Triosephosphate Isomerase Deficiency: E105D Mutation in Unrelated Patients and Review of the Literature

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Established Facts

- The first step towards the diagnosis of triosephosphate isomerase is clinical suspicion and knowledge of the disorder.
- Patients should be diagnosed prior to neurologic involvement and evaluated for new treatment options.

Novel Insights

- Triosephosphate isomerase should be considered in the differential diagnosis of elevated C3 carnitine levels in acylcarnitine analysis.

Abstract

Introduction: Chronic haemolytic anaemia, increased susceptibility to infections, cardiomyopathy, neurodegeneration, and death in early childhood are the clinical findings of triosephosphate isomerase (TPI) deficiency, which is an ultra-rare disorder. The clinical and laboratory findings and the outcomes of 2 patients with TPI deficiency are reported, with a review of cases reported in the literature. *Case Presentation:* Two unrelated patients with haemolytic anaemia and neurologic findings who were diagnosed as having TPI deficiency are presented. Neonatal onset of initial symptoms was observed in both patients, and the age at diagnosis was around 2 years. The patients had increased susceptibility to infections and respiratory failure, but cardiac symptoms were not remarkable. Screening for inborn errors of metabolism revealed a previously unreported metabolic alteration determined using tandem mass spectrometry in acylcarnitine

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analysis, causing elevated propionyl carnitine levels in both patients. The patients had p.E105D (c.315G>C) homozygous mutations in the *TPI1* gene. Although severely disabled, both patients are alive at the ages of 7 and 9 years. ***Discussion:*** For better management, it is important to investigate the genetic aetiology in patients with haemolytic anaemia with or without neurologic symptoms who do not have a definitive diagnosis. The differential diagnosis of elevated propionyl carnitine levels using tandem mass spectrometry screening should also include TPI deficiency.

Introduction

Triosephosphate isomerase (TPI or TIM) is an anaerobic glycolysis enzyme that is ubiquitously expressed in all cells and is responsible for the reversible conversion of dihydroxyacetone phosphate (DHAP) to D-glyceraldehyde 3-phosphate [Schneider et al., 1995]. Chronic haemolytic anaemia, increased susceptibility to infections, cardiomyopathy, neurodegeneration, and death in early childhood are the clinical findings of TPI deficiency, which is an ultra-rare disorder. TPI deficiency is inherited autosomal recessively and caused by mutations in the *TPI1* gene [Sarper et al., 2013]. Fewer than 50 clinically affected patients have been described in the literature to date. The p.E105D substitution (formerly identified as p.E104D) is the most common pathogenic variant, accounting for about 80% of patients with TPI deficiency [Schneider et al., 1995]. Here, we report the clinical and laboratory findings and outcomes of 2 patients with TPI deficiency to highlight the importance of disease awareness.

Case Presentations

Case 1

A 10-month-old boy with haemolytic anaemia and acquired loss of developmental functions was referred to the division of paediatric metabolism for differential diagnosis. He was the first child of non-consanguineous parents with an unremarkable family history, born with 3,620 g at 39 weeks of gestation with no reported complications during pregnancy. On the second day after birth, the newborn was admitted to the neonatal unit with jaundice. Total bilirubin was elevated to 22 mg/dL. When he was aged 1 month, he was evaluated for prolonged jaundice, and his haemoglobin level was 3 g/dL. The diagnosis was haemolytic anaemia requiring multiple blood transfusions until the age of 6 months because of relapses.

Neuromotor development history revealed that he had been able to sit with aid at the age of 6 months, but he was unable to sit independently thereafter. At the age of 9 months, he was hospitalized with pneumonia and respiratory failure requiring intubation. On physical examination, no dysmorphic appearance was noted. The liver and spleen were palpable at the costal margins. He had severe axial hypotonia, hypoactive deep tendon reflexes, poor eye tracking, extensor Babinski sign, and isochoric pupils. Lower and upper extremity muscle strength was 3/5.

In laboratory investigations, the blood count was unremarkable except for macrocytic anaemia (white blood cell count, 7.8×10^9/L; absolute neutrophil count, 3.4×10^9/L; haemoglobin level, 8.3 g/dL; erythrocytes, 3.36×10^6/μL; haematocrit, 26%; platelet count, 215×10^9/L; mean corpuscular haemoglobin concentration, 32 g/dL; and mean corpuscular volume, 10^9 fL). The reticulocyte count was elevated to 13%, and the direct Coombs test was negative. In the blood smear, macrocytic erythrocytes were consistent with haemolysis. Erythrocyte glucose-6-phosphate dehydrogenase and pyruvate kinase activities were normal. Bone marrow aspiration showed normocellular bone marrow, with moderate hyperplasia and dominance in the erythroid series.

Biochemical tests and immunoglobulins were normal. Initial metabolic screening tests including blood ammonia, lactate, quantitative plasma amino acids, urinary organic acids, transferrin isoelectric focussing, and plasma very long-chain fatty acids were within normal limits. Blood acylcarnitine profiles determined using tandem mass spectrometry (MSMS) showed elevated propionyl carnitine (C3) and normal free carnitine (C0) (C0: 52.1 μmol/L, normal range: 10–90 μmol/L; C3: 8.6 μmol/L, normal range: 0–4.9 μmol/L). To exclude metabolic causes of C3 elevation, determination of urinary organic acid analysis using gas chromatography mass spectrometry (GCMS) disclosed no pathologic excretions of organic acids including methylmalonic acid. Plasma vitamin B_{12}, homocysteine, and folate levels were normal.

The ophthalmologic evaluation revealed pallor of the optic discs bilaterally. Cranial magnetic resonance imaging showed cerebral atrophy, ventricular enlargement, and sulcal widening. Electroencephalography displayed disorganization and multifocal sharp wave activity. Muscular biopsy disclosed diameter difference in both fibre types, with angular atrophic fibres. Type I fibres had single, sparse, and interspersed hypertrophic fibres. Cardiac evaluation using an echocardiogram showed no structural abnormalities.

Respiratory symptoms started with wheezing at the age of 7 months. An otolaryngology examination disclosed bilateral vocal cords to be paralytic, and he had to be tracheostomized at the age of 11 months. He had multiple hospitalizations due to infections. The requirement of multiple blood transfusions due to severe anaemia ensued. After a febrile illness at the age of 2 years, the ability of eye tracking was lost and social awareness was minimal. He became ventilator- and wheelchair-dependent with progressive muscle weakness.

Genetic analysis allowed the identification of a homozygous pathogenic variant in the *TPI1* gene, p.E105D (c.315G>C), consistent with TPI deficiency. Segregation analysis confirmed that both parents were heterozygous carriers of the pathogenic *TPI1* variant.

On the last admission to the outpatient clinic, he had severe hypotonia and quadriparesis and muscle wasting in all extremities. He is currently aged 7 years and has recurrent urinary tract infections. He has been in a vegetative state for almost 4 years (Fig. 1).

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Fig. 1. Progression of clinical features in case 1. **a** The 7-month-old boy can sit with support. **b** At 11 months, ventilator-dependent with progressive muscle weakness. **c** At age 2 years, loss of developmental milestones after infection. **d** At 7 years of age, vegetative state.

Case 2

A 19-month-old girl with haemolytic anaemia and developmental delay was referred to the division of paediatric metabolism. She was the first child of third-cousin parents, born after 38 weeks of an uncomplicated pregnancy. She was hospitalized in the neonatal intensive care unit for 38 days due to neonatal jaundice and early sepsis, requiring five blood transfusions immediately after birth, and an exchange transfusion on the second day of life ascribed to maternal-foetal ABO incompatibility. Another blood transfusion was also required at the age of 30 days for non-spherocytic haemolytic anaemia. At 9 months, when the child was examined because of multiple haemolytic crises precipitated by infections, there was a mild psychomotor developmental delay because she was not able to sit independently. At 11 months of age, she was diagnosed as having hereditary spherocytosis through a pathologic osmotic fragility test.

The patient was referred to our unit with symptoms of an inability to walk and sit without support. On physical examination at the age of 19 months, her weight was 7.3 kg (<3 percentile; z-score −3), height was 78 cm (9th percentile; z-score −1.3), and head circumference was 44.5 cm (5th percentile; z-score −1.6). The patient had severe malnutrition, paleness, axial hypotonia with loss of muscle bulk, and muscle weakness. Decreased deep tendon reflexes, muscle atrophy, and hyperelasticity of the joints were detected in the extremities.

Laboratory findings showed severe macrocytic anaemia with haemoglobin 6.5 g/dL, haematocrit 13.1%, mean corpuscular haemoglobin concentration 31 g/dL, mean corpuscular volume 104

Table 1. Clinical characteristics of reported patients with TPI with E105D/E105D, including our patients

Patient	Case 1	Case 2	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Sex	M	F	M	F	M	F	F	F	F	M	F	F
Age at symptom onset	Newborn	Newborn	NA	Newborn	2 months	Newborn	6 months	Newborn	Newborn	30 days	On day 1	Newborn
Age at diagnosis	2 years	2 years	On day 2	Newborn	2 months	After death	6 months	6 months	28 months	30 days	On day 1	Newborn
Haemolytic anaemia	+	+	+	+	+	+	+	+	+	+	+	+
Requirement of first blood transfusion	1 month	Newborn	On day 2, week 3 and 6	4 months	Newborn	On day 1	12 months	Newborn	On day 1	NA	Newborn	Newborn
Neurologic symptom onset	9 months	9 months	1 year	13 months	14 months	23 months	12 months	8 months	9 months	10 months	1 year	3 months
Neurologic symptoms	Loss of acquired functions, hypotonia, generalized muscle weakness	Hypotonia, muscle weakness, decreased deep tendon reflexes, muscle atrophy	Distal muscle weakness, hypotonia, amyotrophy	Loss of acquired functions, generalized muscle weakness, and hypertonia	Neuromotor retardation	Slowing of development, distal muscle weakness, abolition of the deep tendon reflexes	Muscle weakness, hypotonia, nystagmus	Neuromuscular disturbance with progressive muscular hypotonia, vanishing deep tendon reflexes	Hypotonia with decreased deep tendon reflexes	Hemiparesis, progressive neuromuscular dysfunction, optic atrophy	Delayed developmental milestones, progressive neuromuscular dysfunction	Delayed developmental milestones
Cardiomyopathy	–	–	–	–	–	–	–	–	–	–	–	–
Increased susceptibility to infection	+	+	–	–	–	+	+	+	+	-	+	+
Respiratory failure	11 months	3 years	–	13 months	14 months	24 months	15 months	12 months	CPAP ventilation at night	–	27 months	–
Duration of follow-up	7 years	9 years	6 years	20 years	21 months	24 months	NA	NA	NA	26 months	27 months	3 years
Exitus	–	–	–	–	21 months	24 months	–	–	–	26 months	–	–
TPI activity UI/g haemoglobin	NA	NA	200 (N: 1,080–1,600)	NA	NA	NA	Low	470 (N: 2,180±254)	518 (N: 785–2,472)	315 (N: 2,111±397)	57 (N: 2,111±397)	364 (N: 2,111±397)
Bone marrow biopsy	Normocellular	Normocellular	NA	Congenital dyserythropoietic anaemia	NA	NA	NA	NA	NA	NA	NA	NA
Electromyographic studies	NA	Normal	Spinal motor neuron involvement	Normal	NA	NA	NA	NA	Decreased motor nerve conduction	Normal	NA	NA

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Table 1 (continued)

Patient	Case 1	Case 2	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Muscle biopsy	Both fibre types included with diameter difference and angular atrophic fibres; type I fibres had single, sparse and interspersed hypertrophic fibres	Myopathic	Fibre-type grouping and target fibres, both characteristic of denervation	Normal	NA	NA	NA	NA	Type 2 fibre atrophy	NA	NA	Type 2 fibre atrophy
Reference	Present study	Present study	Valentin et al., 2000	Harris et al., 2020	Sarper et al., 2013	Aissa et al., 2014	Yenicesu et al., 2000	Pekrun et al., 1995	Linarello et al., 1998	Schneider et al., 1995	Schneider et al., 1995	Schneider et al., 1995

NA, not available; M, male; F, female; CPAP, continuous positive airway pressure.

fL, normal white blood cell count 8.868 × 10⁹/L, platelet count 95,000/mm³, elevated total bilirubin 24.63 mg/dL, and direct bilirubin 18.58 mg/dL. Plasma amino acids, very long-chain fatty acids, serum transferrin isoelectric focussing, and urine organic acids with GCMS were unremarkable. The acylcarnitine profile by MSMS revealed normal C0, while C3 was elevated (C0: 62.8 µmol/L, normal range: 10–90 µmol/L; C3: 7.1 µmol/L, normal range: 0–4.9 µmol/L) and methylmalonic acid in the urine was negative by GCMS. The plasma vitamin B_{12}, folic acid, and homocysteine levels were all normal.

Bone marrow aspiration was normocellular. The ophthalmologic fundus examination was normal. The brain stem electric response audiometry (BERA) test was reported as normal. The electromyography was normal, she had no cardiomyopathy, and the brain magnetic resonance imaging was unremarkable. No epileptic activity was observed in the electroencephalography. Muscle biopsy showed signs of myopathy. In the follow-up, multiple hospitalizations were required due to haemolytic crises, recurrent lower respiratory tract infections, and gastroenteritis. At the age of 3 years, she was admitted to the intensive care unit due to pneumonia. Tracheostomy was required, and the patient lost most of the acquired developmental milestones.

Molecular analysis using next-generation sequencing disclosed a p.E105D (c.315G>C) homozygous mutation in the *TPI1* gene, which was previously reported to be associated with TPI deficiency. Currently, the patient is aged 9 years and remains under follow-up. She is on assisted ventilation with a home-type mechanical ventilator.

Discussion

We reported 2 unrelated patients with TPI deficiency and similar mutations. Chronic haemolytic anaemia, recurrent infections, cardiomyopathy, developmental delay, and progressive neurologic deterioration are variably combined in the different phenotypes in patients with TPI deficiency. Anaemia may be present soon after birth, whereas severe and life-threatening neuromuscular impairment develops during or soon after infancy [Rosa et al., 1985]. Sarper et al. [2013] reported a boy with TPI deficiency who required transfusion on the first postnatal day and at 2 months. During follow-up, haemolytic anaemia was mild and no transfusions were required, but the boy died at the age of 17 months because of respiratory failure . Although patients with TPI deficiency usually need a transfusion in the neonatal period, Yenicesu et al. [2000] published a case report of a patient who did not need a transfusion until the age of 12 months. This patient also had an elevated sweat chloride test suggestive of cystic fibrosis.

The neurologic development of our patients was normal during the first 8 months and then ceased to improve, especially during infection periods, and loss of acquired functions was subsequently observed. Aissa et al. [2014]

reported a girl with TPI deficiency who had distal weakness, respiratory failure, and chronic haemolytic anaemia, which was always triggered by recurrent bronchiolitis.

Schneider et al. [1995] reported a patient with TPI deficiency with delayed physical milestones. This patient's mental milestones were normal, and the child was clinically stable with chronic haemolytic anaemia [Rosa et al., 1985]. Serdaroglu et al. [2011] reported a 15-year-old boy with homozygosity for the Val231Met mutation who manifested muscle weakness with normal motor and mental development, appearing as weakness of the lower limbs and difficulty with long-distance walking and electrophysiologic and clinical findings of neuropathy and muscle involvement. TPI deficiency should be suspected in the presence of myopathy accompanying haemolytic anaemia. Valentin et al. [2000] reported a patient whose electromyographic studies were consistent with spinal motor neuron involvement, a muscle biopsy was compatible with denervation, and a nerve biopsy was normal. Other published articles showed type 2 atrophy [Schneider et al., 1995; Linarello et al., 1998] and normal muscle biopsy [Harris et al., 2020]. There is no specific finding for TPI deficiency on muscle biopsy.

In TPI deficiency, symptoms are progressive, and the condition is usually fatal before the age of 6 years. Both of our patients are alive with extensive supportive care, including assisted mechanical ventilation. To date, only 1 patient has been described in the literature as homozygous for this mutation who was alive at the age of 20 years with both wheelchair and ventilator dependency [Harris et al., 2020]. In our patients, cardiac symptoms were not remarkable. Similarly, cardiomyopathy was not reported in other patients with the homozygous E105D mutation in the literature. Table 1 shows the characteristics of patients with TPI deficiency reported with E105D/E105D in the Human Gene Mutation Database until September 2021, including our patients (case 1 and case 2).

The exact incidence of TPI deficiency is currently unknown, but fewer than 50 patients have been reported worldwide to date [Schneider et al., 1995]. TPI deficiency could be underdiagnosed because TPI activity is not always assayed in cases of haemolytic anaemia. The TPI activity assay is not available in most countries as in our country and is not routinely assayed. It should also be noted that in patients who are frequently transfused with erythrocyte suspensions, the TPI activity might be within the normal range. In this case, the TPI activity of the parents may help in evaluating the heterozygous state.

A deficiency in TPI results in the accumulation of DHAP because TPI catalyses the interconversion of D-glyceraldehyde 3-phosphate and DHAP. The accumulat-

ed DHAP can be cleaved to form advanced glycation end products that are toxic to cells in large concentrations [Orosz et al., 2009]. We identified C3 carnitine elevation using MSMS during haemolysis episodes in both of our patients. There was no mention of elevation in C3 in any of the previously published case reports. Other publications may not have analysed acylcarnitines during haemolysis episodes. We suggest that this C3 carnitine elevation is due to the increased conversion of DHAP to propionate. Further studies are needed to confirm the presence of this relationship. The absence of secondary carnitine deficiency, normal vitamin B_{12}, homocysteine, and folate levels in patients and no methylmalonic aciduria disclosed other aetiologies of C3 carnitine elevation.

Linarello et al. [1998] published a case report of a patient who was diagnosed as having TPI, whose osmotic fragility test was interpreted as abnormal in the hereditary spherocytosis range, similar to our case 2. Hereditary spherocytosis was not considered due to the presence of non-spherocytic haemolytic anaemia and neurologic findings in the patients. However, defects in only three of the glycolytic enzymes (TPI, phosphoglycerate kinase, and glucose-6-phosphate isomerase) should be considered in the differential diagnosis of patients with neurologic disorders [Harris et al., 2020].

A genotype-phenotype relationship has been proposed, especially because specific mutant alleles acting on TPI protein dimerization have been shown to correlate with more severe neurologic findings in patients [Roland et al., 2016]. In our patients, the TPI deficiency was associated with the pathogenic homozygous mutation E105D, which causes severe clinical symptoms. This mutation is believed to cause impaired dimerization of the enzyme, which is crucial for its catalytic activity; other variants can also impair substrate binding to the active site [Oliver et al., 2017]. Valentin et al. [2000] reported that an E105D homozygous patient exhibited a milder phenotype than a patient with a compound heterozygous mutation in another family.

Currently, no curative treatment is available for TPI deficiency. Enzyme replacement therapy, bone marrow transplantation (BMT), and gene therapy are potential therapeutic strategies for the treatment of inherited metabolic disorders. Ationu et al. [1999] established that the active enzyme contained in transfused red cells could reverse the metabolic defect of TPI deficiency and confirmed the feasibility of enzyme replacement therapy for TPI deficiency. It should be noted that frequent red cell transfusion therapy increases the risk of viral infections and iron overload.

Fogle et al. [2019] showed that a ketogenic diet or triheptanoin treatment was efficacious in improving neurologic function in a Drosophila TPI model. Conway et al. [2018] showed that BMT successfully restored all haematologic parameters in the Tpi1F57S/F57S mutant strain and increased red blood cell enzyme function in RBC19 mice. They concluded that the Tpi1F57S/F57S mouse strain emerged as a model of haematologic defects associated with TPI deficiency only [Conway et al., 2018]. The effect of BMT on neurologic findings has not yet been demonstrated.

Conclusion

The diagnosis of TPI deficiency is suspected based on haemolytic anaemia, developmental delay, loss of developmental milestones, and neurologic findings because TPI activity is not typically assayed in cases of haemolytic anaemia. Neurologic manifestations are irreversible and can lead to neurologic deficits and death. If patients with haemolytic anaemia do not have a definitive diagnosis, they should be referred for either a TPI enzyme assay or molecular genetic testing. Thereby, patients can be diagnosed without severe neurologic involvement and evaluated for potential treatments. TPI should be considered in the presence of neonatal jaundice, haemolytic anaemia, neurologic dysfunction, and in the differential diagnosis of elevated C3 carnitine levels in acylcarnitine analysis.

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References

Aissa K, Kamoun F, Sfaihi L, Ghedira ES, Aloulou H, Kamoun T, et al. Hemolytic anemia and progressive neurologic impairment: think about triosephosphate isomerase deficiency. Fetal Pediatr Pathol. 2014 Aug;33(4):234–8.

Ationu A, Humphries A, Wild B, Carr T, Will A, Arya R, et al. Towards enzyme-replacement treatment in triosephosphate isomerase deficiency. Lancet. 1999 Apr;353(9159):1155–6.

Conway AJ, Brown FC, Hortle EJ, Burgio G, Foote SJ, Morton CJ, et al. Bone marrow transplantation corrects haemolytic anaemia in a novel ENU mutagenesis mouse model of TPI deficiency. Dis Model Mech. 2018 May;11(5): dmm034678.

Fogle KJ, Smith AR, Satterfield SL, Gutierrez AC, Hertzler JI, McCardell CS, et al. Ketogenic and anaplerotic dietary modifications ameliorate seizure activity in Drosophila models of mitochondrial encephalomyopathy and glycolytic enzymopathy. Mol Genet Metab. 2019 Apr;126(4):439–47.

Harris C, Nelson B, Farber D, Bickel S, Huxol H, Asamoah A, et al. Child Neurology: triosephosphate isomerase deficiency. Neurology. 2020 Dec;95(24):e3448–51.

Linarello RE, Shetty AK, Thomas T, Warrier P. Triosephosphate isomerase deficiency in a child with congenital hemolytic anemia and severe hypotonia. Pediatr Hematol Oncol. 1998 Nov–Dec;15(6):553–6.

Oliver C, Timson DJ. In silico prediction of the effects of mutations in the human triose phosphate isomerase gene: towards a predictive framework for TPI deficiency. Eur J Med Genet. 2017 Jun;60(6):289–98.

Orosz F, Oláh J, Ovádi J. Triosephosphate isomerase deficiency: new insights into an enigmatic disease. Biochim Biophys Acta. 2009 Dec; 1792(12):1168–74.

Pekrun A, Neubauer BA, Eber SW, Lakomek M, Seidel H, Schröter W. Triosephosphate isomerase deficiency: biochemical and molecular genetic analysis for prenatal diagnosis. Clin Genet. 1995 Apr;47(4):175–9.

Roland BP, Zeccola AM, Larsen SB, Amrich CG, Talsma AD, Stuchul KA, et al. Structural and genetic studies demonstrate neurologic dysfunction in triosephosphate isomerase deficiency is associated with impaired synaptic vesicle dynamics. PLoS Genet. 2016 Mar;12(3):e1005941.

Rosa R, Prehu MO, Calvin MC, Badoual J, Alix D, Girod R. Hereditary triose phosphate isomerase deficiency: seven new homozygous cases. Hum Genet. 1985;71(3):235–40.

Sarper N, Zengin E, Jakobs C, Salomons GS, Mc Wamelink M, Ralser M, et al. Mild hemolytic anemia, progressive neuromotor retardation and fatal outcome: a disorder of glycolysis, triose- phosphate isomerase deficiency. Turk J Pediatr. 2013 Mar–Apr;55(2): 198–202.

Schneider A, Westwood B, Yim C, Prchal J, Berkow R, Labotka R, et al. Triosephosphate isomerase deficiency: repetitive occurrence of point mutation in amino acid 104 in multiple apparently unrelated families. Am J Hematol. 1995 Dec;50(4):263–8.

Serdaroglu G, Aydinok Y, Yilmaz S, Manco L, Özer E. Triosephosphate isomerase deficiency: a patient with Val231Met mutation. Pediatr Neurol. 2011;44(2):139–42.

Valentin C, Pissard S, Martin J, Héron D, Labrune P, Livet MO, et al. Triose phosphate isomerase deficiency in 3 French families: two novel null alleles, a frameshift mutation (TPI Alfortville) and an alteration in the initiation codon (TPI Paris). Blood. 2000 Aug;96(3):1130–5.

Yenicesu I, Kalayci O, Semizel E, Kavak U, Gümrük F, Ferec C, et al. Triosephosphate isomerase deficiency with elevated sweat chloride test: report of a case. Turk J Pediatr. 2000 Oct–Dec; 42(4):319–21.