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Case report

A case report of Harel-Yoon syndrome associated with ATAD3A gene variants

Xia Huang, Hua Jiang and Hua Ren*

Department of Pediatrics, Yanan University Affiliated Hospital, Yan'an 716000, China

Correspondence: Email: 664510424@qq.com.

Abstract: In this study, we reported a rare case of Harel-Yoon syndrome (HAYOS) caused by a mutation in the ATAD3A gene on chromosome 1p36.33. A 34-day-old female infant presented with the chief complaints of "intermittent irritability and poor feeding for 8 days, worsening over the past hour." Laboratory investigations revealed hyperammonemia and lactic acidosis. Cardiac injury biomarkers and inflammatory markers were elevated. Echocardiography indicated cardiac insufficiency and cardiomyopathy. Both parents were phenotypically normal, non-consanguineous, and had no family history of inherited disorders. Further whole-exome sequencing (including mitochondrial DNA) identified a heterozygous missense variant, c.1582C>T (p.Arg528Trp), in the ATAD3A gene in the proband. This was confirmed to be a de novo variant, leading to a diagnosis of HAYOS. This variant was classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines and constitutes the genetic etiology of HAYOS in this patient. We summarized the clinical characteristics of this case and reviewed the relevant literature. This report expands the known genotype-phenotype spectrum associated with ATAD3A gene variants and enhances clinical recognition and diagnostic capabilities for this rare disorder.

Keywords: ATAD3A gene; Harel-Yoon syndrome (HAYOS)

1. Introduction

Harel-Yoon syndrome (HAYOS) is a rare mitochondrial disorder, with an overall prevalence of <1/1,000,000. The condition typically manifests in the neonatal or infantile period and is characterized by global developmental delay, hypotonia, intellectual disability, hypertrophic

cardiomyopathy, and lactic acidosis, among other features [1].

HAYOS is caused by mutations in the ATAD3A gene on chromosome 1p36.33. ATAD3A encodes a mitochondrial AAA+ ATPase protein. Since 2016, when Dr. Harel T and Dr. Yoon WH first identified ATAD3A abnormalities as the cause of HAYOS in eight patients from seven families, this syndrome has been recognized as resulting from either autosomal dominant or recessive inheritance. HAYOS presents with complex and diverse clinical features, exhibiting a highly individualized nature [2].

Despite a recent surge in research uncovering this syndrome, it remains a rare disorder that is clinically challenging to diagnose and manage. This report details a rare case of HAYOS caused by an ATAD3A gene mutation. It aims to highlight the condition's rarity and complexity in the clinical setting. By providing a comprehensive description of the case characteristics, we seek to enhance recognition and therapeutic skills among clinicians, advance related research, and summarize reported cases to guide evidence-based clinical decision-making.

2. Case presentation

A 34-day-old female infant was admitted to the hospital, presenting "intermittent irritability and poor feeding for 8 days, worsening acutely over 1 hour". Eight days before admission, the infant developed episodes of irritability without an identifiable precipitating cause. These episodes were characterized by profuse sweating and lasted approximately 30 minutes, occurring three to four times daily. Symptoms typically resolved spontaneously or following flatus. Poor feeding accompanied these episodes, with occasional non-projectile vomiting of small volume. No specific treatment was administered during this period. One hour before admission, the infant experienced a significantly prolonged episode of irritability accompanied by generalized cyanosis, prompting hospital presentation.

The infant is the second child of her mother (G2P2), born via full-term cesarean delivery with a birth weight of 3.2 kg. Apgar scores were normal, with no history of intrauterine asphyxia or resuscitation at birth. The mother received regular prenatal care, which was unremarkable. The parents deny consanguinity and report no significant family genetic history. The infant has had persistent feeding difficulties since birth, characterized by laborious sucking and prolonged feeding intervals. Her sibling (the first child) is healthy.

Positive Physical Examination Findings: The infant weighed 3.6 kg and was 50 cm long. Vital signs included a temperature of 36.9 ℃, heart rate of 166 beats per minute (tachycardia), respiratory rate of 60 breaths per minute (tachypnea), and oxygen saturation of 95% on supplemental oxygen. The infant exhibited respiratory distress characterized by tachypnea and grunting respirations, along with poor mental status. Generalized cyanosis was present. The extremities were cool to the touch with mottled skin. Muscle tone was slightly decreased. Cardiac examination revealed tachycardia with diminished heart sounds and a grade II murmur audible over the precordium. Pulmonary auscultation revealed coarse breath sounds with audible crackles (rhonchi). The abdomen was soft with normoactive bowel sounds.

Ancillary examination: Arterial blood gas analysis revealed: pH < 6.74, SO_2 68%, PCO_2 58.4 mmHg, PO_2 90 mmHg, L-lactate 19.8 mmol/L, HCO_3^- 7.4 mmol/L. Complete Blood Count: White blood cell (WBC) count 19.41 × 10^9/L, neutrophils 26.3%, lymphocytes 63.9%, monocytes 8.3%. Red blood cell (RBC) count 4.53 × 10^{12}/L, hemoglobin 156 g/L. C-reactive protein (CRP) < 5 mg/L, high-sensitivity CRP (hs-CRP) 0.4 mg/L. The measured values of myocardial injury biomarkers were as

follows: Myoglobin 154.5 ng/mL and creatine kinase-MB (CK-MB) 14.92 ng/mL. The N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 57,390 pg/mL. The plasma ammonia concentration was 58.07 μmol/L. Plasma amino acid and acylcarnitine analysis by tandem mass spectrometry revealed no significant abnormalities in amino acid levels and no abnormalities in acylcarnitine concentrations. Echocardiography revealed findings suggestive of left ventricular noncompaction that could not be ruled out; a mid-interatrial septal defect, consistent with a patent foramen ovale; and reduced left ventricular systolic function, with an ejection fraction (EF) of 44% (Figures 1 and 2). Cranial ultrasound showed no significant abnormalities; chest radiograph revealed bilateral bronchopneumonia. Chest radiograph: Bilateral bronchopneumonia. Electrocardiogram: ST-segment changes. We performed comprehensive genetic testing, including analysis of the mitochondrial genome.

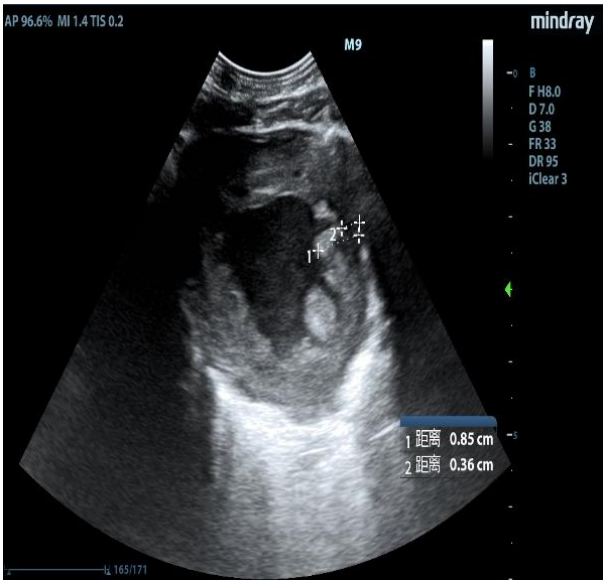

Figure 1. Left Ventricle, Long-Axis View.

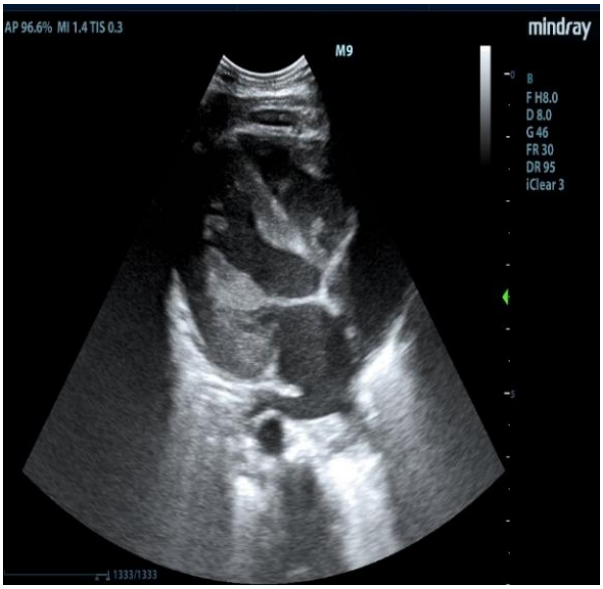

Figure 2. Left Ventricle, Short-Axis View.

Figures 1 and 2 reveal the presence of multiple coarse trabeculations and deep recesses within the left ventricular cavity, presenting a mesh-like appearance. The non-compacted myocardium measured approximately 4.7 mm in thickness, while the compacted myocardium measured approximately 2.8 mm.

Genomic DNA was extracted from peripheral blood samples (2 mL, EDTA-anticoagulated) collected from the pediatric patient and both parents. A genomic library was constructed from this DNA. Targeted capture of the exonic regions and adjacent splice sites (approximately 20 bp flanking each exon) of the genes of interest, along with the entire mitochondrial genome, was performed using probe hybridization, followed by enrichment of the captured regions. Quality control was conducted on the enriched libraries, which were subsequently sequenced on a high-throughput sequencing platform.

Whole-exome sequencing (WES) analysis encompassing the exonic regions and flanking splice sites identified a heterozygous missense variant (M1) in the ATAD3A gene in the proband: c.1582C>T (p.Arg528Trp). This variant results from a cytosine to thymine substitution at nucleotide position 1582 of the cDNA (corresponding to position 1528 in some transcript annotations), leading to the replacement of arginine by tryptophan at codon 528 (Figure 3). Sanger sequencing revealed that neither parent carried the M1 variant. This finding suggested that the variant arose de novo in the proband or resulted from gonosomal mosaicism in one parent.

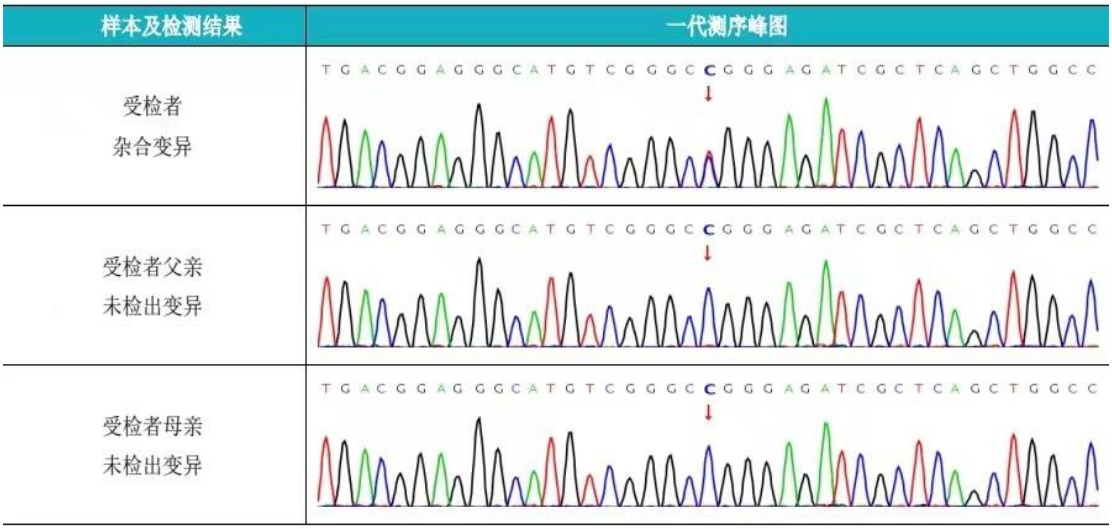

Figure 3. High-throughput sequencing results of genomic DNA from the pediatric patient and his/her parents.

Genetic analysis identified a heterozygous c.1528C>T mutation in the ATAD3A gene of the proband, resulting in the p.Arg582Trp (p.R582W) amino acid substitution. Both parents were confirmed to be wild-type at this locus.

Note: The observed variant may represent the complementary sequence to the reference sequence; for instance, the variation designated as G>A can equivalently be represented as C>T.

Following six days of supportive and symptomatic treatment, including acidosis correction, volume expansion, cardiotonic therapy, diuresis, and myocardial nutrition, the child improved and was discharged. Post-discharge management involved oral medications with scheduled follow-up visits.

Following discharge, the infant exhibited recurrent episodes of irritability, which progressively

increased in duration and were accompanied by feeding difficulties. Approximately one month later, the infant was brought to our hospital again due to persistent irritability refractory to soothing, generalized cyanosis, and stridor.

Complete Blood Count: White blood cell count (WBC)19.81 × 10^9/L, neutrophils 82.0%, lymphocytes 12.2%, red blood cell count (RBC) 3.50 × 10^{12}/L, and hemoglobin (Hb) 106 g/L. Chest Computed Tomography (CT): Bronchopneumonia in the left lung. Cardiac Ultrasound (Echocardiography): Left ventricular enlargement with hypertrophy of the left ventricular wall and interventricular septum. The findings in the apical region of the left ventricle were suggestive of noncompaction cardiomyopathy. The mid-portion atrial septum findings were consistent with a secundum-type atrial septal defect (ASD). Left ventricular systolic and diastolic functions were normal. Color Doppler flow imaging demonstrated a left-to-right shunt at the atrial level and trace tricuspid regurgitation. Left ventricular ejection fraction (LVEF) was 66%.

Treatment included supportive and symptomatic therapy with cardiotonic agents, diuretics, anti-infection therapy, and myocardial nutrition support.

The infant presented persistent crying and irritability refractory to comfort measures, necessitating continuous sedation management with Midazolam. Following diagnosis establishment, treatment had to be discontinued. The patient was discharged after the legally authorized person(s) signed the discharge documentation.

3. Discussion

HAYOS is a rare mitochondrial disorder with an overall prevalence of less than 1 in 1,000,000. The disease typically presents in the neonatal or infantile period and is characterized by global developmental delay, hypotonia, intellectual disability, optic atrophy, axonal neuropathy, hypertrophic cardiomyopathy, lactic acidosis, and excessive generation of Krebs cycle intermediates. Variable features may include spasticity, seizures, ataxia, congenital cataracts, and dysmorphic facial features.

3.1. Mitochondrial diseases

Mitochondrial diseases represent a heterogeneous group of metabolic and/or neurological disorders caused by dysfunction of oxidative phosphorylation, affecting multiple body systems. The incidence in adults is approximately 1:4300, while that in live births is 1:5000 [3]. Mitochondrial membranes undergo a continuous cycle of fission and fusion to ensure the proper functioning of mitochondrial DNA and proteins [4]. ATAD3A, identified by Geuijen in 2005 [5], regulates this fission-fusion process.

3.2. The ATAD3A gene

The AAA+ domain-containing protein ATAD3A is a mitochondrial membrane protein that forms hexamers. Within mitochondria, ATAD3A is described as spanning the inner and outer membranes, with its C-terminus oriented towards the matrix and an N-terminal region localized to the outer membrane. ATAD3A forms homomeric domains via its N- and C-terminal regions and exhibits a periodic distribution pattern along the mitochondrial network, which contributes to maintaining mitochondrial structural morphology [6]. It is essential for maintaining the structure and function of

mitochondrial DNA (mtDNA). In recent years, an increasing number of ATAD3A mutations have been identified, which may impact mitochondrial structure, mtDNA distribution and quantity, respiratory chain complex activity, and ATAD3A oligomerization [7]. Researchers have reported that loss of ATAD3A results in growth and developmental defects in humans, mice, and *Caenorhabditis elegans* [8]. ATAD3A is now recognized as one of the five most commonly associated genes with childhood mitochondrial disorders [6].

3.3. The ATAD3A gene and HAYOS

The ATAD3A gene (MANE Select v0.95 transcript NM_001170535.3, ENST00000378756.8 (ATAD3A-203), encoding a protein of 586 amino acids from a 2,481 nt transcript, is at chromosome 1p36.33. Spanning approximately 22.5 kb, it comprises 16 exons. Tandem duplication of ATAD3A has resulted in the ATAD3 gene cluster, characterized by the sequential arrangement of ATAD3A, ATAD3B, and ATAD3C [9]. Studies indicate that the ATAD3 protein paralogs belong to the AAA subfamily of AAA+ ATPases. Furthermore, evidence suggests that ATAD3C, despite being truncated relative to ATAD3A, can produce a correctly folded AAA protein [10].

The genetic architecture comprising three highly homologous paralogous arrays at this locus predisposes the region to rearrangements [11]. Structural variants, including deletions, duplications, and rearrangements, represent the most common mutations within the ATAD3 locus [12]. Impaired ATAD3A function results in a spectrum of disorders. Biallelic loss-of-function pathogenic variants cause neonatal-lethal pontocerebellar hypoplasia, hypotonia, and respiratory insufficiency [13]. Recessive hypomorphic variants lead to milder phenotypes. Monoallelic dominant missense pathogenic variants cause developmental delay, mild intellectual disability, hypotonia with spasticity, and cardiomyopathy, constituting HAYOS (MIM#617183) [13]. Monoallelic duplications within the ATAD3 gene cluster locus (encompassing the ATAD3A, ATAD3B, and ATAD3C genes) cause the multisystem chromosome 1p36.33 duplication syndrome/ATAD3 gene cluster duplication syndrome, characterized by severe cardiomyopathy, hypotonia, and variable neurological manifestations [14].

3.4. Structural visualization and mechanism of functional impairment of the ATAD3A p.R528W mutation

In this study, genomic DNA was extracted and used to construct a sequencing library. Target regions covering exonic and splice-site sequences of relevant genes, along with the complete mitochondrial genome, were captured and subjected to high-throughput sequencing. Variants identified in the proband were validated, and parental samples were sequenced to determine inheritance.

The infant harbored a heterozygous missense variant in the ATAD3A gene, c.1582C>T (p.R528W). This mutation was visualized within the three-dimensional model of the ATAD3 protein (Figure 4: Wild-type; Figure 5: Mutant). The p.R528W mutation is within the AAA+ domain, a region responsible for ATP binding and hydrolysis that is critical for maintaining protein conformation and function. This point mutation is predicted to have several detrimental effects:

(1) Structural stability: Substitution of arginine with tryptophan may alter local charge distribution, potentially disrupting protein folding or stability.
(2) ATPase activity: The mutation is likely to impair ATP binding or hydrolysis efficiency, compromising the core function of the AAA+ domain.

(3) Oligomerization capacity: Since ATAD3A functions as a hexamer, the mutation may hinder its self-assembly or interactions with other mitochondrial proteins.

(4) Mitochondrial function: These defects are expected to lead to abnormal mitochondrial membrane architecture, impaired mtDNA maintenance, and dysfunctional oxidative phosphorylation, consistent with the clinical manifestations of HAYOS.

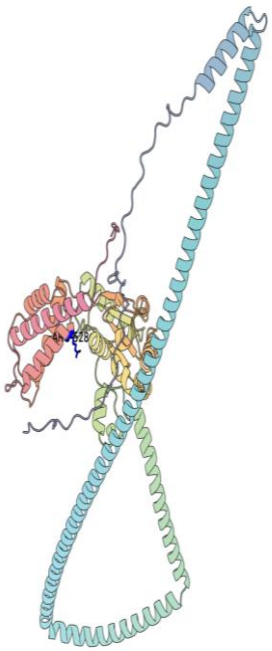

Figure 4. Wild-type.

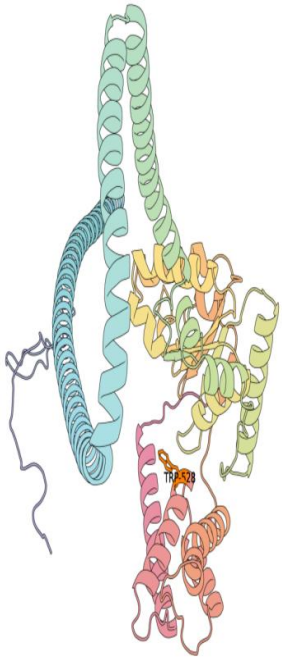

Figure 5. Mutant.

Thus, the p.R528W mutation is inferred to cause loss of function or dominant-negative effects by perturbing protein structure and interactions, resulting in mitochondrial dysfunction. This mechanism aligns with the patient's clinical presentations, including cardiomyopathy, lactic acidosis, and developmental delay, supporting the pathogenicity of this variant.

Genetic testing revealed that neither parent carried the identified variant, suggesting that it likely arose de novo or resulted from parental gonadal mosaicism. According to the ACMG guidelines, and in light of the clinical manifestations observed in the infant, including weak crying since birth, feeding difficulties, intermittent irritability, significantly elevated blood ammonia and lactic acid levels, cardiac insufficiency, and echocardiographic evidence of cardiomyopathy, the heterozygous missense variant was classified as pathogenic, supporting the diagnosis of HAYOS.

There is no targeted treatment for HAYOS caused by variants in the ATAD3A gene. Management primarily consists of symptomatic support and rehabilitative care. It is worth noting that a previous study revealed a case of refractory epilepsy in a patient with HAYOS that was unresponsive to multiple anti-epileptic drugs but was successfully managed with a ketogenic diet, which significantly reduced seizure frequency [15].

3.5. Limitations

This study has two major limitations. First, the detailed treatment information for the patient is insufficient. Specifics regarding drug dosages, treatment duration, and quantifiable efficacy measures are lacking. Furthermore, potential therapeutic options, such as a ketogenic diet (KD), were not explored. Second, the identified p.R528W variant was de novo, with both parents confirmed as wild-type. Additional evidence is required to substantiate the pathogenicity of this variant, and sibling testing was not performed. Nevertheless, this report documents the heterozygous c.1582C>T (p.R528W) missense variant in the ATAD3A gene, providing significant clues for research into HAYOS.

3.6. Innovation

The ATAD3A c.1582C>T (p.R528W) variant reported in this study has been confirmed by multiple studies as a common hotspot mutation responsible HAYOS [3,11,12,15]. This variant mediates the classic mitochondrial disease phenotype observed in the patient by impairing the function of the AAA+ domain.

Although the p.R528W variant is not novel, this case provides important supplementary information regarding its association with extremely early-onset and severe disease progression. Compared to previously reported cases [3,11], the distinct features of this patient include:

(1) Very early and abrupt onset: The patient developed symptoms at 26 days of age and was hospitalized at 34 days due to severe metabolic derangements and cardiac dysfunction. This represents a notably earlier presentation than the typical infantile onset described in most literature, suggesting that the p.R528W variant can lead to acute decompensation in the neonatal period.

(2) Severity and dynamic changes in cardiac function: Initial echocardiography revealed significantly reduced left ventricular systolic function (EF = 44%) along with signs of non-compaction cardiomyopathy. Although cardiac function improved temporarily with active supportive treatment (EF recovered to 66%), structural abnormalities, including left ventricular enlargement and interventricular septal hypertrophy persisted. This pattern of acute, partially reversible, functional impairment offers a more nuanced clinical perspective on the cardiac impact of this variant.

(3) Prominent neurological manifestation characterized by irritability: The patient presented persistent, inconsolable crying accompanied by hyperhidrosis and cyanosis, which may reflect central nervous system dysfunction resulting from severe lactic acidosis and energy deficiency. Although non-specific for mitochondrial disease, this symptom was particularly prominent in this case and was as a core sign of acute deterioration.

4. Conclusions

Through whole-exome sequencing (including mitochondrial DNA analysis), we identified a heterozygous missense variant, c.1582C>T (p.R528W), in the ATAD3A gene, which is associated with HAYOS in the Chinese pediatric patient. Furthermore, its ultra-early onset during the neonatal period, along with features such as acute severe yet partially reversible impairment of cardiac function, broadens our understanding of the phenotypic spectrum associated with this common variant. For infants presenting acute metabolic disturbances and cardiomyopathy, HAYOS and ATAD3A gene sequencing should be included in the differential diagnosis, even in very young patients, to facilitate early diagnosis and genetic counseling.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

Xia Huang was responsible for patient admission, physical examinations, and ancillary examinations; she also drafted the initial manuscript. Hua Jiang conducted the data analysis and results interpretation; he assisted in data collation. Hua Ren designed the research framework, critically reviewed the entire manuscript, assisted in manuscript submission, and oversaw the study integrity.

Ethics approval of research

This research has received ethical approval from the Ethics Commission of Yanan University Affiliated Hospital (IIT-R-20250154). Written informed consent was obtained from the patient.

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