Molecular Genetics and Metabolism 148 (2026) 109872

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Research Paper

Transaldolase deficiency – natural disease course towards adulthood

Viktoria Bea Horvath [a], Konstantinos Tsiakas [b], Heiko Brennenstuhl [c], Daniela Choukair [d], Nicole Hammann [a], Moritz Niesert [a], Alexander Fichtner [a], Holger Prokisch [e,f], René Santer [b,e], Matias Wagner [e,f], Georg F. Hoffmann [a], Denisa Weis [g,1], Dominic Lenz [a,*,1]

[a] Heidelberg University, Medical Faculty Heidelberg, Center for Pediatric and Adolescent Medicine, Department I, Im Neuenheimer Feld 430, Heidelberg 69120, Germany
[b] University Children's Hospital, University Medical Center Eppendorf, Hamburg, Germany
[c] Heidelberg University, Medical Faculty Heidelberg, Institute of Human Genetics, Heidelberg, Germany
[d] Heidelberg University, Medical Faculty Heidelberg, Center for Pediatric and Adolescent Medicine, Department I, Division of Pediatric Endocrinology and Diabetes, Heidelberg, Germany
[e] Institute of Neurogenomics, Helmholtz Center Munich, Munich, Germany
[f] Institute of Human Genetics, TUM School of Medicine and health, Technical University of Munich, Munich, Germany
[g] Department of Medical Genetics, Kepler University Hospital Med Campus IV, Johannes Kepler University Linz, Linz, Austria

ARTICLE INFO

Keywords:
TALDO1
Transaldolase deficiency
Pentose phosphate pathway
Acute liver failure
Hypergonadotropic hypogonadism
Chronic kidney disease

ABSTRACT

Transaldolase deficiency is a rare metabolic disease caused by pathogenic variants in the *TALDO1* gene. Transaldolase plays an important role in the ribose-5-phosphate production, maintaining the NADPH-dependent lipid biosynthesis and cellular redox homeostasis. A small number of patients, predominantly children, have been reported, with a wide range of phenotypic presentations, including liver and kidney disease, involvement of the hematopoietic and endocrine systems, as well as possible early death. We aim to provide further insight into the clinical progression of transaldolase deficiency in adolescence and adulthood.

We report on three adult patients with genetically confirmed transaldolase deficiency, including two novel genetic variants in *TALDO1*. Although the patients have been symptomatic since newborn age, initially with hepatomegaly and cytopenias, they were only diagnosed during adolescence or adulthood. Genetic analysis was performed only at 17, 26, and 32 years, respectively, which, however, did not reveal any genetic variants that would be expected to cause a milder disease course. In adulthood, the dominant clinical features were hypergonadotropic hypogonadism, osteopenia, renal and hepatic involvement.

In conclusion, when reporting three new adult cases and comparing them with 47 accessible cases from the literature, our findings suggest that, even if clinical manifestations begin in the neonatal period, the overall phenotype may remain relatively mild, with gradual progression. This means that patients presenting with otherwise unexplained progressive liver disease, kidney dysfunction, cytopenia, and hypergonadotropic hypogonadism should be tested for transaldolase deficiency. We recommend closely monitoring patients with known transaldolase deficiency regarding the above-mentioned problems.

1. Introduction

Transaldolase deficiency is caused by biallelic pathogenic variants in the *TALDO1* gene, located on chromosome 11p15.5 (OMIM: #606003, GenBank accession no. NM_006755.2) [1]. This rare autosomal recessive metabolic disorder may present prenatally with hydrops fetalis and intrauterine growth restriction (IUGR), and is characterized by facial dysmorphism, cytopenias (anemia, thrombocytopenia, and/or leukopenia), hepatic cirrhosis, and additional cardiac, renal, and endocrine involvement [2,3]. Transaldolase (EC 2.2.1.2) catalyzes a crucial step in the pentose phosphate pathway, namely, the reversible transfer of a three-carbon unit from sedoheptulose-7-phosphate to glyceraldehyde-3-phosphate, as a result producing fructose-6-phosphate and erythrose-4-phosphate [4]. This metabolic step links the non-oxidative phase of the

* Corresponding author at: University Hospital Heidelberg, Center for Pediatric and Adolescent Medicine, Department of Pediatrics I, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany.
E-mail address: dominic.lenz@med.uni-heidelberg.de (D. Lenz).
[1] Equal contribution.

https://doi.org/10.1016/j.ymgme.2026.109872
Received 8 January 2026; Received in revised form 25 February 2026; Accepted 28 February 2026
Available online 3 March 2026

pentose phosphate pathway to glycolytic intermediates (Fig. 1) [4,5]. The pentose phosphate pathway provides precursors for the aromatic amino acids, for ribonucleic acid (RNA), and deoxyribonucleic acid (DNA) synthesis; moreover, it plays a key role in inactivating the reactive oxygen species (ROS) and in biosynthetic processes (reductive biosynthesis) by generating reduced nicotinamide adenine dinucleotide phosphate (NADPH) [4]. Transaldolase deficiency was first described in 2001 in a Turkish girl residing in the Netherlands [6]. To date, about 50 cases of transaldolase deficiency have been published in the literature, caused by 17 distinct genetic variants and demonstrating a wide range of phenotypic variability. Notably, early-childhood mortality is relatively high, and only a limited number of affected individuals have been reported to survive into adulthood [7,8]. Here, we present the phenotypic and genotypic characteristics of three adult patients - two female and one male - who underwent longitudinal monitoring. We specifically highlight the clinical features observed in these adult cases to support the medical management of this multisystemic metabolic disorder.

2. Patients and methods

Individuals aged 18 years or older with biallelic variants in *TALDO1* were included in this multicenter study. The medical history of all subjects was thoroughly reviewed. Clinical data, laboratory results, genetic findings, and longitudinal follow-up information were collected via a case report form (CRF).

To enhance clarity and ensure participant anonymity, the patients were labeled as P1, P2, and P3.

Quantification of urinary sugars, polyols and seven-carbon sugars was performed using gas chromatography–mass spectrometry (GC–MS) [9] and liquid chromatography–tandem mass spectrometry (LC–MS/MS) [10,11].

The listed Human Phenotype Ontology (HPO) terms were selected to describe the clinical phenotype, as shown in supplementary table S1.

To search for published cases, PubMed was screened using the MeSH term "transaldolase deficiency". Furthermore, the references of all publications were screened for further relevant publications in May 2025. Inclusion criteria were genetically confirmed transaldolase deficiency with clinically apparent manifestations. Based on the literature reviewed, we arrived at a total of 47 published cases at our disposal, although we acknowledge the existence of further cases that were reported in earlier publications but were not available to us for evaluation [2,6–8,12–30]. In addition, there are our 3 cases, bringing the total number of cases included in this study to 50. All tables and figures were designed using Microsoft Word, Biorender, and R Studio, the ggplot2 package.

3. Results

3.1. Genetic and biochemical studies

Three adult individuals (from Austria, Germany, and Turkey) with pathogenic variants in *TALDO1* (NM_006755.2) were included in the study (for genotype *see* Table 1). The genetic variants found in patient 2 (c.131_133del, p.(Thr44del); deletion of exon 3) were not previously reported in the literature. The c.131_133del was classified as "likely pathogenic" (PP4_mod, PM3, PM2_supp, PM4_supp) and the exon 3 deletion as "pathogenic" (PVS1, PM2_supp, PM3_supp, PP4_mod) according to ACMG-AMP criteria [31]. Fig. 2 shows the localization of the known *TALDO1* variants.

In almost all of these variants, a severe functional impairment can be assumed, which would be consistent with the early manifestation of clinical symptoms. But despite the fact that all three patients showed an early-onset form (i.e., a manifestation prenatally or before 1 month of age), none of them were diagnosed during childhood. Instead, the diagnoses were established later, via gene sequencing at 17 years (P3), 26 years (P2), and 32 years (P1), respectively. In all our patients, the

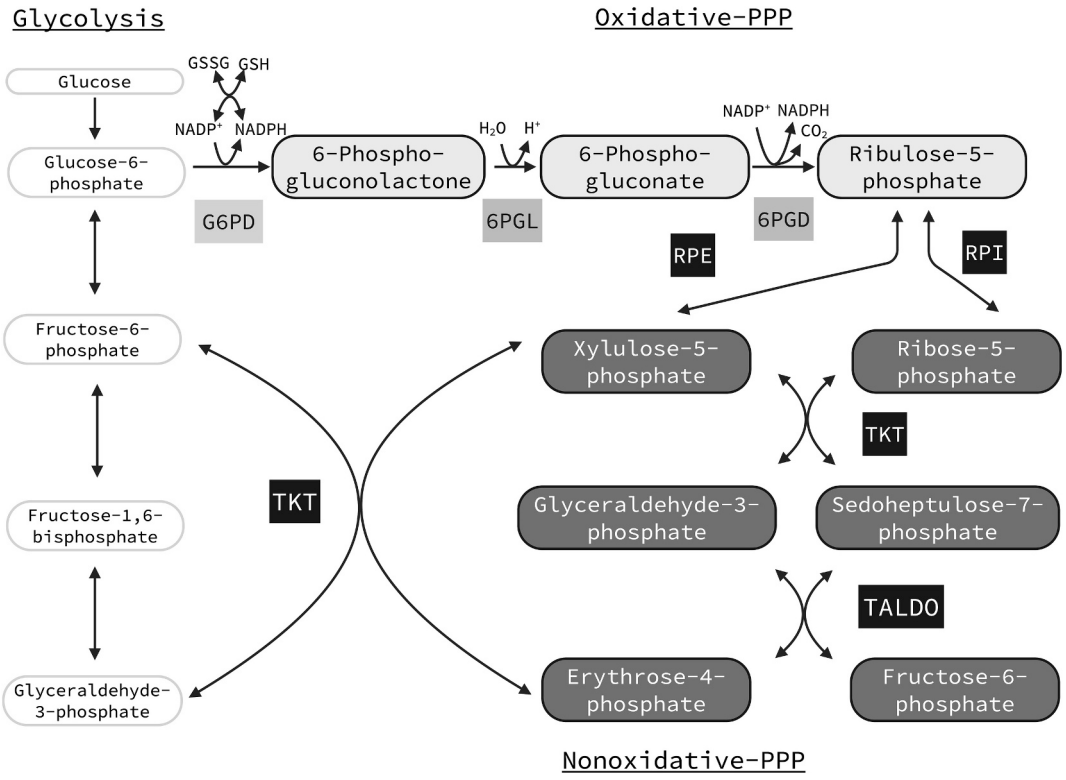

Fig. 1. Schematic overview of the pentose phosphate pathway and its connection to glycolysis. Abbreviations: G6PD: glucose-6-phosphate dehydrogenase, 6PGL: 6-phosphogluconolactonase, 6PGD: 6-phosphogluconate dehydrogenase, RPE: ribulose-phosphate 3-epimerase, RPI: ribose-5-phosphate isomerase, TKT: transketolase, TALDO: transaldolase, PPP: pentose phosphate pathway, GSSG: glutathione disulfide, GSH: glutathione, NADP: nicotinamide adenine dinucleotide phosphate.

Table 1
Genetic variants of *TALDO1* alleles in our study population with the derived change of amino acid sequence. Abbreviations: PID patient identification, NA: not available.

PID	Allele 1 cDNA (NM_006755.2)	Allele 1 protein change (NP_006746.1)	Allele 2 cDNA (NM_006755.2)	Allele 2 protein change (NP_006746.1)
P1	c.574C > T	p.(Arg192Cys)	c.574C > T	p.(Arg192Cys)
P2	c.131_133del	p.(Thr44del)	deletion of exon 3	NA
P3[†]	c.345dupA	p.(Asp116ArgfsTer80)	c.345dupA	p.(Asp116ArgfsTer80)

[†] known consanguinity of parents.

diagnosis was supported by elevated urine polyols (*see* Table 2).

3.2. Clinical course

The following sections will provide a detailed description of the organ involvement in the three patients.

3.2.1. Liver anomalies

All three patients developed hepatomegaly during infancy, which persisted over the years. In patient one (P1), liver enzymes were elevated in the neonatal period, with a plasma aspartate transaminase (AST) activity of 53 U/L (ref.: <31 U/L) and alanine transaminase (ALT) activity of 62 U/L (ref.: <34 U/L), and they remained mildly elevated over time. In addition, cholecystolithiasis was detected in the neonatal period and persisted on follow-up imaging over the years. At 29 years of age, a liver biopsy was performed due to severe esophageal variceal bleeding. Histology showed progressive liver remodeling, but no definitive evidence of cirrhosis. The esophageal varices were then attributed to portal hypertension, with a possible additional contribution from concomitant pulmonary hypertension (*see* below). Carvedilol was subsequently initiated to manage the portal hypertension. By 34 years of age, cirrhosis was confirmed histologically, consistent with the ultrasound and MRI findings. Splenomegaly was noted in infancy and persisted over time.

Patient 2 (P2) showed elevated liver enzymes from the neonatal period through adolescence, with plasma ALT activity levels up to 61 U/L (ref.: <35 U/L) and AST up to 42 U/L (ref.: <37 U/L). At 10 months of age, a liver biopsy showed hepatic steatosis with portal fibrosis and glycogen accumulation. Because of the persistently elevated liver enzymes, an increased lactate level of 3.5 mmol/L, and chronic kidney disease (stage II–III), a mitochondrial disorder was initially considered the most likely diagnosis. Due to renal carnitine loss and the suspected mitochondrial disorder, she was treated with carnitine until receiving the definitive diagnosis of transaldolase deficiency. By the age of 20 years, this patient had developed cholecystolithiasis, too. Splenomegaly was intermittently present from the age of 4 years.

P3 showed a borderline plasma AST activity (73 U/L) (ref.: <77 U/L) and an elevated ALT activity of 111 U/L (ref.: <49 U/L) during the third month of life, with otherwise normal liver function. Liver enzymes normalized after the first year and remained within normal range. Liver biopsy was performed at 7 months of age, due to the early death of his sister with liver cirrhosis. It showed moderate microvesicular parenchymal steatosis, with sparse disseminated single-cell necrosis, without any signs of cirrhosis, inflammation, or cholestasis.

3.2.2. Hematological anomalies

During the newborn period, all three patients presented with anemia without requiring transfusions. It spontaneously resolved completely in P2, to a large extent in P3, whereas P1 continues to have anemia to date. In P1, anemia was first noted in infancy (erythrocytes 3.15 × 10^12/L; ref.: 4–5.3 × 10^12/L) and persisted into adulthood; at 38 years, erythrocytes were 3.33 × 10^12/L (ref.: 4.1–5.1 × 10^12/L) with hemoglobin 12.4 g/dL, MCV 101 fL, RDW 12.5%, and reticulocytes 72 × 10^12/L (ref.: 25–100 × 10^12/L), consistent with normocytic anemia.

P2 presented in the postnatal period with anemia (exact laboratory values not available), which resolved spontaneously, and the erythrocyte counts stayed within normal limits thereafter.

In P3, normocytic anemia (Hb: 10 g/dL, MCV: 85 fL, erythrocyte count: 3.36 × 10^12/L) was observed during early infancy. Anemia resolved at kindergarten age but recurred in a very mild form (Hb 12.7 g/dL) with normal MCV, MCHC, and slightly increased reticulocytes (108 × 10^12/L; ref.: 25–105 x 10^12/L) in early adulthood.

Regarding leukocyte counts, P1 initially showed fluctuating leukocyte counts from 3.1 to 5.4 G/L (ref.: 6–21 G/L). By the age of one year, the leukocyte count was 3.8 G/L (ref.: 5–17 G/L). With 34 years, pancytopenia persisted, with a leukocyte count of 0.89 G/L (ref.: 4–10 G/L). P2 presented with agranulocytosis at birth, which later resolved; between the ages of 3 and 5 years, however, she developed recurrent granulocytopenia (minimal: 675/ μL). At 4.5 years, she had an increased susceptibility to infection, with recurrent upper respiratory tract infections, for which an adenoidectomy eventually led to clinical improvement. In a recent laboratory assessment at 28 years, leukopenia of 2.91 G/L (ref.: 4–10 G/L) was detected again. In P3, neutropenia was observed during the newborn period, which resolved and did not recur beyond kindergarten age. Granulocytes showed a normal phagocytic function and an impaired respiratory burst. P3 suffered from frequent urinary tract infections in infancy and later from otitis media. He also required hospitalizations for surgical intervention and intensive antibiotic treatment due to recurrent skin abscesses in various sites.

Thrombocytopenia was identified only in P1 with a progressive decline in platelet count over the years (neonatal period: 110 G/L, 39 years of age: 23 G/L – ref.: 150–370 G/L).

None of our patients required regular transfusion or granulocyte colony-stimulation factor during routine follow-up. However, P1 experienced severe esophageal variceal bleeding and underwent multiple liver biopsies. In the context of these acute events and given the bleeding risk associated with thrombocytopenia—particularly around biopsy procedures—she received red blood cell and platelet transfusions.

3.2.3. Cardiopulmonary anomalies

In P1, an atrial septal defect (ASD) was identified in the newborn period. At 10 years, a heart catheterization confirmed an 8 mm ASD II without a hemodynamically significant shunt; therefore, surgical closure was not indicated. Moreover, an increase of the pressure in the right ventricle and the pulmonary arterial vascular system was observed. In adulthood (at the age of 28 years), the patient presented with exertional dyspnea as a sign of NYHA II cardiac insufficiency. Further investigations revealed marked pulmonary arterial hypertension on both echocardiography and right heart catheter examination, which was responsible for right heart failure and possible congestion of the azygos vein and downhill esophageal varices. Therapy with macitentan and inhaled iloprost resulted in clinical improvement; the patient is currently classified as NYHA I under sildenafil therapy. During spiroergometrical examination at 36 years, oxygen saturation dropped to 85% at peak exertion. This result might reflect the underlying metabolic disease; however, an association with pulmonary arterial hypertension cannot be excluded.

In P2, ASD II was diagnosed during the neonatal period, which closed spontaneously during childhood without the need for intervention. Additionally, the patient developed sinus bradycardia (HF <45/min, especially at night) in adulthood. P2 showed no abnormalities during spiroergometry.

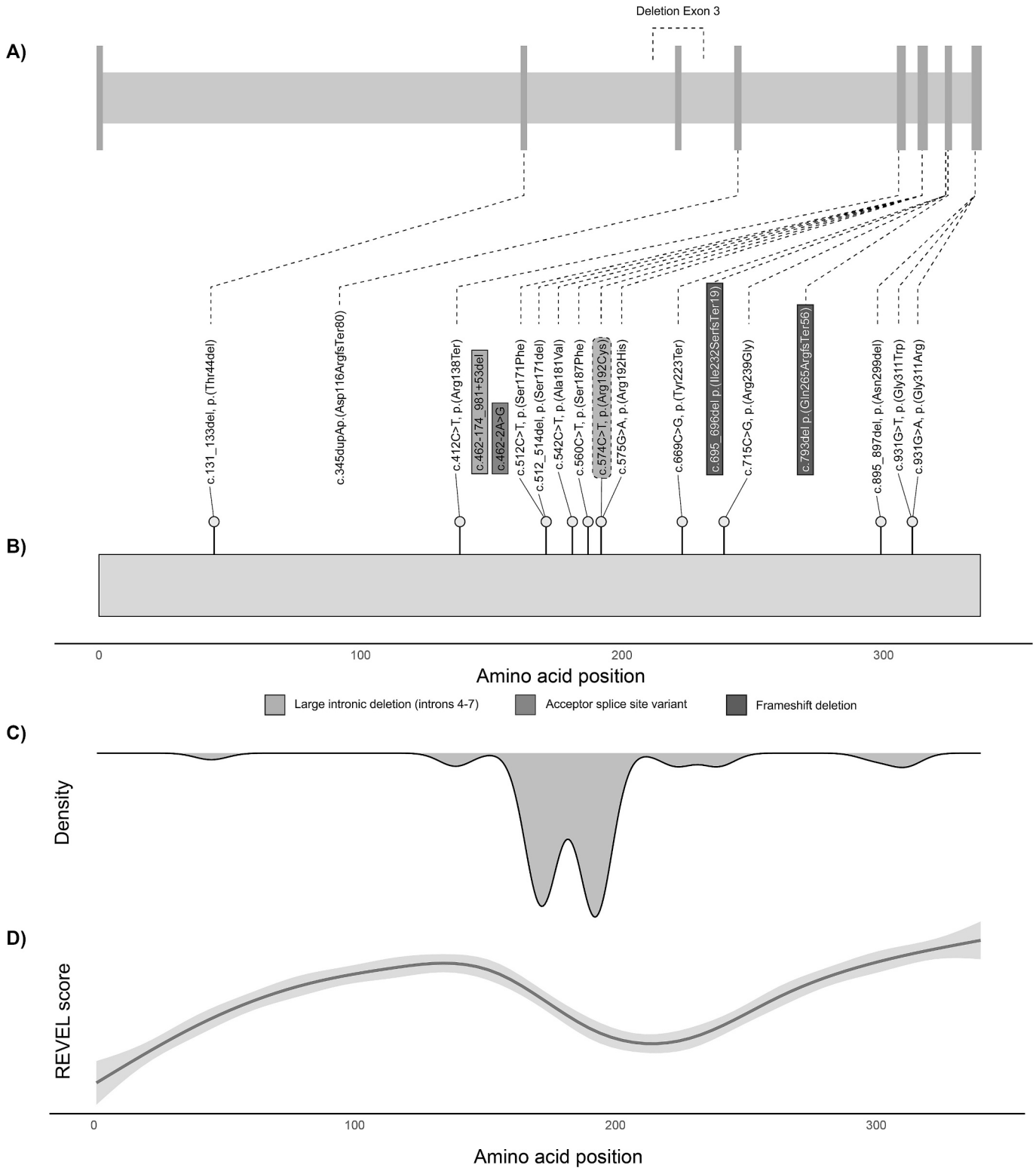

Fig. 2. Localization of *TALDO1* variants. All known pathogenic variants including affected region of the encoded protein. (a) Exon-Intron structure of *TALDO1* gene. (b) Amino acid sequence. (c) Density plot of known pathogenic variants. (d) In silico effect prediction of *TALDO1* missense variants using REVEL score (rare exome variant ensemble learner, a predicting method for the pathogenicity of missense variants based on individual tools) [63].

In P3, rapid exhaustion and fatigue were noticed early in toddlerhood without signs of myocardial or pulmonary dysfunction. He was not able to participate in sport activities. At the age of 17 years, spiroergometry revealed decreased peak oxygen uptake and an exercise-induced severe lactic acidosis. Echocardiography and thoracic x-ray were unremarkable. Spirometry and plethysmography were normal in adolescence, but at the age of 21 years, slight restrictive changes with impaired ventilation and diffusion, without obstruction, were documented. The same findings were confirmed upon a control examination one year later, indicating a permanent lung disease.

Table 2
Urinary sugar and polyol levels in our patients, Abbreviations: H: high (elevated level).

Sugars, polyols (mmol /mol creatinine)	P1 (reference range)	P2 (reference range)	P3 (reference range)
Erythritol	89 (14–88) H	118 (0–65) H	98 (14–88) H
Threitol	58 (0–35) H	17 (0–19)	22 (0–35)
Xylitol	5 (0−12)	1 (0–6)	3 (0–12)
Arabitol	128 (6–60) H	67 (0–50) H	115 (6–60) H
Ribitol	40 (0–7) H	23 (0–8) H	31 (0–7) H
Galactitol	1 (0–15)	2 (0–4)	8 (0–15)
Perseitol	5 (0–1) H	272 (0–0.02) H	2 (0–1)
Sedoheptulose	333 (<9) H	0 (0−13)	195 (<9) H
Mannoheptulose	15 (<3) H	1 (0–2)	15 (<3) H

3.2.4. Renal anomalies

At 23 years of age, routine assessment in primary care by P1 revealed elevated serum creatinine and urea despite an eGFR ≥90 mL/min/1.73 m^2, consistent with chronic kidney disease (CKD) stage 1. Renal function declined gradually over the following years, reaching CKD stage 3a with an eGFR of 50 mL/min/1.73 m^2 by the age of 34 years. Further diagnostic evaluation confirmed the diagnosis of renal tubular acidosis type II as well. She receives a potassium substitution.

Similarly, in P2, elevated serum creatinine concentrations were observed at the age of 8 years. The diagnostic work-up revealed mixed tubular and glomerular proteinuria (for laboratory values *see* supplementary table S2). The decreased eGFR (35 mL/min/1.73 m^2 at 13 years) corresponded to CKD stage 3. At the age of 22 years, the new finding of intermittent microhematuria led to a kidney biopsy showing histological features consistent with focal segmental glomerulosclerosis (FSGS).

A tubulopathy was diagnosed in the third patient (P3) at kindergarten age and has persisted over time. P3 had recurrent urinary tract infections (*Escherichia coli*) during infancy, with the first occurrence in the newborn age. Left-sided vesicoureteral reflux I° was shown. Tubular proteinuria was diagnosed during the third year of age and has persisted over time. The patient was treated for many years with angiotensin-converting enzyme (ACE) inhibitors and currently with candesartan. Kidney function was normal until primary school age. Later, he showed an increased serum creatinine concentration (at the time of this report 1.57 mg/dL) and mild generalized aminoaciduria. Renal failure has slowly progressed to CKD stage 3.

3.2.5. Skin anomalies

Cutis laxa occurred in P1 during the newborn period and normalized over time. Both P1 and P3 individuals presented with dry skin and a widespread network of visible blood vessels, first observed in infancy and continuously present. P3 still has thin and loose skin with reduced elasticity and sagging folds, but without permanent wrinkles. P2 showed no transaldolase deficiency-related skin anomalies.

3.2.6. Endocrine abnormalities

P1 had primary amenorrhea. Hypergonadotropic hypogonadism was identified at the age of 23 years (LH: 89.8 mU/mL (ref. postmenopausal: 11.3–40 mU/mL), FSH: >170 mU/mL (ref. postmenopausal: 21.7–153 mU/mL), estradiol <20 pg/mL (ref. postmenopausal: <20 pg/mL)). Abdominal MRI revealed the absence of ovaries. At 28 years of age, the patient developed hyperprolactinemia in the absence of structural abnormalities of the sella turcica on MRI. The condition was presumably transient, with prolactin levels having normalized by 39 years of age. Hypoparathyroidism was diagnosed in adulthood.

Following menarche at 15 years of age, P2 exhibited oligomenorrhea (3–4 menstrual cycles per year), while thelarche and pubarche were otherwise normal. Between 25 and 28 years of age, laboratory testing confirmed hypergonadotropic hypogonadism, with low estrogen levels and elevated gonadotropins (exact values not available). Hormone replacement therapy was started with estradiol and dienogest. As a secondary complication of kidney disease, hyperparathyroidism was diagnosed and treated with vitamin D_3 since the age of ten years.

In the male patient P3, increased FSH (10.5 U/L, ref.: 0.4–3.8 U/L), with otherwise normal sexual hormone levels, was first measured at the age of 9 years due to hirsutism. No testicular growth or voice changes evolved during the following years. Plasma testosterone concentrations were almost undetectable with very high FSH (>200 U/L) and LH (186 U/L, ref.: 1.5–9.3 U/L) concentrations, indicating a hypergonadotropic hypogonadism. Treatment with testosterone started only at the age of 22 due to noncompliance. He also suffers from gynecomastia.

Osteopenia was noted during early adulthood (T score of bone density measurement in femoral neck: −1.7 at the age of 28 years) in P2 and in P1 osteoporosis (T score in femoral neck: −3.3 at 33 years). P3 was found to have osteoporosis at the age of 20 years: his T score of the left femoral neck was −3.7. Vitamin D_3 deficiency (9.1 μg/L; ref.: >30 μg/L) was detected, although the level had previously been normal. P1 is receiving osteoporosis therapy with vitamin D_3 and calcium supplementation, as well as denosumab administered every six months. P2 is on vitamin D_3 and vitamin K2 supplementation. P3 is under treatment with vitamin D_3 and calcium supplementation.

Thyroid function proved to be normal in all three individuals.

3.2.7. Growth

P1 exhibited normal growth, with a final height z-score of −0.4, at 166 cm (minimum −1.2 at 6 years). Body weight was low at 3 months (z-score − 1.2); it improved until 1.2 years (−0.37) but subsequently remained suboptimal in adolescence, with a weight z-score around −2.

P2 showed normal growth (height z-score 0.37 at 28 years; nadir −1.57 at 6 years). Her final height is 164 cm. The weight development stayed in the normal range (z-score − 1.34 at 8 years, improving to −0.59 at 28 years).

P3 was growing appropriately until the 6th year, reaching around the 50. percentile, but between 6 and 12 years, the z-score gradually decreased to −0.67 and further to −1.75 during adolescence. His height is 165 cm. Until preschool age, the relative weight decreased to a z score of −1.64, and later during adolescence to −2.33, with a current z-score of −1.88.

3.2.8. Neuromuscular abnormalities

All patients showed motor delay until approximately six years of age, after which it resolved. Hypotonia was observed in P1 and P2 and improved by age three, while in P3 it continued into adolescence and was the reason for intensive physiotherapy. Due to muscular hypotonia and fatigue, and the suspicion of a mitochondrial disorder, P3 was treated with a vitamin cocktail (B_1, B_2, Q_{10}, and carnitine) during preschool age. Indeed, his fibroblasts showed diminished complex II activity, and urine 2-oxoglutarate concentration was increased. EEG and brain MRI at 9 years were normal.

The highest level of education was completion of secondary education in one patient and vocational training in the other two; all patients are working in their respective fields of training.

3.2.9. Other

Prenatal findings included polyhydramnios in two individuals (P2, P3). Inguinal hernia was observed in P1 and P2. Mild facial dysmorphism was present in P1 and P2. P1 experienced an acute ischemic stroke at 28 years of age, presenting with left-sided hand weakness. A right frontotemporal ischemic event was identified on MRI, which resolved completely, both clinically and radiologically, without residual deficits.

3.3. Phenotypic spectrum of the published cases

Reviewing the available literature, 47 cases of transaldolase deficiency were identified, with a total of 17 distinct pathogenic *TALDO1*

gene variants. We contribute another three adult cases and two previously unreported gene variants. Among these 50 patients, eight had died before the age of one year.

Most patients first presented during early infancy (40/50), with symptoms as listed above. Hematologic abnormalities, mainly cytopenias, were common: anemia (27/50), thrombocytopenia (32/50), and leukopenia (11/50). Hepatic involvement was also frequent and was already evident in 45 patients during infancy. Cardiac anomalies were reported in 30 cases, most commonly atrial septal defect, patent ductus arteriosus, patent foramen ovale, and myocardial hypertrophy. Splenomegaly occurred in 42 patients.

Skin anomalies including, wrinkled or dry skin, telangiectasia, neonatal edema, and hemangiomas, were primarily noted in infancy and childhood (32 cases).

Renal involvement (tubulopathy, glomerulonephritis, or chronic kidney disease) was documented in 22 cases, of whom 9 cases had presented in infancy.

Endocrinologic problems affecting gonadal hormones or genital development were reported in 19 cases, among them 10 cases with presentation during infancy (with enlarged clitoris, microphallus, or cryptorchidism). Notably, among the cases with an overall milder presentation of transaldolase deficiency, hypergonadotropic hypogonadism was described in 9 cases. Impaired bone mineral status (osteoporosis or osteopenia) was identified in 11 patients.

For a better overview, the common phenotypical features of the 50 case reports and their frequencies are summarized in Fig. 3.

4. Discussion

Transaldolase deficiency is caused by pathogenic variants in the *TALDO1* gene, which comprises seven coding exons. Seventeen gene variants have already been described in transaldolase-deficient patients; however, to date, no clear phenotype-genotype association has been established. Here, we present three additional affected patients with two already published variants, c.345dupA [8], c.574C > T [16], each homozygous, as well as two novel variants found in one individual: deletion of exon 3 and c.131_133del. Homozygosity in 2 out of 3 patients confirms the high consanguinity rate in affected families, which has been reported to be up to 81% in earlier publications [32]; however, in our study, only in one case was consanguinity confirmed.

Transaldolase is the second enzyme of the non-oxidative part of the pentose phosphate pathway [4,33], which plays a significant role in human metabolism. Transaldolase deficiency has been associated with reduced intracellular NADPH availability, due to increased NADPH-dependent diversion of sugars to polyols by aldose reductase [34]. Decreased NADPH has been linked to impaired mitochondrial membrane potential and increased susceptibility to apoptosis (e.g., H_2O_2- and CD20-induced apoptosis) [35]. The reduced availability of NADPH, a critical cofactor for reductive biosynthesis - including lipid and cholesterol synthesis [36,37] - results in secondary glutathione (GSH) depletion, thereby exacerbating cellular oxidative stress and impairing redox homeostasis [38]. The regeneration of reduced GSH (from the oxidized GSSG) depends on the NADPH synthesized in the pentose phosphate pathway [38]. In addition, in transaldolase deficiency, the intracellular accumulation of potentially hepatotoxic sugar-phosphates (sedoheptulose-7-phosphate), polyols (erythritol, arabitol, ribitol), and C7

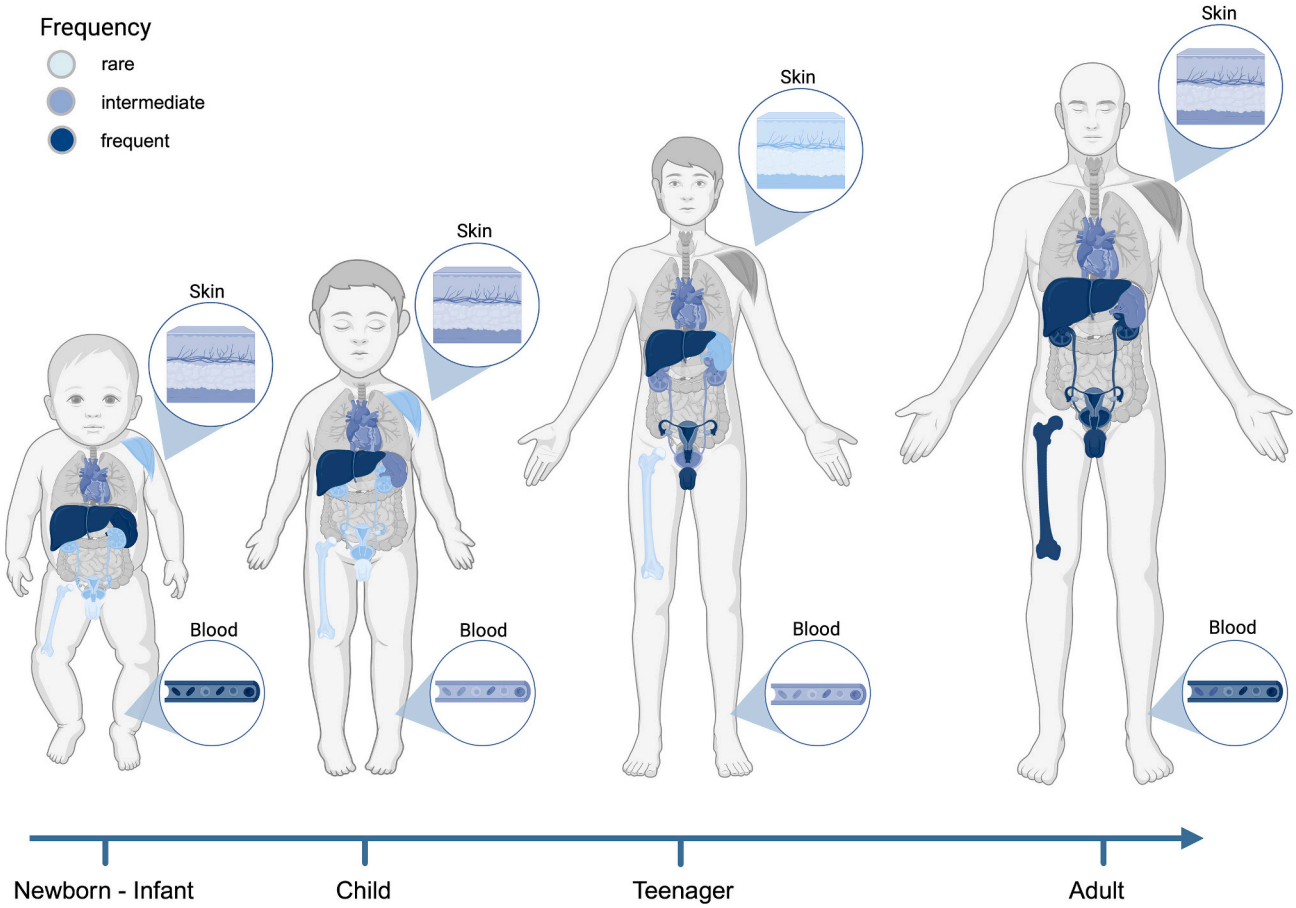

Fig. 3. Frequency of organ involvement depending on age in transaldolase deficiency. Definitions of frequency: rare - <33%, intermediate - <67%, frequent - >68% of the included cases. Age groups: Newborn-Infant (<1 year), Child (1–9 years), Teenager (10–18 years), Adult (>18 years).

monosaccharides (mannoheptulose, sedoheptulose) may induce hepatocellular injury through osmotic stress [39] and disruption of redox homeostasis [32,34,40]. Nonetheless, emerging data have associated circulating polyols (erythritol, xylitol) with increased thrombotic and cardiovascular risk, so it may be reasonable to consider limiting intake of foods containing these sugar alcohol sweeteners in transaldolase deficiency [41,42].

For a better understanding of the disease mechanism, a comprehensive assessment of sugar, polyol, and NADPH levels across patients would be very informative. Variations in these measures, together with aldose reductase activity, may contribute to phenotypic heterogeneity and help explain differences in disease severity. However, given the small cohort size, meaningful interpretation would require inter-study comparisons, which might be challenging due to the possible age-dependency of urinary polyols [43] and the different pre-analytical/analytical methods used to measure NADPH levels [44]. In our study, comparison with previously reported cases was limited because most published pediatric cases are not age-matched to our cohort; the literature on adult patients is sparse; and quantitative metabolite values are often not reported [8,22]. We therefore propose prospective studies with standardized sampling conditions, harmonized pre-analytical procedures, and healthy control samples analyzed in the same laboratory using identical protocols. Lastly, comparison with other pentose phosphate pathway disorders (e.g., glucose-6-phosphate dehydrogenase deficiency) could also be of interest.

In recent years, evidence has emerged linking transaldolase deficiency to autoimmunity [45]. At the molecular level, altered regulation of apoptosis has been described in transaldolase deficiency, which may contribute to an increased risk of autoimmune disease [38,46]. In addition, there is increasing evidence of mechanistic overlap between systemic lupus erythematosus (SLE) and transaldolase deficiency [38,40,47–49]. Transaldolase-deficient mice show marked hepatic activation of mTORC1 [50], resembling the pattern observed in lupus-prone mouse models [51]. Notably, inhibition of mTOR signaling with rapamycin may protect against liver injury in transaldolase deficiency and prevent liver disease in SLE [50,52]. In clinical studies, *N*-acetylcysteine (NAC) reduced mTOR activation, and improved disease activity in patients with SLE [53]. In *TALDO1* knockout mice, lifelong NAC treatment prevented acetaminophen-induced liver failure and the development of hepatocellular carcinoma [54]. Furthermore, as reported by Winans et al., mTOR-dependent impaired secretion of paraoxonase 1, together with antiphospholipid antibody production, has been proposed to contribute to autoimmune mechanisms in the pathogenesis of cirrhosis in transaldolase deficiency [50]. Taken together, these findings suggest that redox imbalance and downstream immune–metabolic pathways may also be relevant in transaldolase deficiency. However, in our cohort, we observed no clinical evidence of autoimmunity. Therefore, we did not pursue a systematic autoimmune work-up in our patients. We acknowledge that this remains an important area for future studies incorporating standardized immune assessment.

Our study reviewed 50 cases of transaldolase deficiency from various geographical regions of the world, demonstrating a broad spectrum of genotypic and phenotypic variability. Information on the disease course in adulthood is scarce. The oldest reported patient with transaldolase deficiency was 42 years old [8], and presented with renal anomalies (proximal tubular dysfunction, CKD stage 3). The patient had a history of “cryptogenic hepatic cirrhosis” and underwent an ASD operation at 28 years. Another previously described adult presented at the age of 32 years with hypergonadotropic hypogonadism and renal insufficiency (CKD stage 2); however, transaldolase deficiency was only considered after this diagnosis had been confirmed in her nephew [7].

Recent reports distinguish between early- and late-onset forms of transaldolase deficiency [7,13,22]. With the early-onset form being associated with a more severe clinical course and increased mortality in early childhood [14,43]. Williams et al. reported on 34 patients, of whom eight had died at a median age of 2.3 years [32]. In the three patients described here, hematological and liver changes occurred neonatally, which classifies them as early-onset cases. Notably, however, none of the patients in our cohort died, and their clinical course was comparatively mild. Hence, disease classification should be reconsidered, as the age of onset does not appear to determine severity.

Hepatomegaly is commonly described (77% of early-onset transaldolase deficiencies [32]). Hepatic involvement can progress to liver cirrhosis [13], hepatocellular carcinoma [16,21], and liver failure. Hepatopulmonary syndrome has been previously reported, too [16,29,55], in our patients, no such finding was observed. As a therapeutic option in patients with transaldolase deficiency and liver failure, a liver transplantation may be necessary [6,16]. Despite the inherent limitations and challenges associated with organ transplantation, it has been proven to be effective and lifesaving for affected individuals. Thus far, in nine cases of transaldolase deficiency, liver transplantation has been performed, at a median age of 12 months (range: 5–40 months) [15,16]. One patient died postoperatively, whereas the others are doing well after 1–2 years of follow-up [15,32,56]. A postoperative bile-duct stenosis occurred in one case and was treated successfully [15]. However, a more extended follow-up might be necessary to determine the course of the disease after liver transplantation [15,21,32,56].

In two cases of adult patients reported to date [7,8], the liver manifestation had already progressed to liver cirrhosis. In contrast, among our three adult patients, two had hepatomegaly and mildly elevated liver enzyme levels. However, in P1 (the eldest of our patients), the hepatic involvement progressed over the years to liver cirrhosis with portal hypertension. Accordingly, we advise close hepatologic surveillance in these patients, with monitoring for progressive liver remodeling and for HCC. Splenomegaly, reported in half of previously published cases [32], occurred in one of our patients.

Moreover, pancytopenia (15%) or involvement of at least one cell line (thrombocytopenia 74%, anemia 76%), is reported in many patients [32]. Affected individuals often require blood transfusions [3,23]. Anemia mostly resolves with age, but it can also persist [8]. Possible explanations for the anemia could be the oxidative stress due to NADPH deficiency or hemolysis; moreover, decreased erythropoietin formation in the kidney involvement, impaired hematopoiesis in the fetal liver, and bleeding [32]. Splenic pooling may account for the observed thrombocytopenia and might contribute to splenomegaly [6]. All three patients had transient anemia accompanied by leukopenia or neutropenia, and one presented with pancytopenia at birth. In adulthood, P1 continued to exhibit pancytopenia, with thrombocytopenia and leukopenia as the most pronounced abnormalities. By contrast, P2 has leukopenia and P3 anemia in adulthood.

Tubular dysfunction occurred in 29% of the reported cases [32]. Interestingly, we observed this feature in all our patients; in one, focal sclerosing glomerulonephritis was an additional manifestation. Reasons may be impaired energy metabolism, accumulation of toxic metabolites [57], autoimmunity [38,45], or oxidative stress due to NADPH depletion [38]. In our adult cohort, we identified renal involvement as a key observation, as all three patients had tubulopathy and chronic kidney disease; therefore, nephrological examination should be included in the standard follow-up protocols of patients with transaldolase deficiency.

Cardiac involvement is commonly reported and includes patent ductus arteriosus, atrial or ventricular septal defects, coarctation of the aorta, and cardiomyopathy [2,6,23,32]. The bradycardia observed in P2 likely reflects exercise-related cardiovascular adaptation. We also noted severe primary pulmonary hypertension in one patient—a finding not previously reported for this disorder. If patients with transaldolase deficiency develop significant pulmonary arterial hypertension, it is essential to consider the possibility of esophageal variceal bleeding. In P1 of our case series, treatment with macitentan, an endothelin receptor antagonist (ERA), and later with sildenafil was associated with a stabilization of pulmonary arterial hypertension (PAH) over several years.

Hypergonadotropic hypogonadism appears to be typically in adolescent and adult patients with transaldolase deficiency [7,22]. It

may go unrecognized during childhood due to the absence of clinical symptoms, which could lead to underreporting. Alternatively, hypogonadism may develop over time, as one of our female patients exhibited some form of menstrual bleeding. The reduced steroid hormone concentration may reflect impaired reductive biosynthesis secondary to NADPH deficiency [40]. Sperm dysmotility has been reported in male *TALDO1* knockout mice [58] but has not, to our knowledge, been reported in humans. In our male patient, no fertility assessment has been performed to date, as there was no clinically driven indication. In a long-term Polish follow-up (4–13 years) [43], osteopenia was present in all pediatric patients. In our study, all three patients had developed osteoporosis, but at a later age. This finding suggests a gradual transition from osteopenia to osteoporosis. It is likely that in adult patients, hypergonadotropic hypogonadism and renal insufficiency add to the risk of bone loss. Hence, an endocrinological consultation including the assessment of sex hormones at the time of diagnosis, with close follow-ups during puberty, as well as hormone replacement therapy and vitamin D_3 supplementation, should be considered.

In all of our patients, we observed a delay in motor development during childhood, whereas in a larger study, only 28% of patients showed mild intellectual disability or motor delay [32]. We acknowledge the lack of systematic assessment of psychosocial and neurocognitive status in our cohort, constituting an important limitation of the present study. Nevertheless, the overall existing data on neurocognitive development remains limited, and prevalence is probably underestimated. For this reason, future studies should implement standardized neurocognitive and psychosocial evaluations to better characterize long-term outcomes.

In our cohort, P1 experienced an acute ischemic stroke, with symptoms being resolved completely without residual impairment. Possible contributing factors include the reported association between elevated polyols and thrombotic risk [41,42], as well as an underlying autoimmune prothrombotic state (e.g., antiphospholipid antibodies) [59]. In light of the complete clinical and radiological resolution, no additional diagnostic evaluation (including investigation for autoimmune etiologies) was performed in our patient.

Williams et al. reported that 50% of the transaldolase-deficient patients exhibit dysmorphic features (including triangular faces and low-set ears), and skin anomalies (e.g., cutis laxa, capillary hemangioma) [32]. In our study, cutis laxa and dry skin were present in two cases; however, cutis laxa was only transient during early childhood. Otherwise, dysmorphic features were only noted during childhood. Inguinal hernias have rarely been reported in the current literature [14,17,25], whereas in our cohort, 2/3 patients had inguinal hernias. The pathogenesis might be similar to that of cutis laxa, suggesting a concomitant connective tissue disorder.

Although many case reports have been published since 2001, plenty of questions remain unanswered. The therapeutic options are limited and mainly consist of symptomatic treatment. In light of the disturbed redox balance, antioxidant therapies—including *N*-acetylcysteine, and vitamins C and E—have been introduced [25,32]. As mentioned above, NAC therapy has been proposed based on its protective effect in preventing hepatocellular carcinoma in mice, and its efficacy in the acetaminophen-induced liver failure in both mice [54] and human trials [60]. Although its role in transaldolase deficiency requires evaluation in larger cohorts to better guide therapeutic decision-making, clinicians could consider administering NAC to selected patients. Antioxidants like Vitamin E and C have been proposed as a therapeutic option for transaldolase deficiency, however, no published data on their beneficial effects have been found.

Additionally, aldose reductase may represent a potential therapeutic target, based on the possible contribution to the elevated risk of hepatocellular carcinoma in transaldolase deficiency. Oaks et al. showed that AR blockade—in mice deficient for both transaldolase and AR—reduced NADPH consumption via AR, attenuated mitochondrial oxidative stress and polyol accumulation, and mitigated liver disease progression to HCC [34]. Pharmacologic inhibition of AR (e.g., sorbinil or zopolrestat) has also been reported to suppress hepatocellular carcinoma cell proliferation [34], suggesting that these agents might be candidates for future studies, under careful consideration of their safety profiles [61].

Lastly, the pharmacological therapy of the disease includes hormone replacement in patients with hypergonadotropic hypogonadism, as well as vitamin D_3 supplementation and, in some cases, calcium for osteopenia [13].

5. Conclusions

In conclusion, transaldolase deficiency has gained increased attention over the last decades. However, the condition remains likely to be underdiagnosed, particularly in less severe cases. Here, we describe three adults with neonatal-onset transaldolase deficiency who have had a relatively mild clinical course, showing clinical features similar to those reported in pediatric patients but developing more gradually over time.

A novel finding in adult patients with transaldolase deficiency is the severe pulmonary hypertension observed in one of our cases, underscoring the importance of monitoring for this complication. All patients with transaldolase deficiency should be closely monitored in a multidisciplinary setting that should include hepatologists, nephrologists, endocrinologists, and cardiologists. Liver involvement may progress from fibrosis to possible cirrhosis, liver failure, and, in rare cases, hepatocellular carcinoma. Endocrinological monitoring plays a key role in initiating hormone replacement therapy and preventing osteoporosis. Renal function should be assessed regularly due to the possible renal involvement. Moreover, we recommend considering transaldolase deficiency as a differential diagnosis in patients with multisystem involvement, including the features outlined above.

Through this work, we aim to raise awareness of the multisystemic phenotype of transaldolase deficiency and its variable types of presentation in adult patients, to help these patients receive the proper diagnostic work-up and ultimately appropriate treatment.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Viktoria Bea Horvath: Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – original draft. **Konstantinos Tsiakas:** Investigation, Data curation, Writing – original draft. **Heiko Brennenstuhl:** Visualization, Writing – review & editing. **Daniela Choukair:** Data curation, Writing – review & editing. **Nicole Hammann:** Data curation, Writing – review & editing. **Moritz Niesert:** Data curation, Writing – review & editing. **Alexander Fichtner:** Data curation, Writing – review & editing. **René Santer:** Data curation, Writing – review & editing. **Matias Wagner:** Data curation, Writing – review & editing. **Denisa Weis:** Methodology, Investigation, Conceptualization, Writing – review & editing. **Dominic Lenz:** Visualization, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization, Writing – review & editing, Writing – original draft. **Holger Prokisch:** Writing – review & editing. **Georg F. Hoffmann:** Writing – review & editing.

Ethics

All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2024 [62]. The study was approved by the ethical committee of the University Hospital Heidelberg (Study number: S-0352014).

Informed consent was obtained from all individuals or, in the case of one minor patient (diagnosis at the age of 17), from his parents.

Funding

This work was conducted without dedicated funding.

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.

Acknowledgements

We are grateful to Robert Stollmayer (Clinic for Diagnostic and Interventional Radiology (DIR), Heidelberg University Hospital, Heidelberg, Germany) for the revision of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2026.109872.

Data availability

Data will be made available on request.

References

[1] K. Banki, et al., The human transaldolase gene (TALDO1) is located on chromosome 11 at p15.4-p15.5, Genomics 45 (1) (1997) 233–238, https://doi.org/10.1006/geno.1997.4932.
[2] N.M. Verhoeven, et al., A newborn with severe liver failure, cardiomyopathy and transaldolase deficiency, J. Inherit. Metab. Dis. 28 (2) (2005) 169–179, https://doi.org/10.1007/s10545-005-5261-6.
[3] V. Valayannopoulos, et al., Transaldolase deficiency: a new cause of hydrops fetalis and neonatal multi-organ disease, J. Pediatr. 149 (5) (2006) 713–717, https://doi.org/10.1016/j.jpeds.2006.08.016.
[4] A. Stincone, et al., The return of metabolism: biochemistry and physiology of the pentose phosphate pathway, Biol. Rev. Camb. Philos. Soc. 90 (3) (2015) 927–963, https://doi.org/10.1111/brv.12140.
[5] T. TeSlaa, et al., The pentose phosphate pathway in health and disease, Nat. Metab. 5 (8) (2023) 1275–1289, https://doi.org/10.1038/s42255-023-00863-2.
[6] N.M. Verhoeven, et al., Transaldolase deficiency: liver cirrhosis associated with a new inborn error in the pentose phosphate pathway, Am. J. Hum. Genet. 68 (5) (2001) 1086–1092, https://doi.org/10.1086/320108.
[7] A. Takaleh, et al., Hypergonadotropic hypogonadism due to transaldolase deficiency: two cases and literature review, JCEM Case Rep. 2 (3) (2024) luae028, https://doi.org/10.1210/jcemcr/luae028.
[8] A.B. Dirim, et al., Late diagnosis of a rare multisystemic genetic disorder: Transaldolase deficiency due to homozygous TALDO1 c.345dupA variant, Nephrology (Carlton) 29 (1) (2024) 55–56, https://doi.org/10.1111/nep.14243.
[9] G. Jansen, et al., Capillary gas chromatographic profiling of urinary, plasma and erythrocyte sugars and polyols as their trimethylsilyl derivatives, preceded by a simple and rapid prepurification method, Clin. Chim. Acta 157 (3) (1986) 277–293, https://doi.org/10.1016/0009-8981(86)90303-7.
[10] M.M. Wamelink, et al., Analysis of polyols in urine by liquid chromatography-tandem mass spectrometry: a useful tool for recognition of inborn errors affecting polyol metabolism, J. Inherit. Metab. Dis. 28 (6) (2005) 951–963, https://doi.org/10.1007/s10545-005-0233-4.
[11] M.M. Wamelink, et al., Detection of transaldolase deficiency by quantification of novel seven-carbon chain carbohydrate biomarkers in urine, J. Inherit. Metab. Dis. 30 (5) (2007) 735–742, https://doi.org/10.1007/s10545-007-0590-2.
[12] J. Xue, et al., Prenatal diagnosis of fetus with transaldolase deficiency identifies compound heterozygous variants: a case report, Front. Genet. 12 (2021) 752272, https://doi.org/10.3389/fgene.2021.752272.
[13] M. Yıldız, et al., A rare cause of hypergonadotropic hypogonadism: transaldolase deficiency in two siblings, J. Clin. Res. Pediatr. Endocrinol. 17 (1) (2025) 97–102, https://doi.org/10.4274/jcrpe.galenos.2023.2022-10-4.
[14] S. Balasubramaniam, et al., Novel heterozygous mutations in TALDO1 gene causing transaldolase deficiency and early infantile liver failure, J. Pediatr. Gastroenterol. Nutr. 52 (1) (2011) 113–116, https://doi.org/10.1097/MPG.0b013e3181f50388.
[15] A. Atasever, et al., Successful liver transplantation in a pediatric patient with transaldolase deficiency, Pediatr. Transplant. 29 (2) (2025) e70049, https://doi.org/10.1111/petr.70049.
[16] T. Grammatikopoulos, et al., Liver disease and risk of hepatocellular carcinoma in children with mutations in TALDO1, Hepatol. Commun. 6 (3) (2022) 473–479, https://doi.org/10.1002/hep4.1824.
[17] M.M. Wamelink, et al., Transaldolase deficiency in a two-year-old boy with cirrhosis, Mol. Genet. Metab. 94 (2) (2008) 255–258, https://doi.org/10.1016/j.ymgme.2008.01.011.
[18] L.H. Rodan, G.T. Berry, N-acetylcysteine therapy in an infant with transaldolase deficiency is well tolerated and associated with normalization of alpha fetoprotein levels, JIMD Rep 31 (2017) 73–77, https://doi.org/10.1007/8904_2016_555.
[19] A. Tylki-Szymańska, et al., Transaldolase deficiency in two new patients with a relative mild phenotype, Mol. Genet. Metab. 97 (1) (2009) 15–17, https://doi.org/10.1016/j.ymgme.2009.01.016.
[20] A. Tylki-Szymanska, et al., Clinical and molecular characteristics of two transaldolase-deficient patients, Eur. J. Pediatr. 173 (12) (2014) 1679–1682, https://doi.org/10.1007/s00431-014-2261-2.
[21] C.A. Leduc, et al., Novel association of early onset hepatocellular carcinoma with transaldolase deficiency, JIMD Rep 12 (2014) 121–127, https://doi.org/10.1007/8904_2013_254.
[22] N.G. Lafcı, et al., Hypergonadotrophic hypogonadism in a patient with transaldolase deficiency: novel mutation in the pentose phosphate pathway, Hormones (Athens) 20 (3) (2021) 581–585, https://doi.org/10.1007/s42000-020-00252-4.
[23] W. Eyaid, et al., Transaldolase deficiency: report of 12 new cases and further delineation of the phenotype, J. Inherit. Metab. Dis. 36 (6) (2013) 997–1004, https://doi.org/10.1007/s10545-012-9577-8.
[24] S.M. Al-Mayouf, R.S. AlTassan, M.A. AlOwain, Systemic lupus erythematosus in a girl with PTEN variant and transaldolase deficiency: a novel phenotype, Clin. Rheumatol. 39 (11) (2020) 3511–3515, https://doi.org/10.1007/s10067-020-05205-1.
[25] A.M. Al-Shamsi, et al., Transaldolase deficiency caused by the homozygous p.R192C mutation of the TALDO1 gene in four Emirati patients with considerable phenotypic variability, Eur. J. Pediatr. 174 (5) (2015) 661–668, https://doi.org/10.1007/s00431-014-2449-5.
[26] E. Banne, et al., Transaldolase deficiency: a new case expands the phenotypic spectrum, JIMD Rep 26 (2016) 31–36, https://doi.org/10.1007/8904_2015_474.
[27] J. Lee-Barber, et al., Apparent acetaminophen toxicity in a patient with transaldolase deficiency, JIMD Rep 44 (2019) 9–15, https://doi.org/10.1007/8904_2018_116.
[28] K. Alqoaer, Z. Asaad, M. Halabi, Severe Infantile Transaldolase Deficiency, Asian J. Pediatric Res. 2 (4) (2019) 1–5, https://doi.org/10.9734/ajpr/2019/v2i430112.
[29] E. Fallata, et al., Chances of liver transplantation in a patient with transaldolase deficiency complicated by hepatopulmonary syndrome, Cureus 15 (2) (2023) e35150, https://doi.org/10.7759/cureus.35150.
[30] B.J. Shayota, et al., Untargeted metabolomics as an unbiased approach to the diagnosis of inborn errors of metabolism of the non-oxidative branch of the pentose phosphate pathway, Mol. Genet. Metab. 131 (1–2) (2020) 147–154, https://doi.org/10.1016/j.ymgme.2020.07.013.
[31] S. Richards, et al., Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet. Med. 17 (5) (2015) 405–423, https://doi.org/10.1038/gim.2015.30.
[32] M. Williams, et al., Clinical, biochemical, and molecular overview of transaldolase deficiency and evaluation of the endocrine function: update of 34 patients, J. Inherit. Metab. Dis. 42 (1) (2019) 147–158, https://doi.org/10.1002/jimd.12036.
[33] B.L. Horecker, et al., The mechanism of pentose phosphate conversion to hexose monophosphate. I. With a liver enzyme preparation, J. Biol. Chem. 207 (1) (1954) 393–403.
[34] Z. Oaks, et al., Cytosolic aldose metabolism contributes to progression from cirrhosis to hepatocarcinogenesis, Nat. Metab. 5 (1) (2023) 41–60, https://doi.org/10.1038/s42255-022-00711-9.
[35] Y. Qian, et al., Transaldolase deficiency influences the pentose phosphate pathway, mitochondrial homoeostasis and apoptosis signal processing, Biochem. J. 415 (1) (2008) 123–134, https://doi.org/10.1042/bj20080722.
[36] R.G. Langdon, The biosynthesis of fatty acids in rat liver, J. Biol. Chem. 226 (2) (1957) 615–629.
[37] G. Popjak, et al., Studies on the biosynthesis of cholesterol. 6. Coenzyme requirements of liver enzymes for synthesis of squalene and of sterol from DL-3-hydroxy-3-methyl-[2-14C] pentano-5-lactone, Biochem. J. 69 (2) (1958) 238–248, https://doi.org/10.1042/bj0690238.
[38] K. Banki, et al., Glutathione levels and sensitivity to apoptosis are regulated by changes in transaldolase expression, J. Biol. Chem. 271 (51) (1996) 32994–33001, https://doi.org/10.1074/jbc.271.51.32994.
[39] P.A. Wilmarth, et al., A systems approach implicates nuclear receptor targeting in the Atp7b(−/−) mouse model of Wilson's disease, Metallomics 4 (7) (2012) 660–668, https://doi.org/10.1039/c2mt20017a.
[40] A. Perl, The pathogenesis of transaldolase deficiency, IUBMB Life 59 (6) (2007) 365–373, https://doi.org/10.1080/15216540701387188.
[41] M. Witkowski, et al., The artificial sweetener erythritol and cardiovascular event risk, Nat. Med. 29 (3) (2023) 710–718, https://doi.org/10.1038/s41591-023-02223-9.
[42] M. Witkowski, et al., Xylitol is prothrombotic and associated with cardiovascular risk, Eur. Heart J. 45 (27) (2024) 2439–2452, https://doi.org/10.1093/eurheartj/ehae244.

[43] P. Lipiński, et al., Long-term systematic monitoring of four polish transaldolase deficient patients, JIMD Rep. 42 (2018) 79–87, https://doi.org/10.1007/8904_2017_83.
[44] D. Azouaoui, et al., Meta-analysis of NAD(P)(H) quantification results exhibits variability across mammalian tissues, Sci. Rep. 13 (1) (2023) 2464, https://doi.org/10.1038/s41598-023-29607-8.
[45] K. Banki, A. Perl, Cell type-specific regulation of the pentose phosphate pathway during development and metabolic stress-driven autoimmune diseases: relevance for inflammatory liver, renal, endocrine, cardiovascular and neurobehavioral comorbidities, carcinogenesis, and aging, Autoimmun. Rev. 24 (5) (2025) 103781, https://doi.org/10.1016/j.autrev.2025.103781.
[46] C.B. Thompson, Apoptosis in the pathogenesis and treatment of disease, Science 267 (5203) (1995) 1456–1462, https://doi.org/10.1126/science.7878464.
[47] D. Shah, et al., Association between T lymphocyte sub-sets apoptosis and peripheral blood mononuclear cells oxidative stress in systemic lupus erythematosus, Free Radic. Res. 45 (5) (2011) 559–567, https://doi.org/10.3109/10715762.2011.555765.
[48] A. Perl, et al., Oxidative stress, inflammation and carcinogenesis are controlled through the pentose phosphate pathway by transaldolase, Trends Mol. Med. 17 (7) (2011) 395–403, https://doi.org/10.1016/j.molmed.2011.01.014.
[49] A. Perl, et al., Comprehensive metabolome analyses reveal N-acetylcysteine-responsive accumulation of kynurenine in systemic lupus erythematosus: implications for activation of the mechanistic target of rapamycin, Metabolomics 11 (5) (2015) 1157–1174, https://doi.org/10.1007/s11306-015-0772-0.
[50] T. Winans, et al., mTOR-dependent loss of PON1 secretion and antiphospholipid autoantibody production underlie autoimmunity-mediated cirrhosis in transaldolase deficiency, J. Autoimmun. 140 (2023) 103112, https://doi.org/10.1016/j.jaut.2023.103112.
[51] Z. Oaks, et al., Mitochondrial dysfunction in the liver and antiphospholipid antibody production precede disease onset and respond to rapamycin in lupus-prone mice, Arthritis Rheum. 68 (11) (2016) 2728–2739, https://doi.org/10.1002/art.39791.
[52] Y. Liu, et al., Liver injury correlates with biomarkers of autoimmunity and disease activity and represents an organ system involvement in patients with systemic lupus erythematosus, Clin. Immunol. 160 (2) (2015) 319–327, https://doi.org/10.1016/j.clim.2015.07.001.
[53] Z.W. Lai, et al., N-acetylcysteine reduces disease activity by blocking mammalian target of rapamycin in T cells from systemic lupus erythematosus patients: a randomized, double-blind, placebo-controlled trial, Arthritis Rheum. 64 (9) (2012) 2937–2946, https://doi.org/10.1002/art.34502.
[54] R. Hanczko, et al., Prevention of hepatocarcinogenesis and increased susceptibility to acetaminophen-induced liver failure in transaldolase-deficient mice by N-acetylcysteine, J. Clin. Invest. 119 (6) (2009) 1546–1557, https://doi.org/10.1172/jci35722.
[55] N. Jassim, et al., Pulmonary manifestations in a patient with transaldolase deficiency, JIMD Rep. 12 (2014) 47–50, https://doi.org/10.1007/8904_2013_243.
[56] M. Stefanowicz, et al., Successful liver transplantation in two polish brothers with transaldolase deficiency, Children (Basel) 8 (9) (2021), https://doi.org/10.3390/children8090746.
[57] Y.G. Loeffen, et al., Nephrological abnormalities in patients with transaldolase deficiency, Nephrol. Dial. Transplant. 27 (8) (2012) 3224–3227, https://doi.org/10.1093/ndt/gfs061.
[58] A. Perl, et al., Transaldolase is essential for maintenance of the mitochondrial transmembrane potential and fertility of spermatozoa, Proc. Natl. Acad. Sci. USA 103 (40) (2006) 14813–14818, https://doi.org/10.1073/pnas.0602678103.
[59] L. Yang, et al., Mechanism of antiphospholipid antibody-mediated thrombosis in antiphospholipid syndrome, Front. Immunol. 16 (2025) 1527554, https://doi.org/10.3389/fimmu.2025.1527554.
[60] Z. Oaks, et al., Transaldolase haploinsufficiency in subjects with acetaminophen-induced liver failure, J. Inherit. Metab. Dis. 43 (3) (2020) 496–506, https://doi.org/10.1002/jimd.12197.
[61] H.M. Krans, Recent clinical experience with aldose reductase inhibitors, J. Diabetes Complicat. 6 (1) (1992) 39–44, https://doi.org/10.1016/1056-8727(92)90047-o.
[62] Association, W.M, World medical association declaration of Helsinki: ethical principles for medical research involving human participants, JAMA 333 (1) (2025) 71–74, https://doi.org/10.1001/jama.2024.21972.
[63] N.M. Ioannidis, et al., REVEL: an ensemble method for predicting the pathogenicity of rare missense variants, Am. J. Hum. Genet. 99 (4) (2016) 877–885, https://doi.org/10.1016/j.ajhg.2016.08.016.

Glossary

6PGD: 6-phosphogluconate dehydrogenase
6PGL: 6-phosphogluconolactonase
ACE: angiotensin-converting enzyme
ACMG-AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology
ALT: alanine transaminase
AR: aldose reductase
ASD: atrial septal defect
AST: aspartate transaminase
CKD: chronic kidney disease
CRF: case report form
DNA: deoxyribonucleic acid
EEG: electroencephalography
ERA: endothelin receptor antagonist
FSGS: focal segmental glomerulosclerosis
FSH: follicle-stimulating hormone
G6PD: glucose-6-phosphate dehydrogenase
GC–MS: gas chromatography–mass spectrometry
GSH: glutathione
GSSG: glutathione disulfide
Hb: hemoglobin
HCC: hepatocellular carcinoma
HPO: Human Phenotype Ontology
LC - MS/MS: liquid chromatography–tandem mass spectrometry
LH: luteinizing hormone
MCHC: mean corpuscular hemoglobin concentration
MCV: mean corpuscular volume
MRI: magnetic resonance imaging
NAC: N-acetylcysteine
NADP: nicotinamide adenine dinucleotide phosphate
NADPH: nicotinamide adenine dinucleotide phosphate
PAH: pulmonary arterial hypertension
PID: patient identification
PPP: pentose phosphate pathway
RDW: red blood cell distribution width
REVEL score: rare exome variant ensemble learner
RNA: ribonucleic acid
ROS: reactive oxygen species
RPE: ribulose-phosphate 3-epimerase
RPI: ribose-5-phosphate isomerase
TALDO: transaldolase
TKT: transketolase