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CASE REPORT

Harel-Yoon syndrome: the first case report from Saudi Arabia

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ABSTRACT

Background: Harel-Yoon syndrome (HAYOS) is a recently described, rare neurodevelopmental disorder characterized by developmental delay, hypotonia, appendicular hypertonia, axonal neuropathy, and other variable features, such as spasticity and optic atrophy. With only a few reports in the literature, both heterozygous and homozygous mutations have been reported in ATPase Family AAA Domain Containing 3A (*ATAD3A*).

Case Presentation: Herein, we present the first case of HAYOS in Saudi Arabia. A 3-month-old girl presented with global developmental delay, hypotonia, bilateral severe sensorineural hearing loss, and vision impairment. Brain magnetic resonance imaging showed mild brain atrophy and delayed myelination. Laboratory tests showed high serum lactate and increased urinary excretion of 3-hydroxy methyl glutaconic acid. Whole exome sequencing revealed a pathogenic heterozygous variant in *ATAD3A* gene (c.1726C>T; p. R576W: NM_018188.4 or c.1582C>T; p. R528W: NM_001170535.1) which is the same recurrent variant reported in patients with the dominant form of HAYOS.

Conclusion: Our report provides further evidence of the clinical relevance of *ATAD3A* gene variant (c. 1726C>T; p. R576W) in the pathogenesis of HAYOS. The therapeutic options for HAYOS are limited to supportive measures as in other mitochondrial diseases.

Keywords: Mitochondrial disorder, HAYOS, *ATAD3A*, whole exome sequencing.

Introduction

Harel-Yoon syndrome (HAYOS: OMIM# 617183) is a recently described neurodevelopmental disorder characterized by global developmental delay (DD), hypotonia, spasticity, and peripheral neuropathy (1). Albeit a few reported cases, the clinical course in HAYOS is highly variable and could include dysmorphic features, hypertrophic cardiomyopathy, optic atrophy, and poor feeding. Laboratory abnormalities could show evidence of mitochondrial dysfunction in the form of increased serum lactate, deficiencies o f m itochondrial respiratory enzymes, and 3-methylglutaconic aciduria. At the molecular genetic level, mutations in ATPase Family AAA Domain Containing 3A (*ATAD3A*) have been reported in patients with HAYOS.

ATAD3A (ATPase Family AAA Domain Containing 3A, OMIM# 612316) gene is located on chromosome 1p36.33 and encodes a 66-kDa mitochondrial membrane protein that is thought to have evolved by duplication of a single ancestral gene (2). ATAD3B (OMIM# 612317) and ATAD3C (OMIM# 617227) are two other human paralogues of *ATAD3A* positioned in tandem on the chromosome (3). *In vitro* studies implicate *ATAD3A* to play a role in mitochondrial dynamics, nucleoid organization, protein translation, cell growth, and cholesterol metabolism (4–7). *In vivo* studies in animal models such as Drosophila and mice revealed that disruption of *ATAD3A* leads to growth arrest during larval development and embryonic lethality at day E7.5, respectively (8,9). High-level expression of *ATAD3A* gene is observed in lung adenocarcinomas and is associated with poor survival in breast cancer patients (10). *ATAD3A* forms homodimers, plays an important role in mitochondrial protein synthesis, and interacts with other proteins, such as GADD45GIP1, STARD9, FAM210A, S100B, and HSP60/HSPD1 involved in mitochondrial RNA metabolism and lipid metabolism (11,12).

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Mutations in *ATAD3A*, which include heterozygous and homozygous variants indicating both autosomal dominant and recessive transmission, have been reported in patients with HAYOS as well as in other neurological phenotypes (1,11,13,14). We report here a Saudi girl who presented with HAYOS symptoms associated with biochemical and radiological abnormalities carrying a *de novo* heterozygous variant in *ATAD3A*.

Case Presentation

A 3-month-old girl presented with a history of stridor since birth, feeding difficulties associated with poor weight gain, extreme irritability and crying, hypotonia, global developmental delay, and impaired hearing and vision. She was born at full-term following uneventful pregnancy and delivery and was discharged home in good condition. She is the third child of healthy parents who are first cousins and have no similar condition reported in their extended family pedigree (Figure 1).

On the first evaluation at 3 months of age, the patient showed failure to thrive and was microcephalic with blonde hair. She had dysmorphic facial features with prominent forehead, deep-seated eyes, short eyebrow, short nose, low set ears, and expressionless face with malar skin telangiectasia. She was not following or fixating and did not startle to noise. She had axial hypotonia with appendicular hypertonia, brisk reflexes, and clonus. It was noted that she had fused labia minora with no other findings suggesting ambiguous genitalia. Other parts of systemic examination were unremarkable. The stridor was attributed to progressive vocal cord dysfunction secondary to the neurological disease. Developmentally, the patient never smiled, did not interact with parents and was not able to follow the moving objects. No abnormal movements were seen or reported (Table 1).

Further evaluation revealed bilateral severe sensorineural hearing loss (SNHL) and vision impairment. Brain magnetic resonance imaging showed mild brain atrophy and delayed myelination. Electroencephalogram revealed no epileptic discharges and nerve conduction velocity was normal. She had unremarkable abdominal ultrasonography and echocardiography. Laboratory tests were unremarkable except for high serum lactate (4 mmol/l; reference range 0.5–2.2 mmol/l) and increased urinary excretion of 3-hydroxy methyl glutaconic acid (3-MGA). The patient showed no noticeable improvement in her developmental milestones on her last evaluation at 20 months of age. She could not roll-over or sit, did not utter any words except a weak cry. She continued to have failure to thrive (weight: 7.5 kg (>2 SD below the third percentile); length 77cm (at the fifth percentile) and head circumference 42 cm (just below the third percentile). She was hypotonic but with appendicular hypertonia and brisk reflexes.

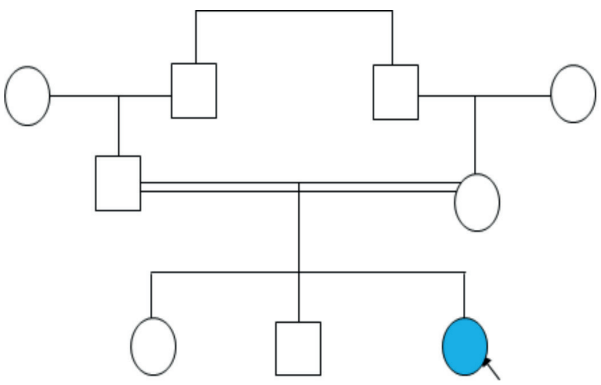

Figure 1. *Pedigree of patient presented in this report.*

Using solo whole exome sequencing (WES), we identified pathogenic heterozygous variant (c. 1726C>T; p. R576W) in *ATAD3A* gene, that was proved to be *de novo* upon parental targeted testing. WES was performed using Agilent SureSelect version 5 kits on an Illumina HiSeq 4000 to an average depth of coverage of 150× with automated adapter trimming of the fastq sequences (BGI Europe). DNA sequence quality metrics were carried out using FASTQC version: 0.11.7 at King Fahad Medical City. Alignment, quality filtering and variant identification were undertaken using commercially available algorithms (DNAStar and Qiagen Clinical Insight-Interpret software). Human reference assemblies were aligned against GRCh37. Computed classification of the *ATAD3A* variant using ACMG criteria supported pathogenic mode. This was based on the variant p. R576W being absent from genomeAD population frequency controls (PM2), multiple lines of computational evidence giving a CADD score of more than 20 supporting pathogenicity (PP3), p. R576W variant being reported in ClinVar as pathogenic but no sufficient functional evidence available (PP5), p. R576W variant being *de novo* in a patient with the disease and no family history (PS2) and other criteria such as report in HGMD as disease causing mutation, data from animal models and the allele frequency in our local KFMC database was 0.05%.

Discussion

Both, heterozygous and homozygous missense mutations in *ATAD3A* were recently identified by WES in patients with HAYOS (1). Only a few cases have been described since then. Here, we describe a Saudi girl with the same *ATAD3A* variant as reported previously in the heterozygous state who was presented with progressive hypotonia, developmental delay, early onset feeding difficulties, vision and hearing impairment, high lactate levels, and increased urinary excretion of 3-MGA, thereby confirming the diagnosis of HAYOS (1). To the best of author's knowledge, this is a first HAYOS report from Saudi Arabia that expands the patient pool with autosomal dominant *ATAD3A* variants.

All the affected cases reported by Harel et al. (1) had severe developmental delay with intellectual disability

Table 1. *Summary of our case and reported cases carrying heterozygous ATAD3A variants.*

Family	Current case	Harel et al Case 1	Harel et al Case 2	Harel et al Case 3	Harel et al Case 4	Harel et al Case 5	Cooper et al case 1	Cooper et al case 2
Gender	F	F	F	M	F	M	F	M
Age at last exam	20 months	9 years	5 years	3 years	5 years	23 months	35 years	3.5 years
Major Reported phenotype	DD, ID , Hypotonia, Spasticity	DD, ID (mild), Hypotonia, Spasticity, peripheral neuropathy	DD, ID, Hypotonia, Spasticity, peripheral neuropathy	DD, ID, Hypotonia, Spasticity, peripheral neuropathy	DD, ID, Hypotonia, Spasticity, peripheral neuropathy	DD, ID, Hypotonia, borderline peripheral neuropathy	Spasticity, peripheral neuropathy	DD, ID, spasticity, peripheral neuropathy
Other	Optic atrophy, SNHL, Mild brain atrophy, Delayed myelination,	optic atrophy, ADHD	-	optic atrophy, Pectus carinatum, hypertrophic cardiomyopathy, Growth hormone deficiency,	optic atrophy, hypertrophic cardiomyo-pathy,	47XXY	Myopia, photophobia	Ptosis, photophobia
Laboratory abnormalities	Elevated lactate, MGA	Not reported	elevated lactate, complex I+III deficiency	elevated lactate, MGA,	elevated lac-tate, MGA, complex II+III, II+CS deficiency	Not reported	Not reported	elevated lactate
ATAD3A variant*	c.1726C>T; p. R576W	c.1726C>T; p. R576W	c.1726C>T; p. R576W	c.1726C>T; p. R576W	c.1726C>T; p. R576W	c.1726C>T; p. R576W	c.1064G>A p.G355D	c.1064G>A p.G355D

*(c.1726C>T; p. R576W: NM_018188.4) is the same as (c.1582C>T; p. R528W: NM_001170535.1).

Abbreviations: ADHD, attention deficit hyperactivity; DD, developmental delay; F, female; M, male; ID, intellectual disability; MGA, methyl glutaconic aciduria; SNHL, sensory neural hearing loss.

and poor or deficient speech as our case. Our patient has dysmorphic facial features that are not a consistent finding among reported cases. Optic atrophy is observed in our patient as well as in three of the previously reported cases but SNHL was not reported before. Cardiac exam is normal in our case, but hypertrophic cardiomyopathy was noted in two of the five described cases. All the reported patients had truncal hypotonia, and most exhibited peripheral spasticity (1). The girl in our report has lactic acidosis and methylglutaconic aciduria suggestive of mitochondrial dysfunction which was also previously reported in some patients.

Our patient has the same variant in ATAD3A (c. 1726C>T; p. R576W) that was also reported in five patients with HAYOS by Harel et al. (1). This missense change is thought to be disease causing through a dominant negative or a gain of function mechanism. Cooper et al. (11) reported another dominantly inherited heterozygous variant (c.1064G>A (p.G355D) in ATAD3A presenting as hereditary spastic paraplegia. In the same original report, Harel et al. (1) also reported two additional families carrying a homozygous *ATAD3A* variant with autosomal recessive mode of inheritance. Desai et al. (13) identified four individuals with a fatal pontocerebellar hypoplasia and respiratory insufficiency syndrome. Affected patients showed early onset respiratory failure and floppiness associated with other features of congenital cataract, dysmorphic features, seizure disorder, and cardiac abnormalities. All died within the first week of life and were found to have biallelic deletions within the *ATAD3* gene cluster on chromosome 1p36.33 and these deletions created an *ATAD3B*/*ATAD3A* fusion gene. In the same report, Desai et al. (13) also reported a fifth patient with later-onset encephalopathy with cerebellar atrophy who has genomic rearrangements affecting the ATAD3C/ATAD3B genes on one allele and ATAD3B/ATAD3A genes on the other. In their original report, Harel et al. (1) reported a newborn with a fatal multisystemic disease with significant pontocerebellar hypoplasia and lissencephaly related to chromosomal 1p36.33 deletion syndrome (1). Peralta et al. reported similar phenotype with fatal neonatal cerebellar hypoplasia in four siblings with homozygous missense variant in *ATAD3A,* suggesting that it is *ATAD3A*, not *ATAD3B*, is responsible for this severe phenotype (14). In another report, five neonates with a lethal metabolic disorder characterized by cardiomyopathy, corneal opacities, encephalopathy, hypotonia, and seizures who harbored a monoallelic reciprocal duplication at the ATAD3 locus was identified (15).

ATAD3A gene belongs to a 3-gene cluster family with *ATAD3B* and *ATAD3C* as its important paralogs with extensive sequence homology. *ATAD3A* gene occupies 22.51 kb of the genome, comprising 634 amino acids with N-terminus domains such as coiled-coil (CC1/2) followed by transmembrane (TM1/2) domains and a conserved ATPase domain in the C-terminus (Figure 2a). The protein position arginine at 576 (R) in *ATAD3A* protein is highly conserved across species (Figure 2b) making it functionally relevant.

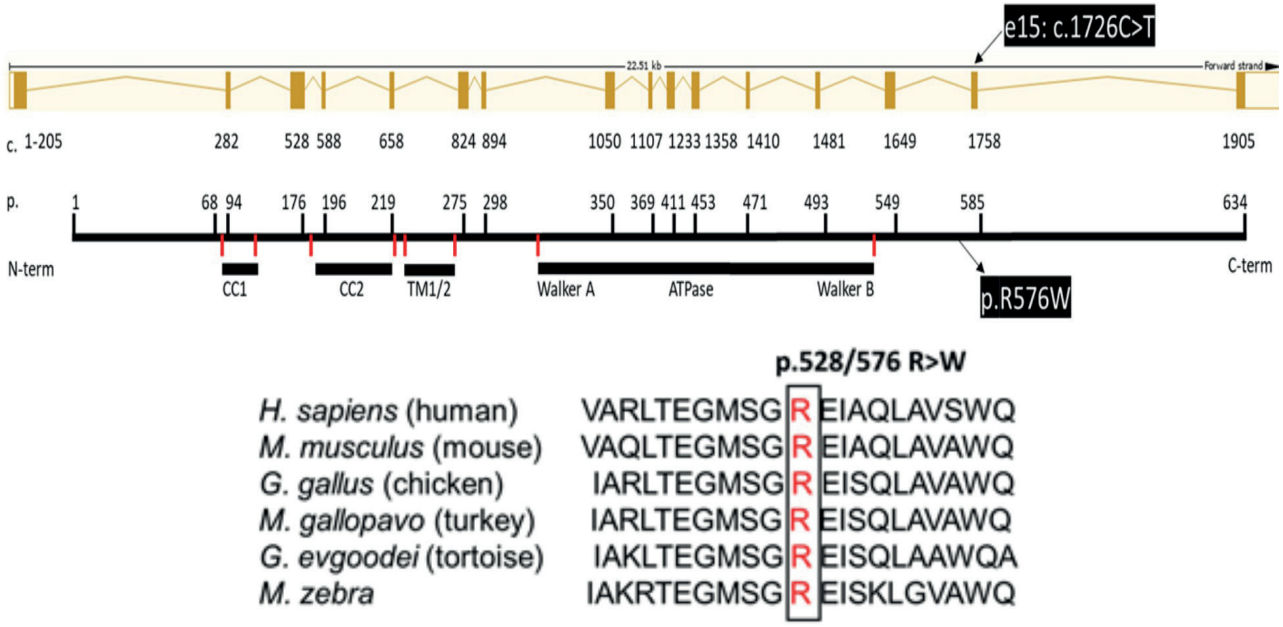

Figure 2. *(a) ATAD3A gene and protein domains. (b) conservation across species and mutation identified in the case.*

Conclusion

In conclusion, here, we presented an infant with HAYOS who harbored the same recurrent variant reported in patients with the dominant form of this disorder. *ATAD3A* is newly described disease gene in which, single nucleotide and copy number variants, are associated with dominant and recessive disorders with variable spectrum of severity. Like other mitochondrial diseases, the therapeutic options for HAYOS are limited to supportive measures for the time being. Future research to better understand the function of the gene and the protein could open more treatment avenues.

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List of Abbreviations

ATAD3A	ATPase Family AAA Domain Containing 3A
HAYOS	Harel-Yoon syndrome
SNHL	Sensorineural hearing loss
WES	Whole exome sequencing

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None.

Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication
An informed consent was obtained from the parents.

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