Prenatal Diagnosis of Fetus With Transaldolase Deficiency Identifies Compound Heterozygous Variants: A Case Report

Jiaxin Xue1,2, Jin Han1*, Xiaopeng Zhao3, Li Zhen1, Shanshan Mei4, Zhiyang Hu5 and Xiuzhen Li6

1Prenatal Diagnosis Center, Guangzhou Women and Children’s Medical Center, Guangzhou, China, 2Department of Obstetrics and Gynecology, Guangzhou Medical University, Guangzhou, China, 3Division of Neonatology, Guangzhou Women and Children’s Medical Center, Guangzhou, China, 4Division of Obstetrics, Guangzhou Women and Children’s Medical Center, Guangzhou, China, 5Shenzhen People’s Hospital, Shenzhen, China, 6Division of Endocrinology, Guangzhou Women and Children’s Medical Center, Guangzhou, China

Transaldolase (TALDO) deficiency is a rare autosomal recessive disorder caused by variants in the TALDO1 gene that commonly results in multisystem dysfunction. Herein, we reported compound heterozygous variants in a Chinese prenatal case with TALDO deficiency using whole-exome sequencing (WES) for trios and Sanger sequencing. The heterozygous variants were located on the TALDO1 gene: NM_006755.2:c.574C>T(Chr11:g.763456C>T), a missense variant in exon 5 paternally inherited; NM_006755.2:c.462-2A>G(Chr11:g.763342A>G), a splicing aberration in intron 4 maternally inherited. The qualitative analysis of urinary polyols in neonatal urine indicated that xylitol + arabitol and ribitol in the proband’s urine were significantly increased. These findings expand the variation spectrum of the TALDO1 gene, provide solid evidence for the counseling of the family in regard to future pregnancies, strongly support the application of WES in prenatal diagnosis, and further prove that effective postpartum treatments could improve prognosis.

Keywords: Transaldolase deficiency, pentose phosphate pathway, TALDO1, prenatal diagnosis, whole-exome sequencing (WES)

INTRODUCTION

Transaldolase (TALDO) deficiency (OMIM 606003), a rare metabolic congenital defect of the pentose phosphate pathway (PPP), is caused by homozygous or compound heterozygous variants of the TALDO1 gene (Wamelink et al., 2008) located on chromosome 11p15. Its main clinical manifestations usually appear in the neonatal period, while they are relatively rare in the antenatal period. The typical symptoms include coagulopathy, thrombocytopenia, liver dysfunction, hepatosplenomegaly, hepatic fibrosis, hemolytic anemia, generalized edema, dysmorphic features, and renal dysfunction that rarely occurs. Prolonged activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT), low cholesterol, high alkaline phosphatase (AKP), as well as elevated total bilirubin (TBIL), direct bilirubin (DBIL), total bile acid (TBA), and β2-microglobulin (β2-MG), can indicate liver and renal dysfunction in some reported cases (Valayannopoulos et al., 2006).
The PPP has two main functions: 1) It provides reduced
nicotine adenine dinucleotide phosphate (the cofactor of redox
reaction for organism biosynthesis), and 2) it offers ribose-5-
phosphate to the nucleic acid. The PPP is divided into oxidative
(nonreversible) and nonoxidative (reversible) enzymatic
reactions/parts. Moreover, TALDO is the second enzyme of
the nonoxidative part tightly linking the PPP and glycolysis
pathway (Verhoeven et al., 2005).

To date, approximately 39 cases diagnosed with TALDO
deficiency have been reported, but the incidence is unclear
(Verhoeven et al., 2001; Eyaid et al., 2013; Rodan and Berry,
2017; Halabi et al., 2019; Lee-Barber et al., 2019; Williams et al.,
2019; Lafci et al., 2021) (Table 3). Yet, the pathophysiology
leading to TALDO deficiency remains unclear due to the low
number of reported cases. TALDO deficiency can also have high
variability in clinical manifestations and outcomes, even within
the same family (Tylki-Szymanska et al., 2009; Leduc et al.,
2014). Herein, we reported a novel compound heterozygous
variant in a Chinese prenatal case with multiorgan dysfunction
confirmed as TALDO deficiency by prenatal molecular
diagnosis.

MATERIALS AND METHODS

Ethics Approval
After receiving written informed consent from both of the
parents, WES (trio analysis of the proband, mother, and
father) was carried out. Our study was approved by the
Ethics Committee of Guangzhou Women and Children’s
Medical Center and Guangzhou Medical University, and it
conformed with the ethical standards of experiments on
human subjects.

Case Presentation
A 33-year-old pregnant woman, gravida 2, para 1, was referred to
our hospital at 34 weeks because of ultrasonic abnormalities. Fetal
middle cerebral artery peak systolic velocity (MCA-PSV) kept
increasing from 24 gestational weeks, reaching 93.97 cm/s [>1.5
MoM (Multiples of the Median)] at 33 gestational weeks. Additional anomalies included a slightly high echo of the right
lobe of the liver, cardiomegaly with the cardiotoracic ratio of 0.61, a small amount of pericardial effusion, and placental thickness
of 46 mm.

Similar manifestations, including cardiac enlargement,
hepatosplenomegaly, placental thickness, elevated MCA-PSV,
high umbilical artery resistance, and intrauterine growth
restriction (IUGR), were observed during the first pregnancy
(II:1). Following fetal distress, at 36 weeks, a baby boy was
born by cesarean section weighing 1,860 g (<10th). His Apgar
scores were normal (9′-10′-10′), while the neonatal peripheral
blood test detected that hemoglobin (HGB) and platelet (PLT)
were low. Repeated examinations of coagulation showed
extended APTT, PT, and TT. Brain ultrasound suggested a
head injury with subependymal hemorrhage. Therefore, II:1
received human immunoglobulin and blood transfusion to
prevent infection and improve blood coagulation. The
neonate did not recover and consequently died of
disseminated intravascular coagulation (DIC), a low-birth-
weight, and hypoproteinemia at 18 days. Clinical findings of
the two affected fetuses (II:1 and II:2) are summarized in
Tables 1, 2.

To assess the risk of recurrence, cordocentesis was performed
for genetic diagnosis, including karyotype analysis and
chromosomal microarray analysis (CMA), to clarify the
potential cause of the disease two times in another hospital,
but the results were negative. Consequently, WES was performed
on the proband and his healthy parents (Figures 1A,B) to search
for potential variants. The detailed examinations during
pregnancy are listed in Table 1.

Metabolite Analyses
Urine xylitol + arabinol and ribitol were measured using gas
chromatography-mass spectrometry (GC-MS). Urine sample
preparation was based on urease pretreatment methods.
Samples were standardized to 0.25 mg creatinine. Derivatization was performed with 100 μl bis-(trimethylsilyl)
trifluoroacetamide + 1% trimethylchlorosilane and was allowed to react at 60°C for 10 min. The metabolites were
chromatographically analyzed as trimethylsilyl compounds.

Whole-Exome Sequencing
Genomic DNA was randomly fragmented and purified using
the magnetic particle method. WES was performed on an
ILLUMINA HiSeq 2,500 sequencer (Illumina, San Diego, CA,
United States) for a minimal of 10.14 Gb read-depth per case.
Sequencing reads after quality control were aligned to the
human reference genome by BWA (hg19). Nucleotide
changes of aligned reads were reviewed using NextGENe
software (Version 2.4.1.2) (SofGenetics, State College, PA,
United States) for a minimal of 10.14 Gb read-depth per case.
Sequencing reads after quality control were aligned to the
human reference genome by BWA (hg19). Nucleotide
changes of aligned reads were reviewed using NextGENe
software (Version 2.4.1.2) (SofGenetics, State College, PA,
United States). Novel variants were filtered against the 1,000
Genomes database (http://www.1000genomes.org/), dbSNP
database (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_/summary.cgi), and the Genome Aggregation database
(gnomad.broadinstitute.org). Databases, including ClinVar
(version: #372716), OMIM (version: #602063.0005), ClinGen
(version: #CA5788214), and Human Gene Mutation database,
were used. In addition, software (SIFT, Polyphen,
MutationTaster, PROVEAN and REVEL) was used to
predict the impact of missense variants. For the splicing
variant, the in silico prediction tools were dbscSNV and
MaxEntScan. Common variants (with high minor allele
frequency in normal population; gnomAD) were eliminated.
Finally, polymerase chain reaction (PCR) was performed to
amplify the affected fragment of TALDO1 gene using specific
primers, and the purified PCR products were applied to Sanger
sequencing to affirm the variant(s).

RESULTS
The umbilical cord blood samples of the fetus (II:2) in 24 and 28
gestational weeks in another hospital showed fetal anemia,
thrombocytopenia, coagulation dysfunction, and elevated liver
variants had a very low carrying rate in some databases: c.462–37TTc(s)

|          | PLT (×10^9/L) | HGB (g/L) | βTBA (µmol/L) | DBIL (µmol/L) | TBIL (µmol/L) | AKP (U/L) | APTT (s) | PT (s) |
|----------|---------------|-----------|---------------|---------------|---------------|-----------|---------|-------|
| 12+      | 123           | 82        | –             | 2.76          | 23.1          | 289       | –       | –     |
| 17+      | 137           | 104       | –             | 3.76          | 23.1          | 359       | –       | –     |
| 22+      | 100           | 110–150   | –             | 0–6           | 0–6           | 39.3      | 1.7–20.0| 15–121|
| 25+      | 16           | 2.8       | 0.57          | 0.50          | 0.50          | –         | –       | –     |
| 27+      | 22           | 26.8–46.1 | –             | 0.50          | 0.50          | 26.8–46.1 | –       | –     |
| 33+      | 33           | 36.0–46.3 | 0.64          | 28            | 18.4          | 36.0–46.3 | 2.8     | –     |
| 37+      | 48           | 38.9–75.4 | 4.0           | 16            | 4.0           | 38.9–75.4 | 4.0    | –     |

Both variants were de

|          | ALB (g/L) | AST (U/L) | LDH (U/L) | HbA (%) | 2-MG (mg/L) | TBA (µmol/L) | HbA, hemoglobin A | LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALB, albumin. |
|----------|----------|-----------|-----------|---------|-------------|---------------|-------------------|---------------------------------------------------------------------|
| 24 weeks | 150      | 240       | 97.8%     | 14.0%   | 17          | 18.4          | 18.4              | 170,388 mmol/mol creatinine (+)                                      |
| 28 weeks | 195      | 240       | 30.0%     | 10.0%   | 18.4        | 18.4          | 18.4              | 193,301 mmol/mol creatinine (+)                                     |
| Newborn  | 390      | 1,679     | 57.7      | 16.5%   | 18.4        | 18.4          | 18.4              | 1,151 mmol/mol creatinine (+)                                       |

The laboratory results of II:2 as determined directly in 24+ and 28+ weeks through the umbilical cord blood tests and after birth between II:1 and II:2.

|        | Test time(weeks) | II:2* | Reference interval | II:2 | II:1b | Reference interval |
|--------|------------------|-------|--------------------|------|-------|--------------------|
|        |                  | 24    | 28                |      |       |                    |
| TT(s)  | –                | –     | –                 | 23.6 | 34.8  | 14–21              |
| PT(s)  | –                | –     | –                 | 30.7 | 31.7  | 11–15              |
| APTT(s)| –                | –     | –                 | 80.5 | 124.7 | 28–45              |
| AKP(U/L)| 289             | 359   | 15–121            | 354  | –     | 118–390            |
| TBLI(µmol/L) | 23.1     | 39.3  | 1.7–20.0          | 83.3 | 157.52| 2–17              |
| DBIL(µmol/L) | 2.76    | 3.89  | 0–6               | 10.0 | 96.3  | 0–7               |
| TBA(µmol/L) | –         | –     | –                 | 18.4 | 75.41 | 0.5–10.0          |
| β2-MG (mg/L)| 10.85  | 4.71  | 0.7–1.8           | 95   | 104   | 135–195           |
| HGB (g/L)| 82       | 104   | 110–150           | 96   | 104   | 135–195           |
| PLT (10^9/L)| 123     | 137   | 100–300           | 79   | 48    | 140–440           |
| Hba (%) | 4.0      | 5.3   | 96.8–97.8%        | –    | –     | –                 |
| LDH (U/L)| 263      | 256   | 110–240           | 989  | 1,679 | 159–322           |
| AST (U/L)| 24       | 0–45  | 26                | 89   | 63    | 5–60              |
| ALB (g/L)| –        | –     | –                 | 23.1 | 16.5  | 40–65             |

The couple decided to continue the pregnancy after genetic counseling. A baby girl was born at 38 weeks, with a
Sequencing of TALDO1 gene (reference cDNA sequence, NM_006755.2) revealed two heterozygous variations, resulting in A to G splicing at nucleotide position 462–2 (c.462-2A>G) and C to T substitution at nucleotide position 574 [c.574C>T(p.Arg192Cys)]. Het, heterozygous.
weight of 2,760 g. Apgar scores were normal (8′-8′-8′) after delivery. At birth, the baby had dysmorphic features (hirsutism, low hair implantation), mild pallor, and cutis laxa. She also presented low skin temperature, quick breath with groaning, thick breath sounds in both lungs with moist rales, and abdominal distention with the visible vascular network. The baby was hospitalized at the Neonatal Department in our hospital for 9 days (Figures 3A,B). She had hepatosplenomegaly and developed jaundice. A peripheral blood test showed HGB of 95 g/L (normal 110–150 g/L) with fragmented red cells on film, thrombocytopenia, and mild neutropenia, consistent with those in utero. Serum TBIL was 83.3 µmol/L (normal 2–17 µmol/L) with DBIL of 10.0 µmol/L (normal 0–7 µmol/L). LDH was also increased to 989 U/L (normal 159–322 U/L) together with marginally elevated transaminases, bile acids and alkaline phosphatase (ALP). Albumin was 23.1 g/L (normal 40–55 g/L) and PT was 31.7 s (normal 11–15 s). The infant received continuous ventilation for 9 days. Fresh frozen plasma and fibrinogen infusion were given to improve thrombocytopenia and coagulation. Blood glucose level was stable and was closely monitored. GC-MS indicated elevated urinary xylitol + arabinol and ribitol levels.

After her condition gradually improved, the patient was discharged from the hospital and was regularly followed up. At the age of 9 months, HGB was still slightly decreased (100 g/L), while red blood cell and PLT were both increased to 4.7 × 10¹²/L (normal 3.5–5.0 × 10¹²/L) and 517 × 10⁹/L (normal 100–300 × 10⁹/L), respectively. DBIL, TBIL, TBA, LDH, and AKP levels were normal, whereas aspartate aminotransferase (AST) mildly elevated to 84 U/L. The dysmorphic features and cutis laxa were not observed. Thus far, the child has shown normal physical and cognitive development.
TALDO deficiency is a rare autosomal recessive error of the PPP caused by a variant in the TALDO1 gene (Williams et al., 2019). TALDO1 gene encodes TALDO implicated as a major modulator between the PPP and glycolysis in a reversible reaction. TALDO catalyzes the conversion of glyceraldehyde-3-phosphate and sedoheptulose-7-phosphate into fructose-6-phosphate and erythrose-4-phosphate, which are also considered targets for the treatments of this condition. In addition, its absence can result in the accumulation of intermediate products (e.g., sedoheptulose, erythritol, and ribitol) and eventually cause lesions of the patent. TALDO deficiency has been associated with a range of phenotypes, including intrauterine lethality together with fetal multimalformation syndrome and hydrops fetalis. The most common clinical manifestations in neonates are cirrhosis, liver failure, hepatosplenomegaly, anemia, thrombocytopenia, dysmorphism, congenital heart defects, and tubulopathy (Verhoeven et al., 2001; Verhoeven et al., 2005; Valayannopoulos et al., 2006; Wamelink et al., 2008; Tylicki-Szymanska et al., 2009; Balasubramaniam et al., 2011; Eyaid et al., 2013). Yet, prenatal diagnosis is very challenging. Abnormal findings in the fetus are rare. Some of the common manifestations in the antenatal period are IUGR (Verhoeven et al., 2001; Valayannopoulos et al., 2006; Wamelink et al., 2008), oligohydramnios, fetal splenomegaly, fetal distress (Wamelink et al., 2008), and hyperchogenic bowel (Banne et al., 2015). Also, TALDO deficiency can be easily misdiagnosed with gestational alloimmune liver disease (GALD). GALD is the result of maternal alloimmune injury, which includes neonatal liver failure (coagulation disorders, ascites, and hypoalbuminemia), intrahepatic, and extrahepatic iron accumulation (hemosiderosis).

In this study, a family that had experienced neonatal death following IUGR, hepatosplenomegaly, anemia with thrombocytopenia, and abnormal coagulation tests in a previous pregnancy (II:1) and recurrent fetal anemia, hepatosplenomegaly in the second pregnancy (II:2), was recruited for WES. A prenatal diagnosis of the fetus confirmed heterozygous variants in the TALDO1 gene in II:2. Yet, prenatal findings were different between II:1 and II:2. Fetal MCA-PSV increased from 24 gestational weeks, which reflected fetal anemia in utero. Additional ultrasound anomalies identified at 33 gestational weeks included slightly high echo of the right lobe of the liver, cardiomegaly with increased cardiothoracic ratio, a small amount of pericardial effusion and placental thickness, all of which suggested a progressive development of fetal anemia. After birth, the postpartum symptoms were clearer and more obvious, including dysmorphic features, liver dysfunction and hemolytic anemia. This case is consistent with the range of phenotypes most commonly observed; however, fetal anemia, liver dysfunction, and coagulopathy are the main manifestations.

The accumulation of sugars and polyols [e.g., sedoheptulose-7-phosphate, ribose-5-phosphate, ribulose-5-phosphate, xylulose-5-phosphate, and C5-polyols (i.e., D-ribitol and D-arabitol)] are believed to be the cause of liver involvement in TALDO deficiency. Higher concentrations of the polyols xylitol + arabitol and ribitol in the urine of the proband could be relevant of the phenotypes in II:2, but could also be related to the younger age, since the polyol concentrations were higher in the neonatal period in other patients and accumulated less when they were older (Wamelink et al., 2008). Although from the same family, patient II:1 had IUGR, anemia, hepatosplenomegaly, DIC, a low-birth-weight, and secondary hemorrhage (subependymal hemorrhage), yet, even considering that molecular analysis was not performed for patient II:1, it was likely that these phenotypes were associated with TALDO deficiency.

To the best of our knowledge, this case is the first prenatal diagnosis of TALDO deficiency in a Chinese population (Verhoeven et al., 2001; Eyaid et al., 2013; Rodan and Berry, 2017; Lee-Barber et al., 2019; Williams et al., 2019; Halabi et al., 2019; Lafci et al., 2021). Both variants of this case were defined as likely pathogenic. One of the variants [c.574C > T (p.Arg192Cys)], reported as pathogenicity in ClinVar (Variation ID: 381,759), was previously reported in an Arab patient, suggesting a founder effect in Arab populations (Wamelink et al., 2008). The other is a novel splicing variant (c.462-2A > G), which is predicted to affect splicing while not exon skipping. The in-silico tools are dbscSNV and MaxEntScan. They all predict altering TALDO1 exon splicing. To date, there have been 13 variants reported to cause this condition worldwide (Table 3). Individuals with the same variant show different clinical manifestations.

The prenatal diagnosis of TALDO deficiency remains a challenge and is usually confirmed by gene analysis. Thus far, there is still no effective treatment for TALDO deficiency. Yet, early and accurate prenatal diagnosis can lead to a better outcome and can provide better aid for prenatal management, including fetal surveillance strategy and appropriate postpartum treatment, as was the case in the present study. In particular, a higher frequency of fetal surveillance with targeted ultrasound can help identify early signs of clinical manifestations (e.g., elevated MCA-PSV, cardiomegaly and placental thickness), which are important prognostic indicators. Most important of all, it is inseparable from the joint efforts of multi-disciplinary team. Currently, there is only one gene known to cause TALDO deficiency. Further studies are warranted to comprehensively characterize the genetic contributions.

In conclusion, our data suggests that TALDO deficiency is a pleiotropic disorder that should be considered when investigating a prenatal case with unexplained hepatosplenomegaly or fetal anemia. Although no specific treatment is currently available, targeted molecular analysis of the TALDO1 gene in amniotic fluid or chorionic villi.
| Case | Variant | Gender | Ethnicity | Consanguinity | Pregnancy | Dysmorphism | Liver dysfunction | Hepatoplenomegaly | Anemia | Thrombocytopenia | Impaired coagulation | Cardiac abnormalities | Neuronal defects | Renal | Respiratory | Developmental delay | Abnormal genitalia | Clinical course |
|------|---------|--------|-----------|--------------|------------|-------------|------------------|------------------|--------|----------------|-------------------|----------------------|-----------------|-------|------------|-------------------|-------------------|----------------|
| 1    | NM_006359.2 c.312_314del | F | Turkey | + | IUGR | - | + | + | + | + | + | ACD | - | - | - | - | Hematopoietinopathy, telangiectasias of her skin, enlarged clitoris |
| 2    | NM_006359.2 c.312_314del | F | Turkey | + | HELLP syndrome | + | + | + | + | + | + | + | ACD, MVP | - | - | - | - | |
| 3    | NM_006359.2 c.312_314del | M | Turkey | + | + | + | - | (Splenic fibrosis) | + | - | + | Cardiomegaly | - | - | - | - | |
| 4    | NM_006359.2 c.312_314del | M | Turkey | + | + | + | - | + | - | + | + | + | PFO | - | + | - | - | |
| 5    | NM_006359.2 c.312_314del | M | Turkey | + | + | + | - | + | - | + | + | + | PFO | - | Chronic renal | - | - | |
| 6    | NM_006359.2 c.312_314del | U | Turkey | + | Oligohydramnion | + | + | + | + | + | + | Cardiomegaly | - | Transient renal | - | - | - | - | |
| 7    | NM_006359.2 c.312_314del | U | Arab | + | IUGR | + | + | + | + | + | + | Splenic fibrosis | + | Tubulopathy | - | Mild delay | Speech delay (Mild) |
| 8    | NM_006359.2 c.312_314del | U | Pakistan | + | + | + | + | + | - | - | - | + | Mild delay | - | Speech delay |
| 9    | NM_006359.2 c.312_314del | U | Poland | + | + | + | + | + | + | - | + | + | + | + | + | + | - | - | Unilateral cryptorchidism, hepatoplenomegaly |
| 10   | NM_006359.2 c.312_314del | U | Poland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 11   | NM_006359.2 c.312_314del | U | Turkey | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 12   | NM_006359.2 c.312_314del | M | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 13   | NM_006359.2 c.312_314del | N | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 14   | NM_006359.2 c.312_314del | U | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 15   | NM_006359.2 c.312_314del | U | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 16   | NM_006359.2 c.312_314del | M | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 17   | NM_006359.2 c.312_314del | U | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 18   | NM_006359.2 c.312_314del | U | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 19   | NM_006359.2 c.312_314del | U | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 20   | NM_006359.2 c.312_314del | M | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 21   | NM_006359.2 c.312_314del | F | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 22   | NM_006359.2 c.312_314del | F | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 23   | NM_006359.2 c.312_314del | E | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 24   | NM_006359.2 c.312_314del | F | Saudi Arabia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 25   | M | Poland | - | IUGR, ascites, and oligohydramnion | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |
| 26   | M | Poland | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | - | - | |

(Continued on following page)
**TABLE 3** (Continued) Summary of clinical manifestations in the current patients with TALDO deficiency.

| Case     | Variant | Sex | Ethnicity | Consanguinity | Pregnancy | Dysmorphism | Liver dysfunction | Hepatosplenomegaly | Anemia | Thrombocytopenia | Impaired coagulation | Cardiac abnormalities | Neonatal edema | Renal | Respiratory | Developmental delay | Abnormal genitalia | Clinical course |
|----------|---------|-----|-----------|---------------|-----------|-------------|------------------|-------------------|--------|----------------|----------------------|---------------------|----------------|-------|------------|---------------------|----------------|-----------------|
| 27°      | NM_006755.2: | c.575G > A; c.462-174_184 + 5del | Gambia | — | | | + | + | + | | | | | | | | | | | | |
| 28°      | NM_006755.2: | c.512C > T | Gambia | — | | | + | + | + | | | | | | | | | | | | | |
| 29°      | NM_006755.2: | c.512C > T | Gambia | — | | | + | + | + | | | | | | | | | | | | | |
| 30°      | NM_006755.2: | c.512C > T | UAE | + | | | + | | | | | | | | | | | | | | | |
| 31°      | NM_006755.2: | c.574C > T | UAE | + | | | + | | | | | | | | | | | | | | | |
| 32°      | NM_006755.2: | c.574C > T | Saudi Arabia | + | | | + | | | | | | | | | | | | | | | |
| 33°      | NM_006755.2: | c.574C > T | UAE | + | | | + | | | | | | | | | | | | | | | |
| 34°      | NM_006755.2: | c.574C > T | Saudi Arabia | + | | | + | | | | | | | | | | | | | | | |
| 35°      | NM_006755.2: | c.574C > T | UAE | + | | | + | | | | | | | | | | | | | | | |
| 36°      | NM_006755.2: | c.574C > T | United States | + | | | + | | | | | | | | | | | | | | | |
| 37°      | NM_006755.2: | c.715G > A | Turkey | — | | | + | | | | | | | | | | | | | | | |
| 38°      | NM_006755.2: | c.793del G | Saudi Arabia | + | | | + | | | | | | | | | | | | | | | |
| 39°      | NM_006755.2: | c.574C > T | China | + | | | + | | | | | | | | | | | | | | | |

**Note.** +, present; −, not present; n, normal; *, patient died/not mentioned; →, change to; ASD, atrium septum defect; PFO, patent foramen ovale; MVP, mitral valve prolapse; ASO, atraum septal defect; LVH, left ventricular hypertrophy; HTN, hypertension; RAD, right atrium dilation; RVH, right ventricular hypertrophy; TR, tricuspid regurgitation; PDA, patent ductus arteriosus; IUGR, intrauterine growth restriction.

*Verhoeven et al., 2001; †Verhoeven et al., 2005; ‡Valayanopoulou et al., 2006; §Wamelink et al., 2008; ¶Fung et al., 2007; ¶¶Tylki-Szymańska et al., 2009; ¶¶¶Balasubramaniam et al., 2011; ¶¶¶¶Eyaid et al., 2013; ¶¶¶¶¶Jassim et al., 2014; ¶¶¶¶¶¶Tylki-Szymańska A et al., 2014; ¶¶¶¶¶¶¶Leduc et al., 2014; ¶¶¶¶¶¶¶¶Al-Shamsi et al., 2015; ¶¶¶¶¶¶¶¶¶Banne et al., 2015; ¶¶¶¶¶¶¶¶¶¶Lee-Barber et al., 2019; ¶¶¶¶¶¶¶¶¶¶Lafci et al., 2021; ¶¶¶¶¶¶¶¶¶¶¶Hadjibi et al., 2019.*
can be valuable in helping those suffering families to make informed reproductive choices.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by The ethics committee of Guangzhou Women and Children’s Medical Center and Guangzhou Medical University. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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