

# Expanding Phenotype of *ATPIA3* - Related Disorders: A Case Series

Child Neurology Open  
Volume 0: 1-5  
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DOI: 10.1177/2329048X211048068  
journals.sagepub.com/home/cno



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## Abstract

Neurologic disorders caused by mutations in the *ATPIA3* gene were originally reported as three distinct rare clinical syndromes: Alternating Hemiplegia of Childhood (AHC), Rapid-onset Dystonia Parkinsonism (RDP) and Cerebellar ataxia, Areflexia, Pes cavus, Opticus atrophy and Sensorineural hearing loss (CAPOS). In this case series, we describe 3 patients. A mother and her daughter showed an intermediate phenotype different from each other with the same heterozygous missense mutation (p.[R756C]), recently described in literature as Relapsing Encephalopathy With Cerebellar Ataxia (RECA). In addition, a third patient showed an intermediate AHC-RDP phenotype and had a likely pathogenic novel de novo missense mutation (p.[L100 V]). These patients support the growing evidence that AHC, RDP and RECA are part of a continuous *ATPIA3* mutation spectrum that is still expanding. Three common features were a sudden onset, asymmetrical neurological symptoms, as well as the presence of triggering factors. When present, the authors argue to perform exome sequencing in an early stage.

## Keywords

*ATPIA3* gene, AHC, RDP, RECA, genetics, intermediate phenotype

Received May 9, 2021. Received revised August 8, 2021. Accepted for publication September 3, 2021.

## Introduction

Alternating Hemiplegia of Childhood (AHC) was first described by Verret and Steele in 1971.<sup>1</sup> In respectively 1993 and 1996 patients with Rapid-onset Dystonia Parkinsonism (RDP) and Cerebellar ataxia, Areflexia, Pes cavus, Opticus atrophy and Sensorineural hearing loss (CAPOS) were published.<sup>2-4</sup> These disorders are very rare; AHC phenotype has an estimated prevalence of 1:1.000.000.<sup>4</sup>

Since 2014, they can be linked to pathogenic variants in the *ATPIA3* gene.<sup>5</sup> The *ATPIA3* gene encodes for the alpha 3 subunit of the Na-K ATPase pump. If the cation pump disfunctions, the resting membrane potential of the neurons in the central nervous system will change. The neuronal uptake of some neurotransmitters, like dopamine, is dependent on a correct Na<sup>+</sup> gradient. An impaired gradient will possibly result in parkinsonism and dystonia.<sup>5,6</sup> Several pathogenic mechanisms, contributing to *ATPIA3* disorders, are revealed. For example in AHC, a clear genotype-phenotype correlation, has been reported. However, there are still many pathogenic mechanisms unknown.<sup>7-10</sup>

Recently, another intermediate phenotype emerged, called Relapsing Encephalopathy With Cerebellar Ataxia (RECA) with a consistent genetic mutation in p.R756.<sup>11</sup> RECA was first described by Dard et al. in 2015.<sup>12</sup>

Clinical criteria of AHC, RDP, CAPOS and RECA are described in Table 1. Hypotonia and hemiplegia are characteristic features in patients with AHC, dystonia in RDP, ataxia in RECA and areflexia and optic atrophy in CAPOS.

Here the authors report on three female Caucasian patients, including a mother and her daughter, all presenting an

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**Table 1.** Phenotypic Spectrum of *ATPIA3*- Related Disorders, Including the 3 Reported Cases.<sup>4-7,11</sup>

	Patient 1	Patient 2	Patient 3	AHC	RDP	CAPOS	RECA
Age at onset	2 years	12 months	7 months	0 to 18 months	9 to 14 months & second -third decade	6 months-5 years	< 5 years
Sudden onset	+	+	+	+	+	+	+
Triggers							
Fever/infection	+	+	+	+	+	+	+
Stress				+	+		
Physical activity				+	+		
Alcohol binges					+		
Fluctuating neurological symptoms							
Hypotonia	+	+	+	+	-	+	+
Dystonia	+			+/-	+	+/-	+
Ataxia					+/-	+	+
Chorea					-	-	+
Bulbar dysfunction	+	+	+		+		+
Dysphagia			+		+	+/-	+
Oculomotor abnormalities	+	+		+	+/-		+/-
Symptoms disappear during sleep		+		+			
Persisting neurological symptoms							
Hypotonia			+	+	-	+	+
Areflexia	+					+	
Dystonia	+			+	+		+
Ataxia	+	+	+	+	+/-	+	+
Chorea		+		+	-	-	+
Bulbar dysfunction	+		+	+	+	-	+
Dysphagia			+		+	-	+
Oculomotor abnormalities				+	+/-	+/-	
Epilepsy	-	-	+	+	-	-	-
Cognitive dysfunction	-	+	+	+	-	-	-
Genetics	Familial c.2266C > T missense variant in exon 17	Familial c.2266C > T missense variant in exon 17	De novo c.298C > G missense variant in exon 4	Mostly de novo mutations in exons 17,18	De novo/ inherited mutations in exons 8, 14, 17	De novo/ inherited c.2452G > A	De novo/ inherited p.R756 variants

Abbreviations: AHC, Alternating hemiplegia of childhood; RDP, Rapid-onset dystonia Parkinsonism; CAPOS, Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss; RECA, Relapsing Encephalopathy With Cerebellar Ataxia.

intermediate phenotype. Exome sequencing was essentially performed as previously described in literature.<sup>13</sup> Briefly, capture of exons was done using an Agilent SureSelect Human All Exon 50 Mb Kit (Santa Clara, CA, USA). Sequencing was performed using a Life Technologies 5500XL machine (Thermo Fisher, Waltham, MA, USA) or an Illumina HiSeq 2000 (San Diego, CA, USA). Read mapping and variant calling were done using LifeScope Life Technologies (Thermo Fisher) for the 5500XL data or BWA (mapping) and GATK (calling) for the Illumina data.<sup>13</sup> Reference sequence for corresponding *ATPIA3* transcript was [NM\_152296.4]. Written informed consent for the

publication of the case descriptions publication was obtained for all patients.

## Case Series

### Patient 1

She was born prematurely at 32 weeks as one of a triplet. At 2 years of age, she developed spastic quadriplegia with dystonia, after an episode of recurrent viral infections with fever. Thereafter, she showed four events with a combination of symptoms including headache, reduced muscle tone in the right arm,

dysphasia and reduced vision. These events resolved rapidly without therapy. Simultaneously, she developed dysarthria, ataxia and dystonia. At physical examination areflexia of the lower extremities was found. Mitochondrial encephalomyopathy was suspected for a long time. The events were classified as cerebral ischemia caused by mitochondrial angiopathy. Several muscle biopsies could not confirm this diagnosis, nor DNA analysis on mitochondrial disorders. Multiple magnetic resonance imaging (MRI) examinations of brain and spinal cord were normal. Blood and urine examination for metabolic screening, cardiological and ophthalmologic screening were all normal.

When her daughter, aged 1 year, was admitted to hospital (patient 2) with unexplained neurological symptoms, Whole Exome Sequencing (WES) was performed, revealing a heterozygous missense variant in the *ATPIA3* gene (c.2266C>T; p.[R756C]). The mother was at that time 33 years old.

### Patient 2

During pregnancy, a thickened nuchal translucency was noticed at 12 weeks gestation. Prenatal chromosomal analysis, a SNP-array, and DNA diagnostics for Noonan syndrome were normal. After birth at physical examination minor dysmorphic features (upslant of the eyes, enlarged tongue, thin philtrum and a short neck) were present. Down syndrome was suspected, but not confirmed by karyotyping. Aged 1 year, she was admitted to hospital with fever, hypotonia, episodes of tonic movements, oculomotor asymmetrical apraxia and rhythmic tongue movements. She lost the ability to sit and stand during this episode. She recovered after some days, but involuntary choreatic movements remained. Moreover, after some years, she developed a mild developmental delay and symptoms of ataxia.

Extensive diagnostic tests were all normal, including an EEG, MRI, metabolic screening (liquor, blood and urine), ophthalmologic and audiologic examination. Targeted WES analysis showed the same heterozygous missense variant (c.2266C>T; p.[R756C]).

### Patient 3

This girl was born after an unremarkable pregnancy and term delivery. At the age of 7 months, she showed stagnation of her motor development after an episode with low body temperature possibly caused by a viral infection. Two months later, she developed a significant hypotonia, which deteriorated to a spastic diplegia. At the age of 2,5 years, she progressed to spastic quadriplegia with an axial hypotonia. A gastrostomy tube was needed for feeding assistance. She was confined to a wheel chair and used a speech computer to communicate. At physical examination, she had mild dysmorphic features, like upslant of the eyes, a large mouth and large ears. She showed dysarthria and drooling. A severe thoracolumbar scoliosis was present. Neurological examination showed symmetric reflexes

of the arms and brisk reflexes of the legs. Later on, she developed absences.

The EEG showed epileptic activity, prominent in the central and temporal regions. A MRI of the brain and cervical spine, metabolic examination (liquor, blood and urine), and a muscle biopsy were all normal.

Ophthalmologic examination showed no optic atrophy. SNP array, DNA analyses of mitochondrial DNA in blood and the *SMI*, *UBE3A*, *SPG4-SPG2*-gene were all normal. WES trio-analysis was performed, showing a novel *de novo* missense variant in the *ATPIA3* gene (c.298C>G; p.[L100 V]). The class (likely pathogenic) was determined using ACMG guidelines,<sup>18</sup> passing the following scores: PS2 (de novo occurrence), PM2 (absent from controls) and PP3 (conserved in orthologues down to *C.elegans*). The combined annotation dependent depletion (CADD) score (PHRED) was 24.7. The results of the in Silico prediction programs are; Align GVG: C0 (GV: 353.86 - GD: 0.00), SIFT: Deleterious (score: 0, median: 4.32), MutationTaster: disease causing (p-value: 1), Polyphen: Humvar: This mutation is predicted to be possibly damaging with a score of 0.765 (sensitivity: 0.76; specificity: 0.86).

## Discussion

We reported three patients with rare *ATPIA3*-related neurological disorders. They all showed a clinical intermediate phenotype (Table 1). Extensive testing, which took many years before a diagnosis became clear, was performed before a WES was put in.

The first and second patient both showed an intermediate phenotype, recently described as RECA.<sup>11</sup> The clinical phenotype in mother and daughter was different from each other, sharing the same mutation (c.2266C>T; p.[R756C]). Patient 1 developed symptoms at the age of 2 years, more typical for RECA than for AHC or RDP. The first neurological symptoms, such as hypotonia, started after a fever episode. After the hypotonia, ataxia becomes prominent in patient 1, and in both patients abnormal movements started. In patient 2, the characteristic ataxia in RECA started after some years.

Until now, two other dominant inherited cases<sup>11,14</sup> and one familial case of a germline mosaicism<sup>15</sup> (2 siblings) are reported with this specific variant in the *ATPIA3* gene.

The third patient showed an intermediate AHC-RDP phenotype. Fluctuating symptoms of drooling, dysarthria, dystonia, and hypotonia were observed. She developed epilepsy, cognitive dysfunction, and showed Gross Motor Function Classification System (GMFCS) scale V. No areflexia, nor optic atrophy, nor hearing loss were present.

Recently, more intermediate cases are described with a catastrophic onset and encephalopathy, although different mutations are reported. Paciorkowski et al. described early infantile epilepsy with encephalopathy (EIEE) as a new phenotype.<sup>16</sup> Shirinzi et al. described a novel *ATPIA3* trinucleotide deletion c.2266\_2268delGAC p.(D756del) with a phenotype consisting in a complex picture of early onset drug-resistant epileptic

encephalopathy, non-epileptic paroxysmal episodes (hypotonia, hemiplegia, apnea, monocular nystagmus) and developmental delay.<sup>17</sup>

In conclusion, in several *ATP1A3* mutations a clear genotype-phenotype relation exists. However, more intermediate phenotypes and new variants emerge. Moreover, published studies have shown that the same pathogenic variant may lead to different phenotypes, such as RDP in one family, and AHC in another.<sup>4-7</sup> The authors therefore conclude that *ATP1A3*-related disorders are part of a large, continuous spectrum instead of separate clinical entities.

In the era of next-generation sequencing techniques in diagnostics, such as WES, the clinical spectrum caused by pathogenic genetic variants will rapidly expand as patients with less specific phenotypes will be molecularly diagnosed.<sup>7</sup>

A multidisciplinary approach, including genetics, will contribute to an early recognition of this rare neurological disorder. This will be helpful to avoid extensive unnecessary diagnostic testing. The common symptoms, like a sudden onset, triggering factors, such as fever, and an asymmetrical presence of neurological symptoms, should initiate genetic investigation early in the diagnostic process. The age-dependent pattern of emergence and progression of different signs and symptoms can be important in the diagnostic process.<sup>8</sup>

At this moment, little is known about treatment and prognosis.<sup>14,19</sup> In the future, more knowledge will be generated on gene-tailored therapy.

### Acknowledgments

None.

### Author Contributions

### Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

### Informed Consent

Verbal informed consent was obtained from the patient(s) or from a legally authorized representative(s) for their anonymized information to be published in this article.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

### Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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### Trial Registration

Not applicable, because this article does not contain any clinical trials.

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