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CASE REPORT

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A novel WDR60 variant contributes to a late diagnosis of Jeune asphyxiating thoracic dystrophy in a Chinese patient: A case report

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Abstract

We report a Chinese patient with JATD presenting a mild skeletal phenotype and with renal insufficiency as the initial symptom of the disease. A novel homozygous c.2789C>T (p.S930L) variant in the *WDR60* gene was identified. Our report will help to improve awareness and diagnosability for this disease.

KEYWORDS

ciliopathies, Jeune asphyxiating thoracic dystrophy, renal failure, skeletal ciliopathies, WDR60 gene

1 | INTRODUCTION

Cilia can be divided into primary/nonmotile cilia and secondary/motile cilia, and they have similar structures but distinct functions. The primary cilium is an immotile microtubule-based structure that protrudes from the cell surface and is distributed in almost all vertebrate cell types. In cells, cilium acts as an antenna and plays a pivotal role in chemical sensation, signal transduction, and control of organogenesis.[1–4]

Defects in the assembly and functions of cilia result in a variety of congenital disorders, known as ciliopathies, characterized by the high heterogeneity of clinical manifestations. Ciliopathies can involve most major tissues and organs and cause a broad spectrum of phenotypes, including skeletal malformations, retinal degeneration, polycystic kidney, infertility, and intellectual disability.[5–8]

Jeune asphyxiating thoracic dystrophy (JATD), also known as asphyxiating thoracic dystrophy or Jeune syndrome (MIM 208500), was first described in 1955,[9] and is characterized by skeletal anomalies, primarily shortened ribs and limbs, brachydactyly and variable polydactyly. The estimated incidence of this disease is about 1 in 126,000 live births.[10] JATD belongs to the ciliopathy diseases

spectrum-skeletal ciliopathies. In addition to JATD, skeletal ciliopathies also encompass short-rib polydactyly syndromes (SRPS; MIM 611263, MIM613091, MIM 263520, MIM 269860, MIM 614091), Mainzer-Saldino syndrome (MZSDS; MIM 266920),[11] Sensenbrenner syndrome or cranio-ectodermal dysplasia (CED; MIM 218330),[12] oral-facial-digital syndrome 4 (OFD4; MIM 258860), and Ellis-van Creveld syndrome (EVC; MIM 225500).[10,12] Apart from distinctive skeletal changes, these diseases often give rise to the involvement of extraskeletal organs, and cause extraskeletal phenotypes including polycystic kidney disease, retinal degeneration, and cardiac, liver, and brain anomalies.[6,10,14,24]

The causative link between JATD and variants in several genes involved in the assembly and transport of cilia has been well established.[13,15,16] The association of the *WDR60* gene, also known as DYNC2I1, with ciliopathies was recognized for the first time in 2013.[17] The WDR60 protein acts as a dynein intermediate chain required for retrograde intraflagellar transport in cilia.[18,19] Variants in *WDR60* can cause either SRPS or JATD phenotypes. To date, only five different variants have been identified, and no case has been reported in the Chinese population.[13,17,20] Here, we describe a Chinese patient with JATD presenting a mild skeletal phenotype, and with renal insufficiency as the initial symptom of the disease. A homozygous c.2789C>T (p.S930L) variant in the *WDR60* gene was identified in the patient. Both parents were heterozygous for the variant, confirming segregation in the family. This report will expand the phenotypic spectrum caused by WDR60 variants and contribute to improving awareness and diagnosability for this disease.

2 | CASE PRESENTATION

The proband was a 46-year-old male patient from healthy consanguineous parents. At approximately 38 years old, he was admitted to a local hospital for dizziness. Examination and laboratory data on admission showed that the blood pressure was 200/110 mmHg, and the serum Cr was 1200 μmol/L. The diagnoses of hypertension and chronic kidney disease (stage 5) were made according to his clinical features and biochemical data at that time. Then, an antihypertensive therapy was taken by administration of antihypertensive drugs to control the blood pressure within the normal range (approximately 140–150 mmHg/90 mmHg), and regular hemodialysis was adopted to improve the survival status and prognosis. One year ago, he was hospitalized to our hospital because of dizziness, headache, and alalia, and brain CT demonstrated hemorrhage in his left brain. Notably, physical examination on admission in our hospital showed disproportional limb shortening, with normal height (170.0 cm), while he presented conspicuous small chest and short extremities with brachydactyly accompanied by deformed teeth (Figure 1). In addition, routine fundoscopy revealed the concurrent existence of bilateral retinitis pigmentosa in this patient (Figure 2). According to the abovementioned clinical signs and the history of kidney failure, the patient was reassessed and the diagnosis of JATD was proposed. Clinical features and representative biochemical data are shown in Table 1. The pedigree is shown in Figure 3.

To confirm the diagnosis, genetic analysis was performed after the patient and his family members gave informed consent. The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Qingdao

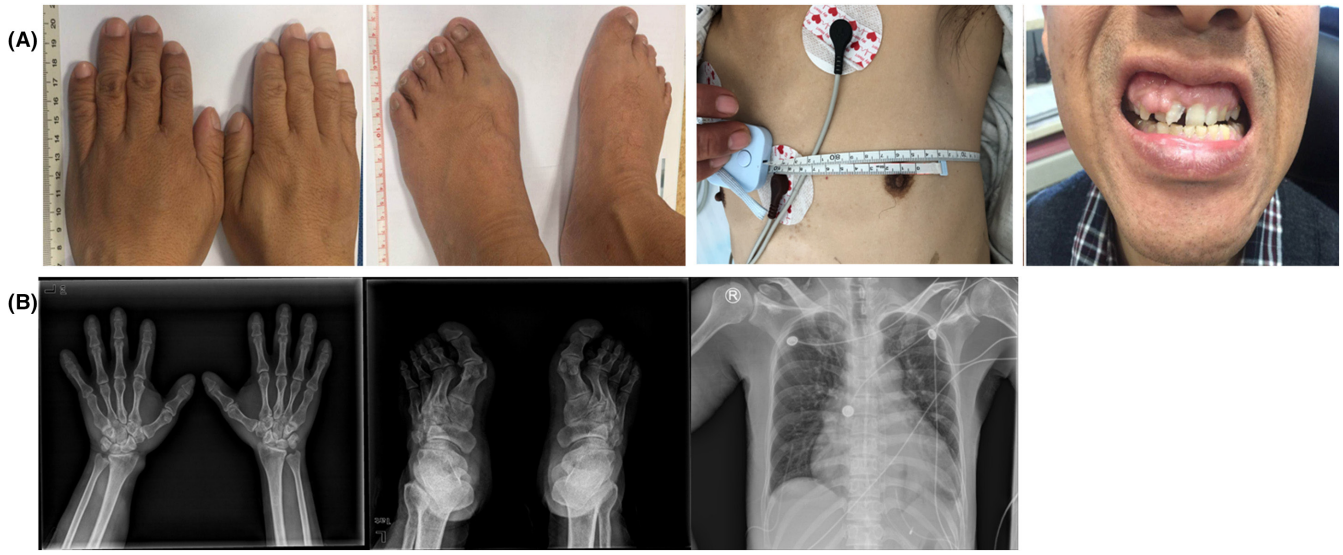

FIGURE 1 Clinical and radiological features of the JATD proband. (A) The proband manifested with a small chest, short extremities with short fingers and toes, and deformity teeth. (B) X-rays of the proband show shortening of the ribs, fingers and toes.

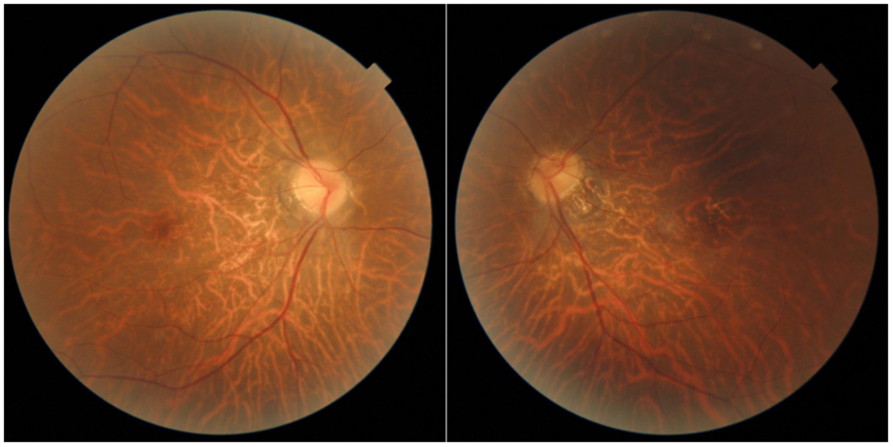

FIGURE 2 Funduscopy revealed the presence of bilateral retinitis pigmentosa in the proband.

TABLE 1 Clinical features and biochemical data of the patient on admission to our hospital for the first time.

Clinical characteristics	Proband	Normal range
Age (years)	45	—
Gender	Male	—
Height (cm)	170.0	167.1(average)
Weight (kg)	60	—
BP (mmHg)	163/66	100–120/60–80
eGFR (ml/min)	7.52	90–120
BUN (mmol/l)	12.58	3.1–8
Serum Cr (μmol/l)	921.11	57–97
Uric Acid (μmol/l)	259.15	208–428
Urine gravity	(anuria)	1.005–1.025
Urine pH	(anuria)	4.6–8.0
Proteinuria	(anuria)	—

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; Cr, creatinine; GFR = glomerular filtration rate, eGFR was estimated by the MDRD formula.

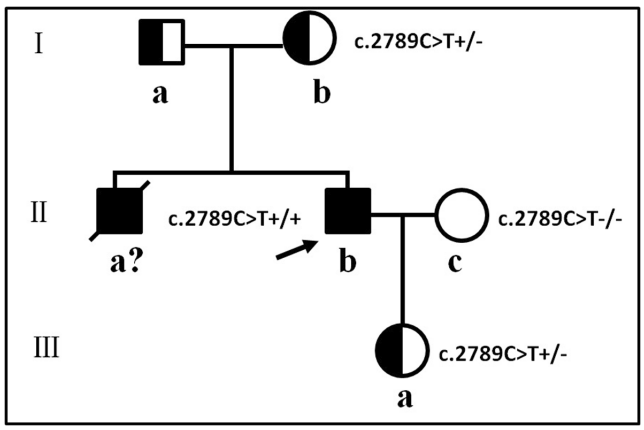

FIGURE 3 Pedigree of the Chinese family with JATD. □, male ○, female; ■, male patient; ●, female patient; ↗, proband.

University. Genomic DNA was extracted from peripheral blood leucocytes using a Blood Genome DNA Extraction KitUSA. High-throughput sequencing was used to analyze all the exon regions and adjacent intronic regions of JATD/SRPS-associated genes that have been reported previously, including *CEP120*, *DYNC2H1*, *EVC*, *EVC2*, *IFT43*, *IFT80*, *IFT122*, *IFT140*, *IFT172*, *NEK1*, *TTC21B*, *WDR19*, *WDR34*, *WDR35*, and *WDR60*.[14,15,17,21–23] After raw data processing, reads that passed were then mapped to the human reference genome (UCSC hg19) using the Burrows Wheeler Aligner (University of California, Santa Cruz, CA, USA). The variant call file (VCF) containing the detected variants was annotated with Variant Effect Predictor v83 and the dbNSFP (Database for Nonsynonymous SNPs' Functional Predictions) v3.1. After the selection process, a novel homozygous variant c.2789C>T (p.S930L) in exon 24 of the *WDR60* gene was found in the proband and the heterozygous variant was detected in his parents and his daughter. The variant was then confirmed by sanger sequencing verification (Figure 4). No other pathogenic variants were identified in the other genes, and c.2789C>T (p.S930L) variant was not found in one hundred unrelated healthy subjects. According to guidelines from the American College of Medical Genetics and Genomics (ACMG, 2015), the variant was preliminarily determined to be likely pathogenic (PM2+PM3+PP3+PP4). PM2: The frequency in normal population database is 0.0003, which is low-frequency variation; PM3: recessive in trans; PP3: protein function predicted as harmful, benign, harmful and harmful, by prediction software SIFT, polyphen-2, Mutation taster, and GERP++, respectively; PP4: patient's phenotype or family history support that this is indeed the causative variant in the patient.

3 | DISCUSSION AND CONCLUSION

Ciliopathies comprise a genetically heterogeneous group of diseases, caused by an underlying dysfunction of the

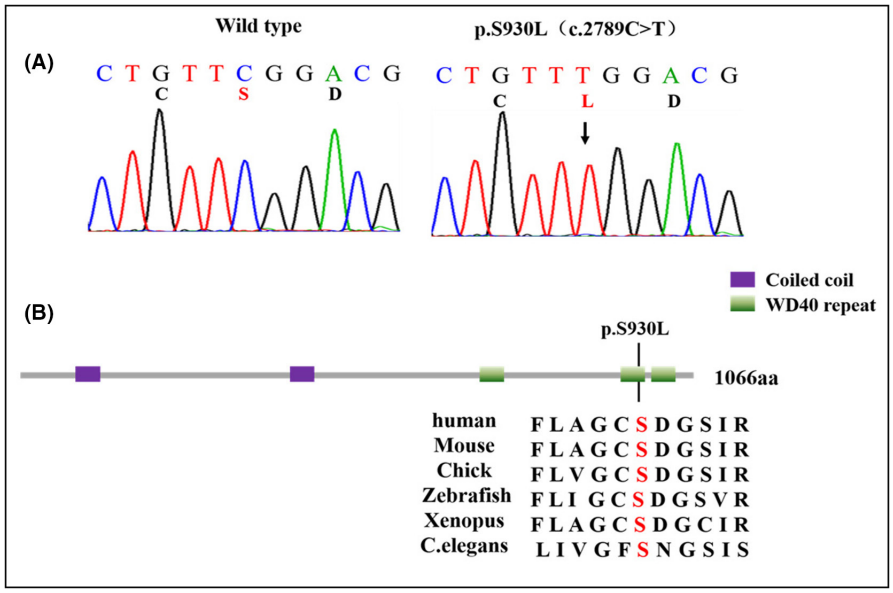

FIGURE 4 Verification of the c.2789C>T variant in the proband and normal individual by Sanger sequenceing (a) and evolutionary conservation of the 930 Serine site by multiple sequence alignment of the WDR60 protein across different species (b).

primary cilium. Skeletal ciliopathies are common forms of ciliopathies, which can be classified into different subtypes according to the clinical manifestations. In addition to the common signs of skeletal development abnormalities, each subtype has its own unique feature different from others.[10]

As the important subtypes of skeletal ciliopathies, the clinical manifestations of JATD and SRPS are highly similar. They both manifest as short ribs, narrow chest, short fingers (toes), with or without polydactyly.[6,17] These signs are usually accompanied by extraskeletal phenotypes such as retinopathy and fibrocystic changes in the liver and kidney. However, the SRPS phenotype is usually more severe than JATD and often leads to embryonic developmental disorders and perinatal death, with a short survival period. However, the relative survival rate of JATD is higher and, approximately 40%, could survive to adulthood.[13,15]

In the present report, the proband was an adult patient and displayed a mild phenotype of skeletal abnormalities, such as a relatively small thoracic cage, which is less conspicuous than that in neonate e cases, possibly attributed to the improvement of respiratory function with age. Since short fingers (toes) of the extremities are very conspicuous in the patient and no other typical radiological features, such as cone-shaped epiphyses, can be distinguished in the patient's radiographs, this further illustrates the high variability of JATD manifestations. It is worth noting that, for this patient, the extraskeletal phenotype-progressive renal failure and retinal degeneration were considerably more noticeable than the skeletal changes, which were not a major concern until visiting our hospital. Notably, the proband's only sibling died of respiratory failure at infancy without definite diagnosis. It is estimated that 60% of JATD cases are accompanied by lethal respiratory distress after birth.[14] Once they overcome respiratory dysfunction through careful nursing at the early stage after birth, the survival rate of infants will be improved. A total of 30% of the surviving JATD patients developed end-stage renal disease, and 50% of the JATD cases presented retinal alterations similar to the proband in this report; however, the age of onset of extraosseous manifestations is still unevaluated to date.[14,25]

To make a definite diagnosis and find the pathogenic gene, a JATD/SRPS panel including fifteen genes was screened by high-throughput sequencing, a novel homozygous variant c.2789C>T (p.S930L) in exon 24 of the *WDR60* gene was found, and multiple sequence alignment indicated the evolutionary conservation of the p.S930L among different species (Figure 4). In silico analysis by four software programs highly suggested that the variant was a pathogenic form. Current evidence has proven that *WDR60* variants can cause varying degrees of phenotypes of JATD or SRPS.[13,17,20] Moreover, one report also confirmed the destructive effect of *WDR60* variation on cilia structure and assembly by immunofluorescence in fibroblasts derived from the affected patient.[17] In our case, the patient was in a very serious condition and denied biopsy, so we could not acquire in vivo evidence of variant disrupting ciliogenesis from this patient. Even so, we have made a point variant mouse model and we will provide a more intensive investigation of the pathogenic mechanism of the c.2789C>T variant in future studies.

In summary, in this report, we identified a novel homozygous variant c.2789C>T (p.S930L) in a JATD patient

with late diagnosis. This report will help to expand our understanding of this disease and enrich the mutational spectrum of the *WDR60* gene.

AUTHOR CONTRIBUTIONS

L.S. conceived and designed the experiments. X.Z., L.C., and A.S. performed the experiments. Z.L., R.Z., and Y.H. performed the data analyses. X.Z. wrote the manuscript. L.S. revised the manuscript. All authors have reviewed the final manuscript and approved submitting for publication.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the affiliated hospital of Qingdao University (No. 20190317). Informed consent was obtained from guardians of the subject.

CONSENT

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not available.

CLINICAL TRIAL REGISTRATION

Not available.

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