have the I758S mutation in the *ATPIA3* gene.²⁵ Since then, oculogyria has not been reported in RDP. To our knowledge, this is the first patient reported with *paroxysmal* oculogyria associated with an *ATPIA3* mutation. This atypical feature initially pointed us to other differential diagnoses of levodopa-responsive oculogyria in children, especially disorders in the monoamine synthetic

Table 2. Phenotype–Genotype Correlations of *ATP1A3*-related Disorders

RDP	I	AHC	I	CAPOS
I274T, E277K, 327Ldel, T370N, W382R, L417P, T613M, S684F, R756H, I758S, F780L, D810Y, D923N	D801N ¹ , G867D, D923N, E951K ¹	S137Y, S137F, Q140L, I274N, E277K, V322D, C333F, T335P, G358C, L371P, G755A, G755S, G755C, L757P, T771N, S772R, N773S, N773I, D801E, D801N, T804I, D805E, M806R, I810F, I810S, S811P, E815K, 2542+1G>A (splice site), 919Vdel, D923N, D923Y, C927Y, C927F, C927W, G947R (2839G>A and 2839G>C), A955D, D992Y, 1013Ydup	E818K	E818K

AHC, Alternating Hemiplegia of Childhood; CAPOS, Cerebellar ataxia, Areflexia, Pes Cavus Optic Atrophy, and Sensorineural Hearing Loss; RDP, Rapid-onset Dystonia–Parkinsonism.

The table demonstrates genotypes reported in the literature that are related to each phenotype classified into typical RDP, typical AHC, typical CAPOS syndrome, shown in pink, green, and blue, respectively.^{5,6,21,26–29} Intermediate (I) forms between each phenotype are shown in grey. Amino acid code alterations are shown in order of the codons.

¹Mutations in our cases.

pathway such as AADC and TH deficiencies. Given the dramatic improvement in our patient and in the other three patients in the same family with a novel AADC mutation,¹⁶ a trial of levodopa in children presenting with unexplained oculogyria seems warranted.

Our two cases expand our current knowledge of the phenotype–genotype variations and natural history of *ATP1A3*-related disorders, and emphasize that AHC and RDP are part of the same spectrum. Recognition of the overlapping phenotypes will help guide clinicians toward a correct molecular diagnosis for their patients.

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