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TRMU Deficiency

Synonyms: *TRMU*-Related Reversible Infantile Respiratory Chain Deficiency, *TRMU*-Related Mitochondrial Hepatopathy, *TRMU*-Related Reversible Infantile Liver Failure

Michaela Reinhart, MD,[1] Colleen Muraresku, MS, LCGC,[2] and Rebecca Ganetzky, MD[2]

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Summary

Clinical characteristics

Infants with untreated TRMU deficiency, a mitochondrial disorder, typically become symptomatic between ages two and four months with transient acute liver dysfunction (including elevated transaminases, abnormal synthetic functions, and/or hepatomegaly), metabolic derangements (severe persistent lactic acidosis, hypoglycemia, hyperammonemia), and poor weight gain. With proper supportive treatment (but not disease-targeted therapy), abnormal liver findings (including coagulopathy) improve or normalize. Likewise, metabolic derangements improve. However, other manifestations typical of a mitochondrial disorder such as persistent lactic acidosis, neurologic dysfunction (including developmental delay / intellectual disability and seizures), cardiomyopathy, and respiratory failure may persist or develop or over time.

Diagnosis/testing

The diagnosis of TRMU deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TRMU* identified by molecular genetic testing.

Management

Targeted therapies: L-cysteine, with or without N-acetylcysteine (NAC), should be initiated as soon as a diagnosis of TRMU deficiency is suspected. Because the endogenous supply of cysteine is normally low in the first few months of life and because the enzyme TRMU requires adequate amounts of cysteine to enable the essential function of thiolating mitochondrial transfer RNAs, the initial manifestations of TRMU deficiency (primarily hepatopathy) may be reversed, ameliorated, or in some cases prevented by exogenous oral cysteine supplementation in infants with TRMU deficiency. To date, two infants treated presymptomatically overall had a milder clinical course than their affected relatives.

Author Affiliations: 1 Division of Human Genetic, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Email: reinhartmb@chop.edu. 2 Mitochondrial Medicine Frontier Program, Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Email: clarkec@chop.edu; Email: ganetzkyr@chop.edu.

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Liver transplantation: Liver transplantation is indicated when hepatopathy does not respond to medical interventions.

Supportive care: Supportive care by a multidisciplinary team of clinicians, including a hepatologist, neurologist, and medical geneticist, is recommended to manage the commonly reported complications of developmental delay / intellectual disability, cardiomyopathy, seizures, and/or respiratory failure.

Surveillance: Routine follow up is recommended to monitor response to L-cysteine and NAC supplementation, to evaluate response to supportive interventions, and to identify emergence of new findings or concerns regarding developmental/educational progress such as persistent neurodevelopmental delay or new onset of seizures that may develop over time.

Agents/circumstances to avoid: Avoid medications that increase metabolic demand (such as corticosteroids) or inhibit mitochondrial activity (such as valproic acid and prolonged propofol infusion) and fasting, as it increases metabolic demand and may exacerbate hypoglycemia. Consider avoiding acetaminophen (paracetamol) during episodes of liver dysfunction based on theoretical concerns for oxidative stress.

Evaluation of relatives at risk: Molecular genetic prenatal testing of fetuses at risk may be performed via amniocentesis or chorionic villus sampling to inform maternal cysteine supplementation (reported in one pregnancy) and to facilitate institution of exogenous cysteine supplementation (as L-cysteine, N-acetylcysteine, or both) at birth. If prenatal testing has not been performed on a pregnancy at risk, supplementation with L-cysteine (and possibly N-acetylcysteine) of an at-risk newborn sib should be offered until molecular genetic testing for the family-specific *TRMU* pathogenic variants has been completed.

Genetic counseling

TRMU deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *TRMU* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *TRMU* pathogenic variants. Once the *TRMU* pathogenic variants have been identified in an affected family member, molecular genetic carrier testing and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for TRMU deficiency have been published.

Suggestive Findings

TRMU deficiency **should be suspected** in children with the following age-related clinical, laboratory, and imaging findings and family history.

Clinical Findings

Infants ages two to four months commonly experience transient liver dysfunction that manifests as one or more of the following findings [Murali et al 2021]:

- Acute liver dysfunction with elevated liver enzymes (gamma-glutamyl transferase and transaminases), hyperammonemia, and jaundice due to conjugated hyperbilirubinemia
- Severe persistent lactic acidosis in the acute setting, likely as a result of disease onset and progression for some time prior to initial diagnostic evaluation
- Persistent hypoglycemia
- Poor feeding with failure to gain weight

Children over age four months, following spontaneous resolution of acute liver failure while receiving symptomatic (but not disease-specific) care, may have the following findings that would suggest TRMU deficiency:

- Leigh-like syndrome
- Cardiomyopathy
- Hepatomegaly
- Poor weight gain
- Lactic acidosis

Table 1. TRMU Deficiency: Frequency of Select Features in Children who were Untreated and Symptomatic at the time of Diagnosis

Feature	# of Persons w/Feature / # Assessed	Comment
Lactic acidosis	44/60	May cause life-threatening metabolic acidosis
Acute liver dysfunction	43/60	
Hypoglycemia	11/28	Persistent despite support of dextrose-containing fluids or continuous feeds
Failure to thrive	33/60	Often poor feeding & oromotor skills
Hepatomegaly	13/60	W/ or w/o liver failure
Hypotonia	15/60	
Jaundice	34/60	Usually predominantly direct hyperbilirubinemia

Based on Schara et al [2011], Gaignard et al [2013], Grover et al [2015], Indolfi et al [2017], Gil-Margolis et al [2018], Murali et al [2021], Vogel et al [2023]

Imaging Findings

Abdominal ultrasound may be normal or show the following abnormalities [Schara et al 2011, Uusimaa et al 2011, Gaignard et al 2013, Indolfi et al 2017, Sala-Coromina et al 2020]:

- Enlargement and hyperechogenicity of the liver
- Diffuse hepatic steatosis and persistent hepatic nodules

Brain MRI findings are variable but often include lesions of the thalami as well as abnormalities of the putamen, basal nuclei, pontine tracts, upper cerebellar peduncles, subthalamic nuclei, and brain stem.

Note: Brain imaging may be normal in some children; in others, repeat imaging after clinical recovery (including resolution of acute liver failure, growth restriction, and motor delay) shows normalization of MRI findings [Schara et al 2011, Uusimaa et al 2011, Gaignard et al 2013, Indolfi et al 2017, Sala-Coromina et al 2020, Murali et al 2021].

MR spectroscopy may show a lactate peak in the acute presentation at age two to four months.

Tissue Biopsies

While not required to either suspect or establish the diagnosis of TRMU deficiency, liver and/or muscle biopsies were often obtained in the past prior to the availability of molecular genetic testing or may have been obtained pending results of molecular genetic testing.

Liver. If performed during the diagnostic evaluation of an infant with acute liver failure, tissue should be flash frozen for biochemical studies and preserved in glutaraldehyde for electron microscopy when feasible.

Histologic findings in TRMU deficiency include bridging fibrosis, portal and perisinusoidal fibrosis, focal eosinophilic ground-glass appearance, micronodular cirrhosis, necrosis, mitochondrial proliferation, micro- and macrovesicular steatosis, canalicular cholestasis, bile duct proliferation, ballooning degeneration, and increased hepatic iron and oncocytic hepatocytes [Zeharia et al 2009, Schara et al 2011, Uusimaa et al 2011, Gaignard et al 2013, Indolfi et al 2017, Gil-Margolis et al 2018, Sala-Coromina et al 2020, Murali et al 2021].

One individual showed periportal hepatocyte copper loading thought to be secondary cholestasis resulting from severe mitochondrial dysfunction [Grover et al 2015].

Electron transport chain enzymology is variable but uniformly shows lower complex IV activity.

Blue native gel electrophoresis also showed the nonspecific findings of abnormal complex assembly particularly affecting complexes I and IV.

Muscle has shown (1) histologic variation in size and shape of cells, intracellular lipid accumulation, and ragged red fibers; and (2) decreased electron transport chain activity of complexes I, III, and IV [Schara et al 2011, Uusimaa et al 2011, Gaignard et al 2013, Sala-Coromina et al 2020, Murali et al 2021].

Skin biopsy is not helpful, as the enzyme TRMU is not required for mitochondrial function in skin [Sasarman et al 2011].

Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Medical Intervention

Medical intervention recommended pending confirmation of the definitive diagnosis of TRMU deficiency is supplementation with exogenous cysteine as L-cysteine, N-acetylcysteine, or both. See Management, Targeted Therapies.

Establishing the Diagnosis

The diagnosis of TRMU deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TRMU* identified by molecular genetic testing (see Table 2).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *TRMU* variants of uncertain significance (or of one known *TRMU* pathogenic variant and one *TRMU* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas genomic testing does not (see Option 2).

Option 1

A mitochondrial disorders panel, cholestasis panel, or acute infantile liver failure multigene panel that includes *TRMU* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the

diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in TRMU Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
TRMU	Sequence analysis [3]	26/28 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	2/28 [4, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Zeharia et al [2009], Schara et al [2011], Uusimaa et al [2011], Gaignard et al [2013], Grover et al [2015], Indolfi et al [2017], Soler-Alfonso et al [2019], Sala-Coromina et al [2020], Murali et al [2021]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Zeharia et al [2009]

Clinical Characteristics

Clinical Description

Infants with untreated TRMU deficiency, a mitochondrial disorder, typically become symptomatic between ages two and four months with transient acute liver dysfunction (including elevated transaminases, abnormal synthetic functions, and/or hepatomegaly), metabolic derangements (severe persistent lactic acidosis, hypoglycemia, hyperammonemia), and poor weight gain.

With proper supportive treatment (but not disease-targeted therapy), abnormal liver findings (including coagulopathy) improve or normalize, as do metabolic derangements. Lactic acidemia typically improves, but typically does not fully normalize. Neurologic dysfunction may persist or evolve over time [Murali et al 2021].

Early targeted therapy (i.e., L-cysteine and N-acetylcysteine [NAC] supplementation) may significantly alter the disease course based on the limited experience to date with two unrelated at-risk sibs who were diagnosed prenatally or shortly after birth. These two children, who were treated presymptomatically, had a milder disease

course with less severe acidosis and liver dysfunction and fewer hospitalizations than their affected sibs [Murali et al 2021].

To date, 62 individuals (60 probands and two at-risk sibs) have been identified with biallelic pathogenic variants in *TRMU* [Zeharia et al 2009, Schara et al 2011, Uusimaa et al 2011, Gaignard et al 2013, Grover et al 2015, Indolfi et al 2017, Gil-Margolis et al 2018, Sala-Coromina et al 2020, Murali et al 2021, Vogel et al 2023].

Untreated Symptomatic Children at the Time of Diagnosis

The following is a description of the features associated with TRMU deficiency in 60 untreated symptomatic children at the time of diagnosis (see Table 3).

Table 3. TRMU Deficiency: Frequency of Select Features in Untreated Symptomatic Children at the Time of Diagnosis

Feature	# of Persons w/Feature / # Assessed	Comment
Liver disease	58/60	• Can incl hepatitis, cholestasis, steatosis, &/or cirrhosis. • Synthetic liver failure & hyperammonemia are common. • Hepatomegaly may or may not be present & may persist beyond the acute episode.
Metabolic findings	43/60	Metabolic acidosis, hypoglycemia, &/or hyperammonemia
Neurodevelopmental delay	24/60	Eventual full attainment of milestones in 60% of persons
Seizures	4/60	
Hypotonia	20/60	
Emesis/diarrhea	28/60	
Cardiomyopathy	5/60	

Liver disease, the most common finding in TRMU deficiency, most frequently manifests initially as elevated transaminases in the absence of evidence of other liver dysfunction. Liver disease may progress to acute liver failure (characterized by coagulopathy and hyperammonemia) typically between ages two and four months. Hyperammonemia likely contributes to hepatic encephalopathy, characterized by depressed mental status.

In the setting of liver dysfunction or cholestasis, jaundice often – but not always – results from direct hyperbilirubinemia.

Abnormal liver findings during the acute phase improve or normalize with proper supportive symptomatic treatment. Twenty-three percent of children have recurrent episodes of liver failure in the first year of life, which most frequently occur in the first five months of life. The largest number of episodes of acute liver failure reported per child was five, which occurred in two unrelated children. One of these children underwent orthotopic liver transplantation and was last followed up at age 13 years; the other had spontaneous resolution of liver disease and is living with their native liver at age 17 years [Vogel et al 2023].

Hepatomegaly, which may or may not develop, does not correlate with the presence of acute liver failure. Variceal bleeding may also occur.

Progression of liver disease can result in fibrosis and/or cirrhosis, as well as macro- and microvesicular steatosis and cholestatic changes.

Metabolic findings in addition to hyperammonemia include lactic acidosis and hypoglycemia.

Although lactic acidosis is a predominant finding in the acute setting, it likely begins some time prior to manifestations of other liver dysfunction. The presence of both hyperalaninemia and lactic aciduria help distinguish chronic lactic acidosis from the acute lactic acidemia that is secondary to acute liver failure.

Hypoglycemia is often persistent and may require dextrose-containing fluids in the acute setting (see Management, Supportive Care). Some infants have required a nasogastric or gastrostomy tube to maintain a glucose infusion rate after recovery of liver function, as the hypoglycemia may persist for some time after hepatic failure resolves.

Hypotonia, a common initial finding, may contribute to failure to gain weight prior to the evaluation that established the diagnosis of TRMU deficiency. Infants may subsequently have poor feeding skills and corresponding poor weight gain if nutrition is inadequate. Growth restriction and poor weight gain may be observed prior to onset of acute liver failure.

Gastrointestinal manifestations such as emesis and diarrhea are common prior to liver decompensation, as toxic metabolites such as ammonia begin to accumulate. Emesis is often the first manifestation that prompts medical evaluation of an affected infant.

Respiratory failure may develop in the acute setting, which may be the result of insufficient respiratory effort from hypotonia. There is also emerging evidence of central apnea.

Leigh syndrome has been observed in two individuals who presented with liver failure, severe hypotonia, acute encephalopathy, and psychomotor regression. At the time of presentation with hepatic findings (ages two to four months), brain MRI suggested Leigh syndrome (see Mitochondrial DNA-Associated Leigh Syndrome and NARP and/or Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview). Seizures were also reported in one child who did not have head imaging, and another child who had brain MRI findings consistent with Leigh syndrome.

Unpublished experience suggests that even infants who are neurologically nearly typical may have brain MRI findings suggestive of Leigh syndrome. Given limited evaluation for neurologic involvement of other affected infants, the prevalence of a Leigh syndrome phenotype may be underestimated [Sala-Coromina et al 2020, Vogel et al 2023].

Dilated cardiomyopathy with impaired myocardial contractility has been observed in five infants [Zeharia et al 2009, Vogel et al 2023].

Nephromegaly and proteinuria that resolved after several months has been observed in one infant [Zeharia et al 2009].

Neurodevelopmental delay of varying degrees is seen in individuals with TRMU deficiency. Swallowing difficulty occurred as early as the first months of life prior to hepatic decompensation [Indolfi et al 2017, Murali et al 2021]. Language development is also affected.

In a retrospective study of 25 individuals, nine had resolution of developmental delays at least several months following recovery of liver function, whereas five had persistent delays. The remaining 11 individuals were either lost to follow up or deceased. The cause of persistent neurodevelopmental delay may be either secondary to acute liver failure or the underlying mitochondrial disorder causing TRMU deficiency [Vogel et al 2023].

Prognosis. Twenty of 60 infants who were symptomatic at the time of initial medical evaluation died: eight from complications of liver failure (one of whom succumbed from variceal bleeding [Gaignard et al 2013]), eight from multiorgan failure, three from cardiorespiratory failure [Zeharia et al 2009, Sala-Coromina et al 2020, Vogel et al 2023], and one from sepsis [Murali et al 2021]. Median age of death was three months [Vogel et al 2023].

Presymptomatically Treated At-Risk Sibs

Liver dysfunction and metabolic derangements were more easily managed in the at-risk infants treated presymptomatically than in their older sibs; however, it should be noted that one child was listed for liver transplantation in the setting of severe hyperammonemia prior to becoming stabilized [Murali et al 2021].

Although cysteine supplementation in the presymptomatic period can mitigate effects of the disease, current evidence is not sufficient to conclude that supplementation will prevent liver dysfunction altogether (see Table 4).

Table 4. TRMU Deficiency: Frequency of Select Features in Children who were Treated Presymptomatically

Feature	Patient 2 [1]	Patient 6 [1]
Liver disease	+	+
Metabolic findings [2]	+	+
Neurodevelopmental delay	–	+
Seizures	–	–
Hypotonia	–	+
Emesis/diarrhea	–	+
Cardiomyopathy	–	–

Based on Murali et al [2021]
1. Patient 6 was previously described by Soler-Alfonso et al [2019]
2. Severity of metabolic findings were milder than those of sibs who were symptomatic at the time of initial diagnosis (i.e., Patient 1 and Patient 5, respectively).

One sib (Patient 2 in Murali et al [2021]), who was pretreated with prenatal L-cysteine supplementation 500 mg twice per day and postnatally with N-acetylcysteine 150 mg/kg per day and L-cysteine 140 mg/kg per day had metabolic derangements including lactic acidosis, hypoglycemia, and hyperammonemia beginning at age two months but did not develop acute liver failure. Elevated transaminases, however, implied liver disease despite pretreatment. He was managed postnatally with bicarbonate supplementation 1.2 mEq/kg per day but did not require long-term bicarbonate treatment. He remained on N-acetylcysteine (110 mg/kg per day) and L-cysteine (85 mg/kg per day) long-term. At the time of publication at age 12 months, he was symptom free and developing normally, despite persistently elevated lactate, transaminases, and conjugated bilirubin [Murali et al 2021]. To date, at age three years, he has remained asymptomatic, with only persistently elevated lactate levels [Authors, personal observation].

The other sib (Patient 6 in Murali et al [2021]), who was treated with cysteine starting at birth, was admitted to the hospital at age six months due to emesis, transaminitis, elevated lactate, and hyperammonemia. He did not develop liver failure but had worsening liver function during the month-long admission. He required blood products due to coagulopathy, intravenous bicarbonate due to acidosis, and lactulose for hyperammonemia. He was listed for liver transplantation during the admission and was discharged on oral sodium citrate / citric acid, N-acetylcysteine, and L-cysteine. At age 26 months the child had stage 4 micronodular cirrhosis, hepatomegaly, and short stature, was able to walk independently, had normal fine motor skills, and had only a few words.

Genotype-Phenotype Correlations

There is no consensus on genotype-phenotype correlations for TRMU deficiency at this time.

- The Yemenite Jewish founder variant c.229T>C (p.Tyr77His) was homozygous in eight infants and compound heterozygous with a splice site variant in another infant, all of whose initial presentation was acute liver failure and lactic acidosis. One other individual had cardiomyopathy and nephromegaly [Zeharia et al 2009].

  Mortality in individuals with the p.Tyr77His variant may be lower than the mortality rate in individuals without this variant (6/23). No deaths were reported in p.Tyr77His homozygotes; one individual who was a compound heterozygote for this variant died at age four months [Zeharia et al 2009].

- The recurrent c.2T>A (p.Met1?) variant, which is observed in multiple ethnicities, may be associated with early mortality despite aggressive medical management. Three individuals with this variant were described in the literature as deceased [Zeharia et al 2009, Sala-Coromina et al 2020, Vogel et al 2023], as well as two additional individuals with this variant who also passed away (these two individuals were brothers, and one was an individual reported in Vogel et al [2023] who passed away after publication [Authors, personal observation]).

Gaignard et al [2013] proposed that *TRMU* variants that cause frameshifts or alternative splicing and subsequent protein truncation could theoretically lead to more severe liver failure and associated complications, including mortality at a young age, whereas *TRMU* missense variants may be correlated with less severe disease and better prognosis. Recent analysis of the phenotypes and outcomes associated with *TRMU* variants in the 62 reported children indicated a significant association (p=0.022) of loss-of-function variants and decreased survival (10/20 children with loss-of-function variants vs 10/42 children with other variants) [Vogel et al 2023]. Average age of follow up of children with two missense or in-frame indel variants was 78 months vs 38 months for children with one or more nonsense, frameshift, or splicing variant(s).

Prevalence

Sixty-two individuals from 56 families with biallelic *TRMU* pathogenic variants have been reported.

TRMU deficiency is particularly common in persons of Yemenite Jewish ancestry due to the founder variant c.229T>C (p.Tyr77His) [Zeharia et al 2009].

Genetically Related (Allelic) Disorders

The *TRMU* variant c.28G>T (p.Ala10Ser) is known to increase the risk of deafness with exposure to aminoglycosides in individuals with the *MT-RNR1* variant 12S rRNA 1555A>G (a variant known to be associated with aminoglycoside-induced deafness). This modifier effect has been reported in multiple population groups including individuals of Chinese, Arab Israeli, and Italian Spanish descent [Guan et al 2006, Meng et al 2017, Chen & Guan 2022].

Differential Diagnosis

The differential diagnosis of TRMU deficiency includes **Leigh syndrome**; other **genetic mitochondrial hepatopathies** (see Mitochondrial DNA Maintenance Defects Overview, Primary Mitochondrial Disorders Overview, Mitochondrial DNA Associated Leigh Syndrome and NARP, and Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview); and – in infants presenting with hypoglycemia and metabolic acidosis – **organic acidemias** (e.g., propionic acidemia, isolated methylmalonic acidemia, and isovaleric acidemia) and **fatty acid oxidation disorders** (e.g., MCAD deficiency, SCAD deficiency, and VLCAD deficiency).

Persistent lactic acidosis. Note that hyperalaninemia and lactic aciduria both help distinguish chronic lactic acidosis from acute lactic acidemia secondary to critical illness. While infants with TRMU deficiency may develop lactic acidosis prior to the acute liver failure (and associated hyperalaninemia and lactic aciduria) that prompted the evaluation that established the correct diagnosis, other causes of persistent lactic acidosis (e.g., **mitochondrial hepatopathies**) should be considered.

Table 5 lists selected disorders of interest in the differential diagnosis of TRMU deficiency.

Table 5. Selected Disorders in the Differential Diagnosis of TRMU Deficiency

Gene	Disorder/Phenotype	MOI	Common Clinical Manifestations	Comment
DGUOK	Deoxyguanosine kinase deficiency	AR	Onset in infancy; progressive liver failure, neurologic abnormalities, poor feeding, hypoglycemia, hyperlactatemia	Similar clinical manifestations, onset, metabolic profile, & disease progression
G6PC1	Glycogen storage disease type 1a (See Glycogen Storage Disease Type I.)	AR	Onset at 3-4 mos; hepatomegaly, growth restriction, hypoglycemia, lactic acidosis, prominent cheeks	Some infants w/*TRMU* deficiency & hypoglycemia & lactic acidosis were initially presumed to have a glycogen storage disorder.
GFM1	Combined oxidative phosphorylation deficiency 1 (OMIM 609060)	AR	Onset at birth; liver failure, cholestasis, poor feeding, seizures & other neurologic abnormalities, lactic acidosis	Combined oxidative phosphorylation deficiency 1 has early-onset liver failure; however, seizures are more predominant than in TRMU deficiency.
MCEE *MMAA* *MMAB* *MMADHC* *MMUT*	Isolated methylmalonic acidemia (MMA)	AR	Metabolic acidosis in infancy, hyperammonemia, hypoglycemia, poor weight gain, cardiomyopathy	Similar clinical presentation, though isolated MMA often presents in 1st wks of life.
MPV17	*MPV17*-related mtDNA maintenance defect	AR	Onset in infancy or early childhood; failure to thrive, acute liver failure, acral ulceration, central & peripheral neurologic abnormalities, lactic acidosis	*MPV17*-related mtDNA maintenance defect has similar manifestations; however, onset is often later & there are more neurologic findings than in TRMU deficiency.
MTO1	Combined oxidative phosphorylation deficiency 10 (OMIM 614702)	AR	Onset in 1st mos of life; hypertrophic cardiomyopathy, poor weight gain, poor feeding, neurologic abnormalities, lactic acidosis	Similarities w/TRMU deficiency are poor feeding & clinical manifestations.
MT-TE	Transient infantile mitochondrial myopathy [1]	Mat	Onset in early infancy; hypotonia, weakness, feeding difficulties, lactic acidosis	Similarities incl infantile reversible mitochondrial disorder primarily causing myopathy.
PCCA *PCCB*	Propionic acidemia	AR	Metabolic acidosis in infancy, hyperammonemia, hypoglycemia, poor weight gain, cardiomyopathy	Similar clinical presentation, though propionic acidemia often presents in 1st wks of life.
POLG	Alpers-Huttenlocher syndrome (See *POLG*-Related Disorders.)	AR	Onset in infancy; liver failure, poor weight gain, seizures & other neurologic abnormalities, vision loss, hyperlactatemia	*POLG*-related disorders are a more common mitochondrial cause of liver failure in infancy.
SERAC1	3-methylclutaconic aciduria w/deafness-dystonia, encephalopathy, & Leigh-like syndrome (See SERAC1 Deficiency.)	AR	Onset in infancy or early childhood; reversible liver failure or hepatic dysfunction, poor weight gain, hypotonia, hearing loss, neurodevelopmental delay or regression, Leigh syndrome, hypoglycemia, & lactic acidosis	Similar presentations of reversible liver failure & metabolic profiles
TUFM	Combined oxidative phosphorylation deficiency 4 (OMIM 610678)	AR	Onset in infancy; hypotonia, respiratory failure, developmental regression, lactic acidosis	May have similar initial presentation to TRMU deficiency

Table 5. continued from previous page.

Gene	Disorder/Phenotype	MOI	Common Clinical Manifestations	Comment
>90 genes	Leigh syndrome (See Mitochondrial DNA-Associated Leigh Syndrome and NARP and Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview.)	AR AD XL Mat	Onset is generally 3-12 mos & has primarily neurologic features incl hypotonia, cerebellar ataxia, & peripheral neuropathy	Should be considered in infants w/ developmental regression & encephalopathy

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MOI = mode of inheritance; mtDNA = mitochondrial DNA; XL = X-linked
1. Mimaki et al [2010]

Management

No clinical practice guidelines for TRMU deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with TRMU deficiency, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with TRMU Deficiency

System/Concern	Evaluation	Comment
Hepatopathy	Primary care provider, followed by hepatologist	Primary care provider should assess liver function & assess for coagulopathy.
Poor feeding / Growth failure	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in infants w/↑ risk of dysphagia &/or aspiration.
Development	Developmental assessment	• To incl motor, adaptive, & cognitive eval • Speech-language eval by speech-language pathologist • Eval for early intervention / special education
Neurologic manifestations	Primary care provider	• Assessment of neurologic status by primary care provider • Referral to neurologist if there are persistent neurodevelopmental delays or seizures develop
	Neurologist	Assess treatment needs based on neurologic findings.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for durable equipment &/or adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Cardiomyopathy	Cardiac eval	To assess cardiac function via electrocardiogram & echocardiogram
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of TRMU deficiency to facilitate medical & personal decision making

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADL = activities of daily living; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for TRMU deficiency.

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

L-cysteine and N-acetylcysteine. Because the endogenous supply of cysteine is normally low in the first few months of life and because the enzyme TRMU requires adequate amounts of cysteine to enable the essential function of thiolating mitochondrial transfer RNAs, the initial manifestations of TRMU deficiency (primarily hepatopathy) may be ameliorated by exogenous oral cysteine supplementation in infants with TRMU deficiency. (See also Molecular Pathogenesis.)

There is no consensus regarding the best method to provide sufficient exogenous cysteine in TRMU deficiency. Because N-acetylcysteine (NAC) also improves redox potential in mitochondrial disease and thus supports mitochondrial function, it is recommended along with cysteine. The limited evidence available suggest that NAC is best used in conjunction with L-cysteine to ameliorate TRMU deficiency, especially in the first year of life.

Treatment with L-cysteine and NAC should be initiated as soon as a diagnosis of TRMU deficiency is suspected.

- Previous studies have used doses of L-cysteine ranging from 85 to 300 mg/kg per day (with a goal of 300 mg/kg per day total) and doses of NAC ranging from 70 to 150 mg/kg per day [Murali et al 2021].
- Infant formulas enriched with L-cysteine may also be considered to reach this supplementation goal. Given the recovery of liver function over time as physiologic compensatory mechanisms may take effect, supplementation should continue for at least the first year of life [Vogel et al 2023]. It should be noted that supplementation alone does not influence native liver survival, as the development of hepatic necrosis does not seem to improve following initiation of supplementation [Vogel et al 2023].

In one study the survival rate beyond the acute decompensation phase in children supplemented with L-cysteine and/or NAC was 84% compared to 61% in those not supplemented [Vogel et al 2023].

Although a small number of infants treated presymptomatically overall had a milder clinical course than affected relatives [Soler-Alfonso et al 2019, Murali et al 2021], evidence to date is not sufficient to conclude that supplementation will prevent liver dysfunction altogether (see Presymptomatically Treated At-Risk Sibs).

Note: Although the direct substrate of TRMU for thiouridylation is taurine and taurine supplementation may theoretically be of benefit [Sasarman et al 2011], no information on its use has been published.

Liver Transplantation

Orthotopic liver transplantation, reported in 11 children with TRMU deficiency, was indicated when the hepatopathy did not respond to medical interventions [Murali et al 2021, Vogel et al 2023]. Median age of liver transplant was four months. Four children received a transplant during their first episode of acute liver failure; six received a transplant following recurrent episodes of liver failure; and one received a transplant after an episode of liver failure at age 11 years due to hepatoblastoma (the only reported instance of hepatoblastoma in an individual with TRMU deficiency). As in other mitochondrial hepatopathies, the risk of childhood liver cancer is theoretically increased [Sokol 2015].

Liver transplantation did not influence overall survival. Two individuals died following transplantation (one from variceal bleeding and one from multiorgan failure) [Vogel et al 2023]. As a result, consideration of liver transplantation should be on a case-by-case basis depending on the individual's clinical situation.

Liver transplantation may also be considered before a trial of targeted therapy in individuals with the p.Met1? variant, who appear to be less responsive to cysteine supplementation.

Note: The underlying *TRMU* genetic change would not affect the function of a transplanted liver.

Supportive Care

Supportive care by a multidisciplinary team including a hepatologist, neurologist, and medical geneticist is recommended (see Table 7).

Table 7. Supportive Treatment in Individuals with TRMU Deficiency

Manifestation/Concern	Treatment	Considerations/Other
Hepatopathy	Standard symptomatic treatment of hypoglycemia, lactic acidosis, coagulopathy, & hyperammonemia	
Poor weight gain / Poor linear growth	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when there are clinical signs &/or symptoms of dysphagia
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Cardiomyopathy	Supportive care until cardiac function recovers	
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Seizures	Anti-seizure medication	Consider brain imaging to evaluate for findings of Leigh syndrome, which could indicate ↑ potential for seizures & require closer monitoring.
Respiratory failure	Respiratory support as required	Consider tracheostomy if concern for central apnea.
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

Routine follow up is recommended to monitor response to L-cysteine and NAC supplementation, to evaluate response to supportive interventions, and to identify emergence of new findings or concerns regarding

developmental/educational progress such as persistent neurodevelopmental delay or new onset of seizures that may develop over time (see Table 8).

Table 8. Recommended Surveillance for Individuals with TRMU Deficiency

System/Concern	Evaluation	Frequency
Hepatopathy	Per treating hepatologist	Annually until liver function normalizes
	Screening for hepatocellular carcinoma & hepatoblastoma	• Annual alpha-fetoprotein & abdominal ultrasounds beginning at age 1 yr [1] • Screening is most important in children who have had advanced fibrosis or cirrhosis.
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Cardiomyopathy	Per treating cardiologist	Annually
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as type or frequency of seizures, changes in tone, & movement disorders.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	As clinically indicated
Family support & resources	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

1. Sokol [2015]

Agents/Circumstances to Avoid

Agents to avoid:

- Those that increase metabolic demand, such as corticosteroids (see below), or inhibit mitochondrial activity, such as valproic acid and prolonged propofol infusion
- Fasting, as it increases metabolic demand and may exacerbate hypoglycemia

Agents to be used with caution:

- Corticosteroids may raise the lactate level because of increased glycogenolysis and gluconeogenesis. If they are indicated they should be given under guidance of a clinician / metabolic specialist who can aid in monitoring metabolic acidosis.
- Because of limited liver oxidative metabolism in the acute period, administration of high concentrations of dextrose will increase lactic acid concentration, which may cause or worsen metabolic acidosis. Therefore, dextrose must be given with care to balance euglycemia with acid-base status.

Evaluation of Relatives at Risk

Prenatal testing of a fetus at risk. Molecular genetic prenatal testing of fetuses at risk may be performed via amniocentesis or chorionic villus sampling to inform maternal L-cysteine supplementation (see Pregnancy Management) and facilitate institution of exogenous cysteine supplementation (as L-cysteine, N-acetylcysteine, or both) at birth (see Management, Targeted Therapies).

Newborn sib. If prenatal testing has not been performed on a pregnancy at risk, L-cysteine supplementation of an at-risk newborn sib should be offered until molecular genetic testing for the family-specific *TRMU* pathogenic variants has been completed. The effects of TRMU deficiency (primarily hepatopathy) may be ameliorated by exogenous oral cysteine supplementation in infants with TRMU deficiency. Earlier supplementation with cysteine has led to better prognosis in two at-risk sibs reported to date [Murali et al 2021]. See Clinical Characteristics, Presymptomatically Treated At-Risk Sibs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

In one instance of prenatally identified TRMU deficiency, the mother received 500 mg of L-cysteine twice daily during the third trimester of the pregnancy with the intent of providing sufficient cysteine to the fetus in the postnatal period when cysteine is an essential amino acid (see Management, Targeted Therapies). This child (Patient 2 in Murali et al [2021]) had a milder course compared to his affected older sister (Patient 1 in Murali et al [2021]) and other children with TRMU deficiency reported by Murali et al [2021].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

TRMU deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *TRMU* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *TRMU* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing TRMU deficiency.

Sibs of a proband

- If both parents are known to be heterozygous for a *TRMU* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *TRMU* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing TRMU deficiency.

Offspring of a proband

- Unless an affected individual's reproductive partner also has TRMU deficiency or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *TRMU*.
- Given the young age of the identified cohort, individuals with TRMU deficiency have not been reported to reproduce (long-term data on individuals with TRMU deficiency are limited).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TRMU* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *TRMU* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing for the reproductive partners of known carriers should be considered. TRMU deficiency is particularly common in persons of Yemenite Jewish ancestry due to a founder variant (see Prevalence).

Prenatal Testing and Preimplantation Genetic Testing

Once the *TRMU* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Liver Foundation**
  Phone: 800-465-4837 (HelpLine)
  www.liverfoundation.org

- **Canadian Liver Foundation**
  Canada
  Phone: 800-563-5483
  Email: clf@liver.ca
  www.liver.ca
- **Childhood Liver Disease Research Network (ChiLDReN)**
  Phone: 720-777-2598
  Email: joan.hines@childrenscolorado.org
  www.childrennetwork.org
- **Children's Liver Disease Foundation**
  United Kingdom
  Phone: +44 (0) 121 212 3839
  Email: info@childliverdisease.org
  childliverdisease.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. TRMU Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TRMU	22q13.31	Mitochondrial tRNA-specific 2-thiouridylase 1	TRMU database	TRMU	TRMU

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for TRMU Deficiency (View All in OMIM)

610230	tRNA 5-METHYLAMINOMETHYL-2-THIOURIDYLATE METHYLTRANSFERASE; TRMU
613070	LIVER FAILURE, INFANTILE, TRANSIENT; LFIT

Molecular Pathogenesis

TRMU encodes the protein 5-methylaminomethyl-2-thiouridylate-methyltransferase (TMRU), a mitochondrial transfer RNA (mt-tRNA) thiouridylase. TRMU uses cysteine as a substrate to thiolate the wobble position, the third position of a codon for mRNA translation, of mt-tRNA(Lys), mt-tRNA(Gln), and mt-tRNA(Glu). Deficiency of this enzyme caused by biallelic *TRMU* pathogenic variants leads to reduction of thio-modified mt-tRNAs and deficiency of mitochondrial proteins needed for energy production.

Because cystathionase, the enzyme responsible for the endogenous cysteine supply, has a physiologic nadir in the first few months of life, cysteine is an essential amino acid during that period. In combination with low cysteine

levels in the body in the first few months of life, the severe reduction of thiolated mt-tRNAs leads to the decompensation (primarily hepatic failure) observed in TRMU deficiency [Zeharia et al 2009, Soler Alfonso et al 2019].

Mechanism of disease causation. Loss-of-function *TRMU* variants or other variants (e.g., missense, indel, frameshift) result in deficiency or decreased activity of the enzyme TRMU.

Table 9. Notable *TRMU* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_018006.5 NP_060476.2	c.2T>A	p.Met1?	See Genotype-Phenotype Correlations.
	c.229T>C	p.Tyr77His	Yemenite Jewish founder variant [Zeharia et al 2009]

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

The authors work in the Mitochondrial Medicine Frontier Program at the Children's Hospital of Philadelphia, within the Division of Human Genetics in the Department of Pediatrics.

- **Michaela Reinhart, MD,** is a Pediatrics-Medical Genetics trainee at the Children's Hospital of Philadelphia with a special interest in metabolic and mitochondrial disorders.
- **Colleen Muraresku, MS, LCGC,** is a Certified Genetics Counselor and the program director of the Mitochondrial Medicine Frontier Program.
- **Rebecca Ganetzky, MD,** is an assistant professor in the Department of Pediatrics at the University of Pennsylvania Perelman School of Medicine; attending physician; assistant director of the metabolic and advanced diagnostics laboratory; principal investigator of an active research laboratory focused on mitochondrial ATP synthase deficiency; and has special clinical interests in primary lactic acidosis and mitochondrial hepatopathy. Email: ganetzykr@chop.edu

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