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Harel-Yoon syndrome caused by a novel variant in ATAD3A: A case report

Shuning Zhang [a,b], Luyao Lin [a], Yuelin Li [a], Chanjuan Peng [a], Yan Lin [a,b], Yongle Liu [a,b], Liyu Liang [a,b], Jiyu Huang [a,b], Qinmei Xie [a,b], Meijun Yang [a,b], Hui Zhu [a,b,*]

[a] Department of NICU, Shengli Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, 350001, PR China
[b] Fujian Provincial Key Laboratory of Critical Care Medicine, Fuzhou, Fujian, 350001, PR China

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ABSTRACT

Objectives: To describe the clinical feature of a very recently identified phenotype associated with ATAD3A variation.
Methods: A neonate with Harel-Yoon syndrome was identified. We describe the proband's clinical and radiological features. The affected newborn and her parents underwent whole-exome sequencing and PCR-Sanger sequencing.
Results: Previously reported clinical manifestations were rare in the neonatal period, including unmanageable seizures necessitating the use of multiple drugs, congenital laryngeal stridor, hypotonia, challenges with feeding, corneal opacity, and subsequent demise due to respiratory failure. Molecular investigations have unveiled the presence of a newly identified heterozygous single-base substitution (c.1517A > C; p.Q506P) within the ATAD3A gene.
Discussion: This study unveils a novel single-base substitution, thereby expanding the mutation spectrum associated with ATAD3A. Furthermore, the clinical characteristics exhibited during the neonatal phase are comprehensively described, potentially facilitating improved clinical recognition of ATAD3A-associated HAYOS.

1. Introduction

ATAD3A is a mitochondrial AAA + ATPase protein localized between the inner and outer mitochondrial membrane [1]. It plays a role in a wide range of cellular processes, encompassing the maintenance and replication of mitochondrial DNA (mtDNA), facilitating cholesterol transport, and conferring resistance to therapy in cancer cells [2]. Since 2016, Dr. Harel T and Dr. Yoon WH were the first to identify mutations in the ATAD3A gene as the cause of Harel-Yoon syndrome (HAYOS) in eight patients from 7 families, the literature has documented the description of over 65 patients with this condition. This syndrome exhibits intricate and diverse clinical characteristics, displaying a highly individualized nature. HAYOS is associated with cerebellar and brainstem atrophy, hypotonia, encephalopathy and death in the first days or weeks of life [2,3]. Individuals who manage to survive into adulthood with ATAD3A-related conditions have been documented to exhibit a milder clinical presentation, which includes developmental delay, cataracts, seizures, as well as optic and cerebellar atrophy [4,5]. Although there has been a gradual upsurge in research pertaining to the discovery of this

* Corresponding author. Department of NICU, Shengli Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, PR China.
E-mail address: zhuhui6154@163.com (H. Zhu).

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syndrome in recent years, it remains a rare disease with challenging clinical diagnostic and therapeutic aspects.

In this case, the clinical manifestations of a chinese neonate who was genetically diagnosed with HAYOS are summarised and analysed in detail to improve the understanding of this disease.

2. Case presentation

2.1. Ethics statement

This study was approved by the Fujian Provincial Hospital Ethics Committee (Approval reference number: K2023-04-042, Date of approval April 17, 2023). Written informed consent was obtained from the legal representatives of the patient to publish this case report and accompanying images.

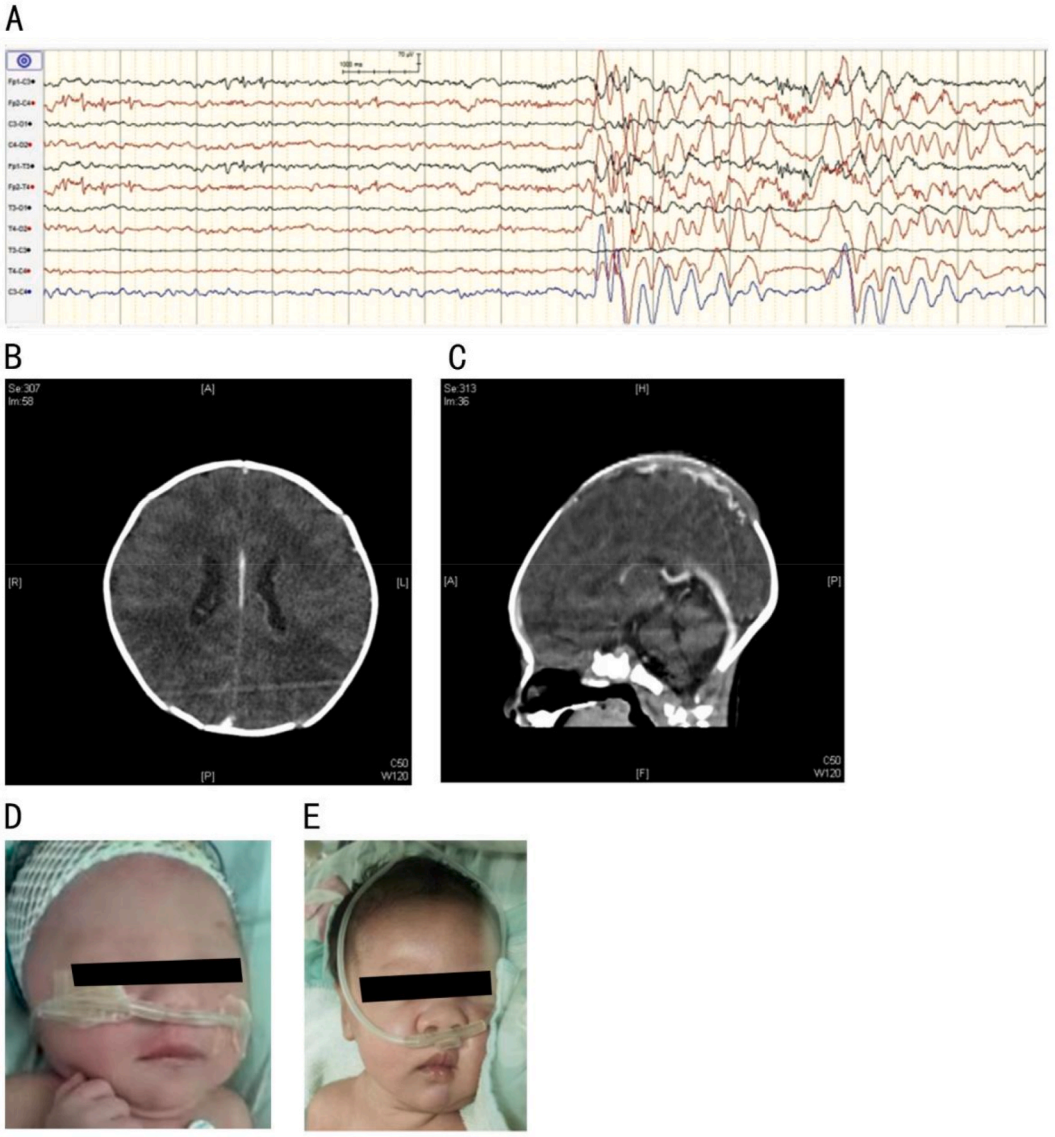

Fig. 1. Clinical manifestations
A. Increased amplitude of all-conductor waves interspersed with scattered spikes on the EEG.
B. Cranial CT scan + enhancement after the onset of convulsions showed slightly hypointense shadows with poorly defined borders in the bilateral frontoparieto-occipitotemporal lobes and parietal ventricles.
C. Cranial CT scan + enhancement after the onset of convulsions in sagittal view, no cerebellar lesions were observed.
D. The neonate's appearance at birth.
E. The neonate's appearance at 30 days after birth. High forehead and small lower jaw appeared.

2.2. Case report

2.2.1. The condition of the patient at birth

The proband was born by caesarean section at 37^{+6} weeks gestation to a 23-year-old mother with a birth weight of 2790g. The neonate's Apgar score was 5-8-9. She was resuscitated after delivery and immediately transferred to the NICU due to intolerable oxygen saturation.

2.2.2. The initial presentation involves respiratory and gastrointestinal symptoms

The cry was inaudible and laryngeal stridor was noticed. To assist breathing and stimulate the respiratory centre, non-invasive positive pressure ventilation and caffeine were administered. The neck and larynx computed tomography (CT) scans exhibited normal findings, while the chest CT revealed the presence of pneumonia. Fibre-optic bronchoscopy was performed at 10 days of age and showed moderate amounts of foamy secretions. No abnormalities were observed in the nasal cavity, epiglottis, or bilateral vocal folds, with the exception of pronounced swelling in the bilateral arytenoid epiglottis folds. Intravenous infusion of methylprednisolone and nebulisation of budesonide suspension were given. Despite these interventions, notable improvement was not observed, and she remained dependent on supplemental oxygen. The patient experienced difficulty in swallowing and was prone to choking, accompanied by an excessive buildup of secretions in the oral cavity and subsequent regurgitant asphyxia shortly after nasal feeding. Recurrent episodes of apnea occurred, ultimately necessitating the use of endotracheal intubation and ventilatory support.

2.2.3. Neurological symptoms including epileptogenesis and related examinations and treatments

The 0.5h electroencephalogram (EEG) monitoring was normal and was carried out after admission because of the presence of hypotonia and flaccid limbs. On day 14, she exhibited fever and recurrent seizures, characterized by heightened muscle tone and

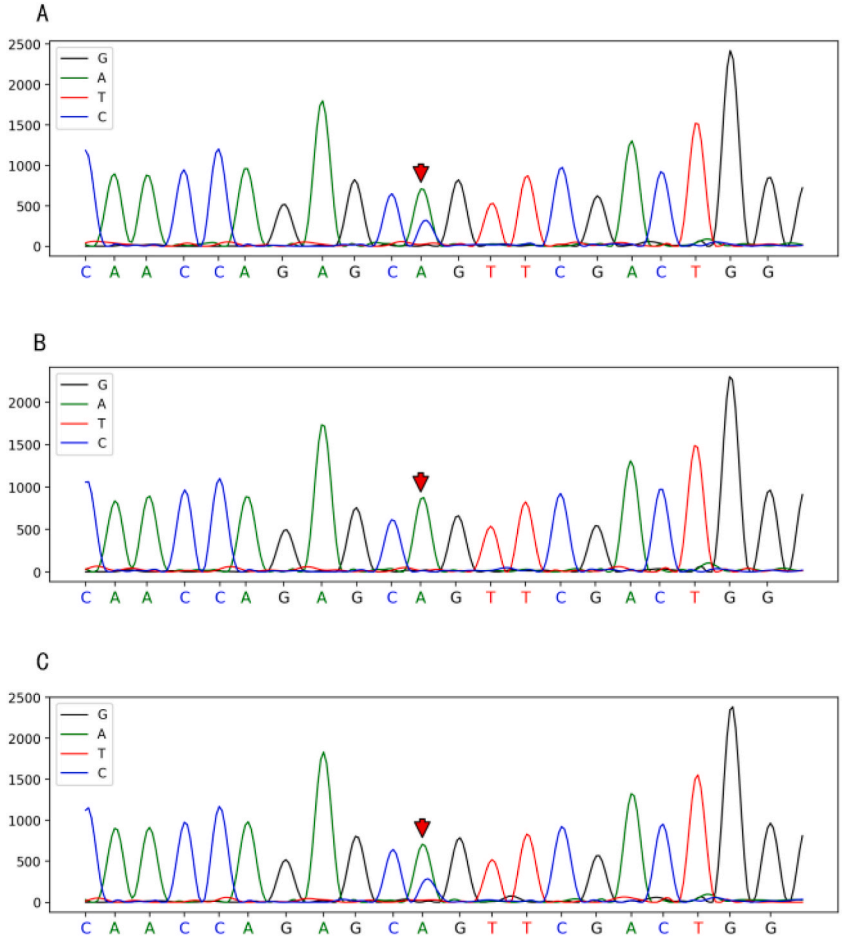

Fig. 2. A. Sequencing diagram of the patient. c.1517 A > C variant in the exon 14 of the ATAD3A gene results in the p.Q506P amino acid mutation.
B. Sequencing diagram of the patient's father. c.1517 A > C variant in the exon 14 of the ATAD3A gene was not detected.
C. Sequencing diagram of the patient's mother. c.1517 A > C variant in the exon 14 of the ATAD3A gene results in the p.Q506P amino acid mutation.

irregular, persistent flailing movements lasting tens of minutes, with an elevation in the amplitude of all-conductor waves interspersed with scattered spikes on the EEG during the same period (Fig. 1A). A lumbar puncture was performed with mildly elevated cerebrospinal fluid (CSF) WBC count. Meanwhile, cranial CT scan + enhancement showed slightly hypointense shadows with poorly defined borders in the bilateral frontoparieto-occipitotemporal lobes and parietal ventricles (Fig. 1B and C). Meropenem was administered for infection control until the CSF results on review were normal. However, she continued to experience recurrent seizures despite the antiepileptic drugs used were gradually increased to phenobarbital + levetiracetam + midazolam. The lower lip persisted in exhibiting mild twitching upon stimulation. No abnormalities were found by blood strand mass spectrometry or urine gas chromatography. Electrolytes were in the normal range on multiple tests and were supplemented or corrected intravenously. Plasma lactate was ranged from 1.6 to 2.2mmol/L.

2.2.4. Other abnormal clinical manifestations and symptoms were observed

Cardiac ultrasound confirmed patent ductus arteriosus (PDA), patent foramen ovale, widened coronary sinus, permanent left superior vena cava and pericardial effusion. She did not open her eyes spontaneously after birth and corneal opacity was confirmed by an ophthalmologist. A noticeable discrepancy was observed in the photographs taken at birth and 30 days post-birth, revealing the emergence of a high forehead and a comparatively smaller lower jaw (Fig. 1D and E).

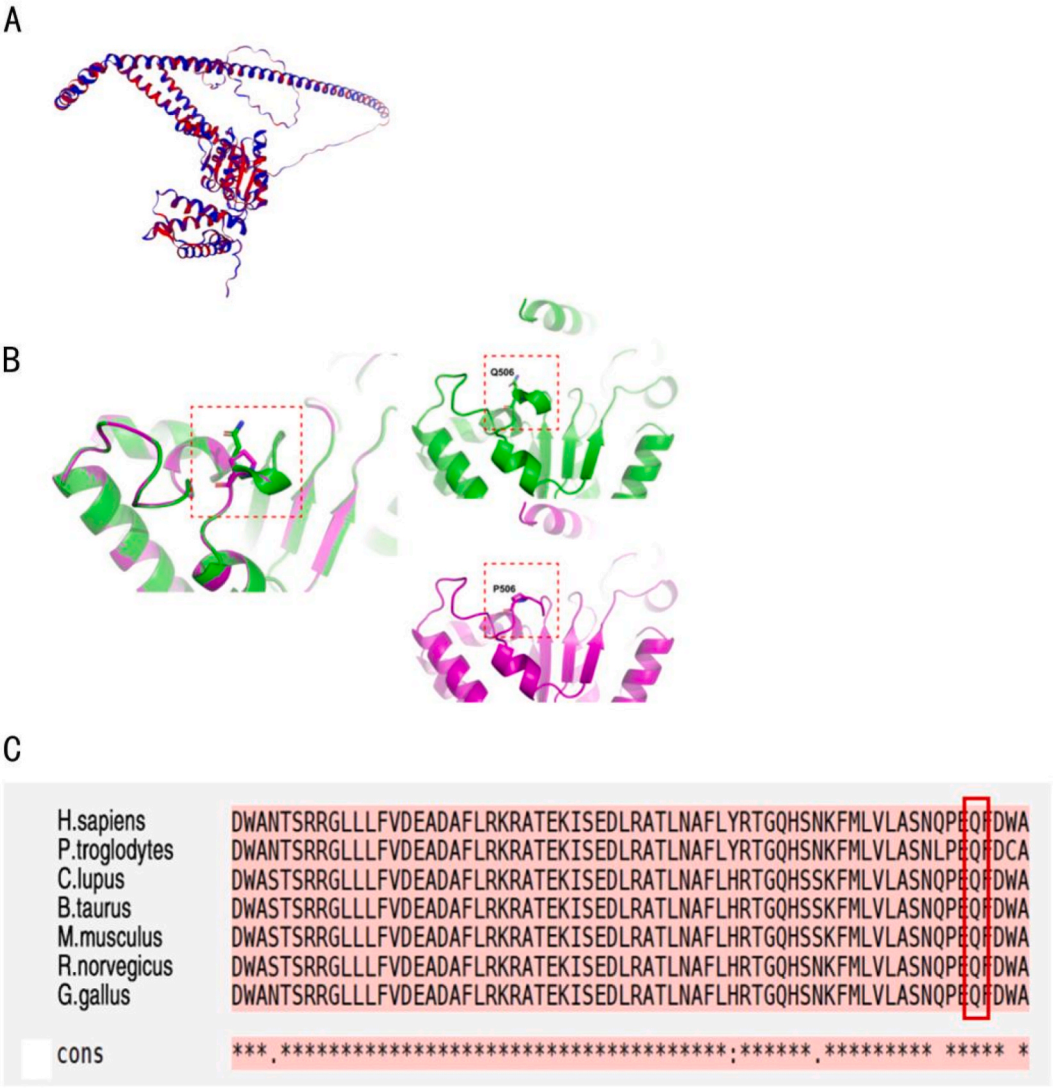

Fig. 3. Prediction of the effect of the ATAD3A (NM_ 018188.4) c.1517A > C (p.Q506P) variant on the tertiary structure of ATAD3A gene
A. Tertiary structure of the ATAD3A protein (Q9NVI7 | SWISS-MODEL Repository (expasy.org)).
B. Prediction of changes in the tertiary structure of ATAD3A after p.Q506P mutation.
C. Conservation analysis of amino acid sequences near ATAD3A p.Q506P.

2.2.5. Main outcome

After recurrent seizures, pulmonary infection, apnea, gastroesophageal reflux, and feeding difficulties, the infant eventually succumbed to respiratory failure.

2.2.6. The patient's mother possesses a personal history predominantly marked by ocular and cardiac anomalies

The neonate's mother has no history of previous births or abortions. According to the clinical record, alternating internal strabismus in both eyes was detected at birth. At the age of 16, she underwent a strabismus operated with low visual acuity in the right eye and cataract in the left eye was also discovered. She was diagnosed with patent ductus arteriosus at 2 years of age and treated by interventional surgery; regular postoperative follow-up results were unknown, and her general physical activities were unrestricted. Echocardiography was performed at 35^{+6} weeks gestational age: PDA after surgery; aortic stenosis (severe) with regurgitation; mitral stenosis (mild) with regurgitation; left atrial enlargement; pulmonary artery dilatation and pulmonary artery pressure increase (mild). Other regular antenatal examinations have been carried out during this pregnancy and have not revealed any abnormalities.

2.3. Genetic analysis

Exome sequencing was performed at a commercial laboratory, after filtering out through clinical phenotype analysis, candidate heterozygous variant in ATAD3A was selected (Fig. 2A), with subsequent validation performed through Sanger sequencing of samples obtained from her parents (Fig. 2B and C). This heterozygote variant was identified in the ATAD3A (NM_018188.4 c.1517A > C) and had never been observed in control databases (The Genome Aggregation Database, Clinvar and HGMD, etc.). This novel ATAD3A variant changes the amino acid from the glutamine to the proline (Q506P). SWISS-MODEL and PYMOL were used to predicted of changes in the tertiary structure of ATAD3A after p.Q506P mutation (Fig. 3A and B). It is predicted to produce an amino acid substitution in a highly conserved region (Fig. 3C). According to ACMG Guidelines [6], this novel c.1517A > C is uncertain significance (evidence PM2+PP3). The presence of this variant was confirmed in the proband's mother by Sanger sequencing (Fig. 2C) and was considered to be inherited in an autosomal dominant manner. No significant result was found in the detection of mitochondrial genomes and copy-number variation.

3. Discussion

Here we reported an independent case of HAYOS associated with the Q506P variant in ATAD3A gene. The proband's clinical manifestations we described were multi-organ involved.

In HAYOS, the different forms of ATAD3A mutations do not show the same degree of disease severity and can vary in clinical presentation. Although in many cases the same organ systems are primarily affected like the nervous system and the eyes in both the monoallelic and biallelic forms [7–9]. Congenital cataracts have previously been ascribed to the core phenotype of ATAD3A deficiency [4,10]. In our investigation, we observed ophthalmic manifestations and cardiac anomalies in both the proband and her mother. However, the mother did not report any medical history related to conditions such as epilepsy, cerebellar atrophy, or developmental delay. It seemed that the mother has a much milder clinical affect. The clinical presentation of the proband is that of a fatal neonatal phenotype. Further investigation is required to determine whether this presentation is related to the intrauterine developmental environment and the genotype-phenotype correlation [11].

This study primarily centered on the clinical manifestations and treatment modalities. Our prediction indicates minimal alteration in protein structure resulting from the mutation at this specific locus. Nonetheless, it is essential to consider that the mutation site resides within a conserved region, possibly serving as a contributing factor. The main limitation of our study, however, is the inability to substantiate the changes of the molecular structure and function of the protein owing to the mutation at this locus. Consequently, further in vitro experiments are imperative to validate its impact on mitochondrial function.

In conclusion, the c.1517A > C variant in ATAD3A can cause HAYOS in Chinese children, with symptoms can appearing in early neonatal. Gene sequencing analysis has demonstrated its ability to aid in the genetic diagnosis of children suspected of having HAYOS in clinics.

Data availability statement

The Data included in article can allow other scholars to reuse these data on the following Link: VCV002499671.1 - ClinVar - NCBI (nih.gov).The ClinVar accession number for the DNA variant data reported in this paper: SCV003918897.

CRediT authorship contribution statement

Shuning Zhang: Writing - review & editing, Writing - original draft, Data curation. **Luyao Lin:** Data curation. **Yuelin Li:** Data curation. **Chanjuan Peng:** Data curation. **Yan Lin:** Writing - original draft, Data curation. **Yongle Liu:** Writing - review & editing, Data curation. **Liyu Liang:** Writing - review & editing, Data curation. **Jiyu Huang:** Writing - review & editing, Data curation. **Qinmei Xie:** Writing - review & editing, Data curation. **Meijun Yang:** Writing - review & editing, Data curation. **Hui Zhu:** Writing - review & editing, Writing - original draft, Project administration, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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