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Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency

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Summary

Clinical characteristics

Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency and trifunctional protein (TFP) deficiency are caused by impairment of mitochondrial TFP. TFP has three enzymatic activities – long-chain enoyl-CoA hydratase, long-chain 3-hydroxyacyl-CoA dehydrogenase, and long-chain 3-ketoacyl-CoA thiolase. In individuals with LCHAD deficiency, there is isolated deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase, while deficiency of all three enzymes occurs in individuals with TFP deficiency.

Individuals with TFP deficiency can present with a severe-to-mild phenotype, while individuals with LCHAD deficiency typically present with a severe-to-intermediate phenotype.

- Neonates with the severe phenotype present within a few days of birth with hypoglycemia, hepatomegaly, encephalopathy, and often cardiomyopathy.
- The intermediate phenotype is characterized by hypoketotic hypoglycemia precipitated by infection or fasting in infancy.
- The mild (late-onset) phenotype is characterized by myopathy and/or neuropathy.

Long-term complications include peripheral neuropathy and retinopathy.

Diagnosis/testing

The diagnosis of LCHAD/TFP deficiency is established in a proband with elevation of long-chain 3-hydroxyacylcarnitine species in plasma and/or increased excretion of 3-hydroxy-dicarboxylic acids in urine in combination with identification of biallelic pathogenic variants in *HADHA* or *HADHB* by molecular genetic testing.

Distinguishing LCHAD deficiency from TFP deficiency requires identification of isolated long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency on enzymatic assay in lymphocytes or skin fibroblasts. TFP deficiency is confirmed by the identification of deficiencies in all three TFP enzymatic activities (long-chain

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enoyl-CoA hydratase, long-chain 3-hydroxyacyl-CoA dehydrogenase, and long-chain 3-ketoacyl-CoA thiolase) in lymphocytes or skin fibroblasts.

Management

Treatment: Avoidance of fasting using frequent feeds, decreasing feeding intervals and supplemental carbohydrates during illness, and continuing overnight feeds in older children as needed for hypoglycemia; medium-chain triglyceride (MCT) or triheptanoin supplementation; low-fat diet; carnitine supplementation in those with carnitine deficiency; feeding therapy and gastrostomy tube as needed; developmental services; and treatment of cardiac dysfunction, peripheral neuropathy, and retinopathy by relevant specialists. Emergency outpatient treatment for mild decompensation includes decreasing the fasting interval, administration of antipyretics for fever, and antiemetics as needed for vomiting. Acute treatment includes hospitalization with intravenous fluid containing at least 10% dextrose, and bicarbonate therapy for severe metabolic acidosis; management of hyperammonemia and rhabdomyolysis; and management of cardiomyopathy per cardiologist.

Prevention of primary manifestations: Avoidance of fasting; supplementation with MCT or triheptanoin; strict dietary management; education of parents and caregivers to ensure prompt treatment; written protocol for emergency treatment.

Surveillance: Monitor nutrition, serum plasma free and total carnitine, acylcarnitine profile, creatine kinase, AST, and ALT with frequency based on age; annual comprehensive fatty acid profile; monitor head size, growth, and development at each visit throughout childhood; neuropsychological testing and quality of life assessments as needed; EKG and echocardiography annually or more frequently as needed; annual neurology evaluation with nerve conduction velocity and electromyography as needed; annual ophthalmology evaluation with electroretinography every two to three years.

Agents/circumstances to avoid: Fasting; inadequate calories during stressors; dehydration; high-fat diets including ketogenic and carbohydrate restricted diet; anesthetics that contain high doses of long-chain fatty acids; intravenous intralipids during acute metabolic crisis.

Evaluation of relatives at risk: Testing of all at-risk sibs of any age is warranted (targeted molecular genetic testing if the familial pathogenic variants are known or plasma acylcarnitine profile, plasma free and total carnitine, and urine organic acid assay if the pathogenic variants in the family are not known) to allow for early diagnosis and treatment of LCHAD/TFP deficiency.

Pregnancy management: Increase MCT intake in the third trimester; high dextrose infusion in the peripartum period. Monitor for HELLP syndrome and acute fatty liver of pregnancy in pregnant females who are heterozygous for an *HADHA* or *HADHB* pathogenic variant (including suspected carriers).

Genetic counseling

LCHAD/TFP deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *HADHA* or *HADHB* 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 pathogenic variants. Once the *HADHA* or *HADHB* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

Table. Synonyms and Included Genes

Disorder	Synonyms	Associated Gene(s)
Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency	• LCHAD deficiency (LCHADD) • Long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency	*HADHA*
Trifunctional protein (TFP) deficiency	• TFP deficiency (TFPD) • Mitochondrial trifunctional protein (MTP) deficiency	*HADHA* *HADHB*

Diagnosis

No consensus clinical diagnostic criteria for long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency or trifunctional protein (TFP) deficiency have been published.

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for LCHAD/TFP deficiency is primarily based on quantification of the analytes 3-hydroxypalmitoyl carnitine (C16-OH) and 3-hydroxyoleoylcarnitine (C18:1-OH) on dried blood spots.

C16-OH and C18:1-OH values above the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing including plasma acylcarnitine and urine organic acid profiles.

If the follow-up biochemical testing supports the likelihood of LCHAD/TFP deficiency, additional testing is required to establish the diagnosis (see Establishing the Diagnosis).

The following medical interventions need to begin immediately on receipt of an abnormal NBS result while additional testing is performed to determine whether this is a true positive NBS result and to establish a definitive diagnosis of LCHAD/TFP deficiency:

- Evaluation of the newborn to ascertain clinical status
- Education of the caregivers to avoid prolonged fasting and to monitor for decreased oral intake, vomiting, or lethargy
- Immediate intervention (to be considered if the newborn is not doing well clinically) possibly including admission to the hospital, fluid resuscitation, infusion of IV dextrose (10% or higher), and cardiac evaluation

Scenario 2: Symptomatic Individual

Supportive – but nonspecific – clinical findings, laboratory findings, and family history include the following.

Clinical findings

- **Neonatal onset (severe)**
  - Hypoketotic hypoglycemia, hepatomegaly
  - Cardiomyopathy
  - Encephalopathy
- **Infantile onset (intermediate).** Recurrent hypoketotic hypoglycemia precipitated by infection or fasting
- **Late onset (mild)**
  - Episodic rhabdomyolysis
  - Exercise intolerance and muscle weakness

- Peripheral neuropathy
- Retinopathy

Supportive laboratory findings

- Nonspecific:
  - Hypoglycemia (nonketotic or hypoketotic) with blood glucose often <45 mg/dL
  - Urinalysis that demonstrates the absence of ketones in the setting of hypoglycemia
  - Metabolic acidosis
  - Lactic acidosis
  - Hyperammonemia: blood ammonia level may be >200 µmol/L in newborns and >100 µmol/L after the neonatal period
  - Elevated liver transaminases (AST, ALT)
  - Elevated creatine kinase (CK), particularly in the late-onset myopathic form. A CK value greater than five times the upper limit of reference is suggestive of rhabdomyolysis (range 1,000-100,000 IU/L). A CK value of >15,000 IU/L at presentation increases the risk for acute kidney injury [Bosch et al 2009].
- Specific:
  - **Plasma acylcarnitine profile.** The elevation of 3-hydroxy derivatives of C16, C18, and C18:1 is highly suggestive of LCHAD/TFP deficiency. The plasma acylcarnitine profile typically shows elevations of C16-OH, C18-OH, C18:1-OH, and elevated ratios of C16-OH/C16 and C18-OH/C18.
  - **Urine organic acid analysis.** Elevations of 3-hydroxy-dicarboxylic acids and lactic acid

Note: Because elevations of these metabolites can be intermittent particularly in individuals with milder disease, follow-up testing is required to establish the diagnosis of LCHAD/TFP deficiency (see Establishing the Diagnosis) [Elizondo et al 2020].

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.

Establishing the Diagnosis

The diagnosis of LCHAD deficiency **is established** in a proband with elevation of long-chain 3-hydroxyacylcarnitine species in plasma and/or increased excretion of 3-hydroxy-dicarboxylic acids in urine in combination with identification of biallelic pathogenic (or likely pathogenic) variants in *HADHA* by molecular genetic testing (see Table 1). Distinguishing LCHAD deficiency from TFP deficiency requires identification of isolated long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency on enzymatic assay in lymphocytes or skin fibroblasts.

The diagnosis of TFP deficiency **is established** in a proband with elevation of long-chain 3-hydroxyacylcarnitine species in plasma and/or increased excretion of 3-hydroxy-dicarboxylic acids in urine in combination with identification of biallelic pathogenic (or likely pathogenic) variants in *HADHA* or *HADHB* by molecular genetic testing (see Table 1). Distinguishing TFP deficiency from LCHAD deficiency requires identification of deficiency in all three TFP enzymatic activities (long-chain enoyl-CoA hydratase, long-chain 3-hydroxyacyl-CoA dehydrogenase, and long-chain 3-ketoacyl-CoA thiolase) in lymphocytes or skin fibroblasts.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Most affected individuals have an abnormal acylcarnitine profile. An individual with persistent abnormal acylcarnitine profile is presumed to have LCHAD/TFP deficiency even if only one pathogenic variant is identified.

Molecular Genetic Testing Approaches

Scenario 1: Abnormal newborn screening (NBS) result. When NBS results and other laboratory findings suggest the diagnosis of LCHAD/TFP deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Serial single-gene testing.** Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.
  - Perform sequence analysis of *HADHA* first. If only one pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
  - If *HADHA* testing is negative, perform sequence analysis of *HADHB*. If only one pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *HADHA*, *HADHB*, and other genes of interest (see Differential Diagnosis) may be considered 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.

Scenario 2: Symptomatic individual. For a symptomatic individual who has findings associated with late-onset TFP deficiency OR neonatal-onset LCHAD/TFP deficiency that has not been treated (because symptoms occurred before NBS results were returned, NBS was not performed, or NBS yielded a false negative result), molecular genetic testing approaches can include **serial single-gene testing** or use of a **multigene panel**.

When the diagnosis of LCHAD/TFP deficiency has not been considered, **comprehensive genomic testing,** which does not require the clinician to determine which gene(s) are likely involved, is an option. 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 1. Molecular Genetic Testing Used in LCHAD/TFP Deficiency

Gene [1, 2]	Proportion of LCHAD/TFP Deficiency Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
HADHA	100% (LCHAD) ~50% (TFP)	<100% [6]	2 persons w/TFP deficiency [7]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of LCHAD/TFP Deficiency Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
HADHB	~50% (TFP)	<100% [6]	≥2 persons w/TFP deficiency [8]

LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; TFP = trifunctional protein

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. See Molecular Genetics for information on variants detected in these genes.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

5. 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.

6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

7. To date, large deletions and/or duplications have not been reported in individuals with LCHAD deficiency. Two large *HADHA* deletions have been reported in individuals with TFP deficiency [Djouadi et al 2016, Bo et al 2017].

8. Two large *HADHB* deletions have been reported in individuals with TFP deficiency [Boutron et al 2011, Aradhya et al 2012]. A third individual with neonatal-onset cardiomyopathy [Wang et al 2012] was reported; the biochemical profile was not described, but this individual likely had TFP deficiency.

Biochemical Testing Approaches

In vitro probe analysis. Skin fibroblasts incubated with palmitic acid and culture medium can be assayed for acylcarnitine after 96 hours of incubation. In individuals with LCHAD/TFP deficiency there is substantial accumulation of C16-OH [Okun et al 2002].

Clinical Characteristics

Clinical Description

Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency and trifunctional protein (TFP) deficiency are caused by impairment of mitochondrial TFP. TFP has three enzymatic activities – long-chain enoyl-CoA hydratase, long-chain 3-hydroxyacyl-CoA dehydrogenase, and long-chain 3-ketoacyl-CoA thiolase. Deficiency of the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase occurs in individuals with LCHAD deficiency, while deficiency of all three enzymes occurs in individuals with TFP deficiency.

LCHAD and TFP deficiency are disorders of long-chain fatty acid oxidation, which typically present with recurrent episodes of hypoketotic hypoglycemia precipitated by fasting or illness. In addition, the other characteristic manifestations of long-chain fatty acid oxidation defects (FAODs) such as cardiomyopathy, liver dysfunction, or rhabdomyolysis may be present. However, peripheral neuropathy and retinopathy are unique complications of these disorders not seen in other FAODs. The clinical presentation represents a continuous spectrum of severity ranging from severe neonatal-onset to mild late-onset forms. Individuals with LCHAD deficiency usually present with a severe-to-intermediate phenotype, while individuals with TFP deficiency typically present with a severe-to-mild phenotype.

Table 2. LCHAD/TFP Deficiency: Frequency of Select Features

Feature	~% of Persons w/Feature [1]		Comment
	LCHAD Deficiency	TFP Deficiency	
Severe neonatal presentation	15%	39%	Often lethal when assoc w/dilated cardiomyopathy
Hypoketotic hypoglycemia	78%	40%	Common in severe neonatal presentation; precipitated by fasting or illness in intermediate phenotype
Liver dysfunction	80%	53%	↑ liver enzymes, cholestasis, or liver failure during metabolic crisis is common in severe & intermediate phenotypes.
Cardiomyopathy	65%	63%	Common in severe neonatal presentation; may be present in untreated intermediate or mild phenotype
Skeletal myopathy	62%	72%	Hypotonia, muscle weakness, exercise intolerance, or episodic muscle pain & myoglobinuria; may be isolated finding in mild phenotype
Peripheral neuropathy	67%	79%	Long-term complication present in most surviving persons despite early treatment
Retinopathy	80%	12%	Long-term complication that may → vision impairment

LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; TFP = trifunctional protein

1. Frequencies are approximations from data published prior to the implementation of newborn screening (NBS) [den Boer ME et al 2002, den Boer ME et al 2003, Spiekerkoetter et al 2003, Spiekerkoetter et al 2004]. NBS has enabled earlier diagnosis and improved outcomes.

Neonatal Onset (Severe/Cardiac Phenotype)

The neonatal-onset (severe/cardiac) presentation is more common in individuals with TFP deficiency than in those with LCHAD deficiency. The main manifestations are the following:

- **Metabolic decompensation.** Newborns present within a few days of birth with a Reye-like syndrome presentation: encephalopathy, hypoketotic hypoglycemia, hepatomegaly with elevated transaminases and hepatosteatosis, and lactic acidosis. Hyperammonemia may also be present. The metabolic decompensation is rapidly progressive and requires immediate intervention. The acute metabolic decompensation is often associated with liver dysfunction manifesting as hepatomegaly, elevated liver enzymes, or liver failure.
- **Neurologic manifestations.** Severe neonatal presentation characterized by hypoglycemia and liver dysfunction is usually associated with encephalopathy manifesting as lethargy, poor feeding, seizures, apnea, or coma.
- **Cardiac manifestations.** The severe form is associated with progressive dilated cardiomyopathy manifesting as arrhythmias and cardiac failure. It is associated with very high mortality.

Infantile Onset (Intermediate/Hepatic Phenotype)

Individuals with the intermediate or moderate severity phenotype present later in infancy. This is the most common presentation in LCHAD deficiency and relatively uncommon in TFP deficiency.

The classic presentation is acute metabolic decompensation precipitated by fasting or infection.

- The metabolic decompensation is characterized by hypoketotic hypoglycemia often associated with lactic acidosis, elevated liver enzymes, and high creatine kinase (CK).
- Infants may present with vomiting, lethargy, poor feeding, and hepatomegaly.
- Associated baseline findings including muscle weakness, feeding difficulties, and hypotonia may be present.
- Other manifestations of this form (more common in previously untreated individuals): cardiomyopathy (dilated or hypertrophic), long QT intervals, liver cirrhosis, cholestasis, developmental delays, and failure to thrive. Cardiomyopathy may be present at baseline or dilated cardiomyopathy may first appear during metabolic crisis even in previously treated individuals.
- Prompt diagnosis and initiation of treatment is crucial for reversal of cardiomyopathy and favorable outcome. Newborn screening has enabled presymptomatic diagnosis and thus improved outcome.

Late Onset (Mild/Neuromyopathic Phenotype)

Individuals with the mild phenotype usually present after infancy with neuromuscular symptoms. The isolated neuromyopathic presentation is typical of mild TFP deficiency and rare in LCHAD deficiency. However, infants with LCHAD deficiency with the intermediate/hepatic phenotype may present later with neuromyopathic symptoms. The common manifestations are the following:

- **Skeletal myopathy** manifests as muscle weakness, exercise intolerance, and hypotonia. Episodic rhabdomyolysis precipitated by prolonged exercise, cold exposure, fasting, or infection is characteristic of this phenotype. These episodes are characterized by diffuse muscle pain, profound weakness, myoglobinuria, and elevations of serum CK (>5x the upper limit of normal), aldolase, aspartate aminotransferase, and alanine transaminase.
- **Neuropathy.** Many individuals present with progressive peripheral neuropathy resembling axonal Charcot-Marie-Tooth disease [Immonen et al 2016a, Grünert et al 2021].

Long-Term Complications

Long-term complications in those with the intermediate and late-onset phenotypes include the following:

- **Peripheral neuropathy** is a unique long-term complication of LCHAD/TFP deficiency. Age of onset ranges from infancy to adulthood (median: age ~7 years) [Grünert et al 2021]. Onset is earlier in individuals with TFP deficiency than in those with LCHAD deficiency. It is progressive and sensorimotor in nature. However, it can be pure sensory or pure motor. Polyneuropathy is described as axonal or axonal with secondary demyelination on electrophysiologic studies. Neuropathy can worsen during metabolic crisis. Early diagnosis and treatment can delay the onset but may not prevent this complication.
- **Retinopathy,** another unique complication, is much more common in individuals with LCHAD deficiency than those with TFP deficiency. It is progressive and correlates with disease severity. Four different stages of retinopathy in LCHAD deficiency have been described [Tyni et al 1998]:
  - Stage 1. Normal to diffuse hypopigmentation of the fundus
  - Stage 2. Pigment clumping in the fovea
  - Stage 3. Macular pallor and migration of pigmentary changes toward the periphery
  - Stage 4. Atrophy of the posterior fundus and further peripheral migration of pigmentary changes

  Visual impairment is present from stage 3 onward. Hence, retinopathy may be missed if fundal imaging and electroretinogram are not done. Approximately half of individuals with LCHAD deficiency have evidence of retinopathy by age two years. Early diagnosis and treatment can slow the progress but may not prevent this complication [Fahnehjelm et al 2016].

Other

Rare manifestations in individuals with LCHAD/TFP deficiency include hypoparathyroidism, neonatal respiratory distress syndrome, and necrotizing enterocolitis [Tyni et al 1997, Diekman et al 2013, Karall et al 2015, van Vliet et al 2018].

Pregnancy Complications

Pregnancy complications such as HELLP (*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count) syndrome and acute fatty liver of pregnancy are seen in about 15%-25% of pregnancies in women carrying a fetus affected with LCHAD/TFP deficiency [den Boer et al 2002, Spiekerkoetter et al 2003, Karall et al 2015]. The pathophysiology of maternal complications is unclear. One hypothesis is that HELLP syndrome is precipitated by the excessive hydroxyacyl derivatives produced by the affected fetus [Kobayashi et al 2015]. An alternative hypothesis is that maternal heterozygosity for LCHAD/TFP deficiency causes hepatic insufficiency [Blish & Ibdah 2005].

Genotype-Phenotype Correlations

***HADHA*.** Homozygous c.1528G>C variants are associated with LCHAD deficiency. Most individuals with LCHAD deficiency have at least one allele with this variant [Ijlst et al 1996]. In the largest cohort of individuals with LCHAD deficiency, c.1528G>C was present in 84 of 98 alleles. Only one individual was homozygous for another variant [den Boer et al 2002]. However, a few individuals who were compound heterozygous for this variant and another pathogenic variant in *HADHA* were reported to have TFP deficiency [Grünert et al 2021]. Enzymatic studies were not provided for those individuals. In the absence of homozygosity for this variant, enzyme assay is needed to distinguish between these conditions.

***HADHB*.** In general, individuals with *HADHB* missense pathogenic variants present with milder phenotypes than those with premature termination or frameshift variants. A missense variant on at least one allele favors the milder phenotype. However, the amino acid p.Arg28 appears critical for TFP function/stability, and variants altering this amino acid lead to the severe presentation when in combination with a severe variant on the other allele [Spiekerkoetter et al 2003].

Although clinical manifestations of *HADHA*- and *HADHB*-related TFP deficiency are similar, the distribution of phenotypes differs. Approximately half of individuals with *HADHA* pathogenic variants present with a severe/lethal phenotype, while 70% of individuals with *HADHB* variants have a milder phenotype [Spiekerkoetter et al 2004].

Prevalence

The incidence of LCHAD deficiency on NBS data from Australia, Germany, and the US was estimated at 1:250,000; TFP deficiency incidence was estimated at 1:750,000 [Lindner et al 2010].

The carrier frequency of the most common *HADHA* pathogenic variant in individuals of European ancestry (c.1528G>C) is estimated to be 1:173 in Estonia, 1:217 in Poland, and 1:240 in Finland [Joost et al 2012]. To date, this variant has not been reported in the Japanese or Korean populations [Purevsuren et al 2009].

LCHAD deficiency is especially frequent in the Pomerania region of Poland near the Baltic Sea, partly as a result of a high carrier frequency (1:73) of *HADHA* variant c.1528G>C in individuals of Kashubian ancestry; the prevalence is estimated at 1:16,900 [Piekutowska-Abramczuk et al 2010, Nedoszytko et al 2017].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *HADHA* or *HADHB*.

Differential Diagnosis

Table 3. Genetic Disorders of Interest in the Differential Diagnosis of LCHAD/TFP Deficiency

Gene(s)	Disorder [1]	Key Features Overlapping w/LCHAD/TFP Deficiency	Distinguishing Features [2]
ACADM	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Intermittent hypoketotic hypoglycemia precipitated by fasting or illness; Reye syndrome-like presentation	Absence of myopathy, cardiomyopathy, peripheral neuropathy, & retinopathy in MCAD deficiency
ACADVL	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	• Severe early-onset form: cardiomyopathy & multiorgan failure • Intermediate form: intermittent hypoketotic hypoglycemia • Late-onset myopathic form: recurrent rhabdomyolysis	Absence of peripheral neuropathy & retinopathy in VLCAD deficiency
CPT1A	Carnitine palmitoyltransferase 1A (CPT1A) deficiency	Intermittent hypoketotic hypoglycemia & liver failure	Absence of peripheral neuropathy & retinopathy in CPT1A deficiency
CPT2	Carnitine palmitoyltransferase II (CPT II) deficiency	• Lethal neonatal form: hypoglycemia, liver failure, cardiomyopathy • Severe infantile hepatocardiomuscular form: intermittent hypoketotic hypoglycemia, liver failure, cardiomyopathy • Late-onset myopathic form: recurrent rhabdomyolysis	• Congenital anomalies (cystic/dysplastic kidneys, neuronal migration defects) may be present in lethal neonatal form of CPT II deficiency. • CPT II deficiency is not assoc w/peripheral neuropathy or retinopathy.
ETFA *ETFB* *ETFDH*	Multiple acyl-CoA dehydrogenase deficiency (MADD)	• Severe neonatal form: hypoglycemia, metabolic acidosis, lactic acidosis, hyperammonemia, hepatomegaly, cardiomyopathy • Late-onset form: recurrent metabolic decompensation consisting of hypoglycemia & metabolic acidosis, recurrent rhabdomyolysis	• Congenital anomalies may be present in severe neonatal form of MADD. • Peripheral neuropathy has been described in MADD, but retinopathy has not been assoc w/MADD.
SLC22A5	Systemic primary carnitine deficiency (CDSP)	Intermittent hypoketotic hypoglycemia precipitated by fasting or illness, skeletal myopathy, cardiomyopathy	Absence of peripheral neuropathy & retinopathy in CDSP
SLC25A20	Carnitine-acylcarnitine translocase (CACT) deficiency	• Severe neonatal form: hypoglycemia, hyperammonemia, liver failure, ↑ CK, cardiomyopathy • Late-onset form (rare): recurrent metabolic decompensation consisting of hypoketotic hypoglycemia	Absence of peripheral neuropathy & retinopathy in CACT deficiency

CK = creatine kinase; LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; TFP = trifunctional protein

1. The disorders listed in Table 4 are inherited in an autosomal recessive manner.

2. These disorders can usually be differentiated with acylcarnitine profile testing.

In addition to the above-mentioned conditions, mitochondrial respiratory chain disorders should be considered in the differential diagnosis of long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) / trifunctional protein

(TFP) deficiency. The common manifestations of LCHAD/TFP deficiency – such as cardiomyopathy, skeletal myopathy, hypotonia, peripheral neuropathy, and retinopathy – are also very commonly seen in mitochondrial respiratory chain disorders. See Primary Mitochondrial Disorders Overview.

Management

A brief outline of treatment recommendations for long-chain fatty acid oxidation defects including long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) / trifunctional protein (TFP) deficiency has been published [Spiekerkoetter et al 2009].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with LCHAD/TFP deficiency, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with LCHAD/TFP Deficiency

System/Concern	Evaluation	Comment
Metabolic decompensation	Consultation w/metabolic physician/biochemical geneticist & specialist metabolic dietitian	Consider transfer to specialist center w/experience in mgmt of inherited metabolic diseases.
	• Blood gas – arterial or venous (e.g., w/i-STAT®), ammonia, lactic acid • Glucose, liver transaminases (AST, ALT) • Electrolytes w/bicarbonate, BUN, creatinine • CK • CBC w/differential & addl eval when infection is suspected	Urgent labs to be obtained if an acute metabolic crisis is suspected
	Plasma free & total carnitine, plasma acylcarnitine profile, & urine organic acids	To be obtained during period of acute metabolic decompensation, if possible
General	Referral to clinical geneticist familiar w/LCHAD/TFP deficiency	For implementation of specialized treatment
Cardiology	Consider cardiology consultation & echocardiography	For eval of cardiomyopathy
Neurology	Consider neurology consultation	For eval of myopathy & peripheral neuropathy
Ophthalmology	Consider ophthalmology consultation	For assessment of vision & retinopathy
Development	Developmental assessment	To incl motor, adaptive, cognitive, & speech/language eval
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of LCHAD/TFP deficiency to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ALT = alanine transaminase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CK = creatine kinase; LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; MOI = mode of inheritance; TFP = trifunctional protein

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management by multidisciplinary specialists including a metabolic physician / biochemical geneticist, specialist metabolic dietitian, cardiologist, neurologist, ophthalmologist, and developmental pediatrician is recommended.

Table 5. Treatment of Manifestations in Individuals with LCHAD/TFP Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Defect of long-chain fatty acid oxidation	**Avoidance of fasting** • Birth-age 3 mos: frequent feeds (every 2-3 hrs) • Age 4-12 mos: feeding interval can be ↑ to every 4 hrs if tolerated by 6 mos. From age 6 to 12 mos, daytime feeding interval every 4 hrs; overnight fasting can be gradually ↑ to 6-8 hrs by 12 mos. • Age 1-3 yrs: daytime feeding interval 4 hrs; overnight fasting up to 10 hrs may be attempted • Age 3+ yrs: overnight fasting up to 12 hrs may be attempted	• ↓ feeding interval by half during periods of illness. • After age 1 yr, if preprandial hypoglycemia remains an issue, consider overnight feedings or 1 gm/kg of uncooked cornstarch at bedtime to ensure sufficient glucose supply overnight.
	MCT supplementation • Low-fat diet recommended • Goal: provide 30% of energy needs from fat incl 7%-15% from long-chain fat & 15%-25% from MCT	MCT can bypass carnitine shuttle & enter mitochondria directly. As medium-chain fatty acid oxidation is intact, it provides important source of calories & is cornerstone of mgmt in long-chain FAOD.
	Triheptanoin (C7) • Approved by FDA in 2020 for treatment of long-chain FAODs; can be used as an alternative to MCT to provide up to 35% of daily calorie intake. • Triheptanoin treatment can ↓ frequency of hospitalizations & rhabdomyolysis [1] & improve cardiomyopathy, hepatomegaly, & hypoglycemia. [2] • Adverse effects are mainly gastrointestinal & transient (e.g., abdominal pain, diarrhea).	Triheptanoin is an odd-chain MCT consisting of 3 7-carbon fatty acids metabolized to acetyl CoA & propionyl CoA. Propionyl CoA provides an anaplerotic effect by replenishing mitochondrial tricarboxylic acid cycle intermediates. Thus, compared to even-chain MCT, triheptanoin provides addl benefits through anaplerosis. [3]
Secondary carnitine deficiency	L-carnitine: 25-50 mg/kg daily in 3 divided doses	Carnitine supplementation is NOT recommended unless there is carnitine deficiency because of concern for cardiotoxicity of long-chain hydroxyacylcarnitine derivatives.
Poor weight gain / FTT	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
DD/ID	Interventions per developmental pediatrician / neurodevelopment specialist	PT, OT, & speech therapy, as indicated
Cardiac dysfunction	Interventions per cardiologist	Early diagnosis & strict dietary therapy can prevent & even reverse cardiomyopathy. [4]
Peripheral neuropathy	Interventions per neurologist	Early diagnosis & strict dietary therapy may delay onset or slow progression but may not completely prevent this complication. [5]

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Retinopathy	Interventions per ophthalmologist	Early diagnosis & strict dietary therapy may delay onset or slow progression but may not completely prevent this complication. [6]

CoA = coenzyme A; DD/ID = developmental delay /intellectual disability; FAOD = fatty acid oxidation disorders; FTT = failure to thrive; LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; MCT = medium-chain triglyceride; OT = occupational therapy; PT = physical therapy; TFP = trifunctional protein
1. Roe & Brunengraber [2015], Zöggeler et al [2021]
2. Roe & Brunengraber [2015], Gillingham et al [2017], Vockley et al [2021]
3. Sklirou et al [2021]
4. Immonen et al [2016b], De Biase et al [2017]
5. Fraser et al [2019], Grünert et al [2021]
6. Fletcher et al [2012], Fahnehjelm et al [2016], Dulz et al [2021]

Table 6. Emergency Outpatient Treatment in Individuals with LCHAD/TFP Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Metabolic decompensation / Hypoglycemia [1]	• ↓ fasting interval by 1/2 of non-sick-day duration. • Encourage intake of sugary drinks (e.g., Gatorade™, juice).	See Table 6 for recommended maximal fasting intervals at baseline.
Fever	Administration of antipyretics (acetaminophen, ibuprofen) if temperature rises >38.5° C	• If there is ↓ oral intake, vomiting, or lethargy, start acute inpatient treatment (see Table 7). • Low threshold for starting inpatient mgmt for infants & young children
Occasional vomiting	Antiemetics [2]	Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food & beverages at home or during transfer to hospital.

LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; TFP = trifunctional protein
1. Parents or local hospitals should immediately inform the designated metabolic center if: (1) temperature rises >38.5° C; (2) persistent vomiting/diarrhea or other symptoms of intercurrent illness develop; or (3) new neurologic symptoms occur.
2. Avoid ondansetron and other medications known to prolong QT intervals in individuals with cardiomyopathy and/or long QT intervals.

Acute manifestations (e.g., lethargy, encephalopathy, intractable vomiting, seizures, severe myalgia, red-colored urine) often occur in the setting of intercurrent illness and/or inadequate caloric intake as a result of poor appetite or prolonged fasting, and should be managed with generous caloric and intravenous fluid support in a hospital setting. Suspected infection should be identified and treated immediately.

Table 7. Acute Inpatient Treatment in Individuals with LCHAD/TFP Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Hypoglycemia	• IV fluid w/high dextrose content (≥10%) to maintain blood glucose >100 mg/dL. [1] • Starting fluid at 1.5x maintenance usually achieves this goal. • Glucose infusion rate of 8-12 mg/kg/min is usually needed for young children.	• High-dose glucose is needed to avoid catabolism. • If there is hyperglycemia, start insulin infusion rather than reducing glucose infusion rate.

Table 7. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Metabolic acidosis	• For severe metabolic acidosis (pH <7.10), initiate bicarbonate therapy. • A common formula for bicarbonate dose: bicarbonate (mEq) = 0.5 x weight (kg) x [desired bicarbonate – measured bicarbonate] • Give 1/2 of calculated dose as slow bolus & remaining 1/2 over 24 hrs.	• Metabolic acidosis usually improves w/ generous fluid & calorie support. [2] • Bicarbonate therapy is needed for severe metabolic acidosis. [3]
Hyperammonemia	• Hyperammonemia improves w/reversal of catabolism. • High-dose glucose infusion w/insulin infusion is helpful in achieving this goal. • If severe hyperammonemia & altered mental status persists after above measures, consider extracorporeal toxin removal procedures such as hemodialysis & hemofiltration.	Although IV sodium benzoate w/sodium phenylacetate have been used in such circumstances, their utility is doubtful.
Rhabdomyolysis	• Start IV fluid containing 10% dextrose & electrolytes as needed at 2x maintenance (in children) to provide adequate hydration & calories & ensure urine output of >3 mL/kg/hr to prevent acute renal failure. [4] • For adults, start IV fluid at 400 mL/hour; tailor to maintain urine output of ~200 mL/hr. [5] • If there is acute renal failure at presentation, consult nephrologist for hemodialysis.	• Avoid treatment of rhabdomyolysis by glucose-free hypotonic IV fluid such as 0.45 normal saline, as it will promote catabolism & worsen rhabdomyolysis. • If hyperglycemia develops due to high dextrose infusion, start insulin infusion.
Cardiac failure	Manage cardiac failure due to cardiomyopathy in collaboration w/cardiologist.	Consider triheptanoin for those persons not taking it, as it was reported to be useful in mgmt of acute cardiomyopathy. [6]

IV = intravenous; LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; TFP = trifunctional protein

1. Monitor blood glucose levels every 1-2 hours initially.

2. Intralipid administration is contraindicated; supplemental calories should be provided in the form of carbohydrates.

3. Note that bicarbonate therapy alone is not sufficient to correct the metabolic acidosis. Correction of metabolic acidosis relies on reversing the catabolic state by providing calorie support from glucose.

4. Szugye [2020]

5. Bosch et al [2009]

6. Triheptanoin was found to be useful in management of cardiomyopathy in both chronic and acute settings [Vockley et al 2016].

Prevention of Primary Manifestations

Avoidance of fasting and supplementation with medium-chain triglycerides (MCT) or triheptanoin remains the mainstay of treatment. Early diagnosis and strict dietary therapy may prevent or delay the onset or slow the progression of long-term complications [Fletcher et al 2012, Fahnehjelm et al 2016, Immonen et al 2016b, De Biase et al 2017, Fraser et al 2019, Dulz et al 2021, Grünert et al 2021].

Education of parents and caregivers is critical to ensure diligent observation and timely initiation of treatment in the setting of intercurrent illness or other catabolic stressors. Prompt administration of high dextrose-containing intravenous fluids is essential to avoid complications such as hypoglycemia, liver failure, rhabdomyolysis, encephalopathy, and coma.

Written protocols for emergency treatment (see Table 8) should be provided to parents, primary care providers / pediatricians, teachers, and school staff. Emergency letters should summarize key information and principles of emergency treatment for LCHAD/TFP deficiency and contain contact information for the primary treating

metabolic center. For any planned travel or vacations, consider contacting a center of expertise near the destination prior to travel dates.

Table 8. Sample Emergency Management Protocol for Individuals with LCHAD/TFP Deficiency

Name:	
Date of birth:	
Medical record number:	
Diagnosis	This person has been diagnosed with long-chain hydroxyacyl CoA dehydrogenase deficiency (LCHAD) / trifunctional protein (TFP) deficiency. LCHAD/TFP deficiency is an inherited disorder of fatty acid metabolism.
Warning signs/symptoms	Intercurrent infections, poor oral intake, vomiting, or diarrhea can precipitate metabolic decompensation leading to vomiting, lethargy, hypoglycemia, metabolic acidosis, lactic acidosis, and muscle breakdown. Prompt provision of adequate calories (reversal of catabolism) and IV fluids is essential. If not adequately treated, individuals can develop severe hypoglycemia, liver failure, heart failure, muscle breakdown, kidney failure, and permanent neurologic damage. Severe morbidity and even death can occur.
Emergency room management	• Start IV fluid immediately even if not clinically dehydrated with 10% dextrose & appropriate electrolytes at 1.5x maintenance rate. It is imperative to prevent or reverse catabolism immediately. • Correct metabolic acidosis by giving sodium bicarbonate if acidosis is severe (pH <7.10 or bicarbonate <10mEq/L). • Do not wait for results of laboratory evaluation before starting IV fluids with glucose. • Monitor blood glucose levels every 1-2 hours initially and maintain glucose levels at >100 mg/dL.
Laboratory evaluation (and other recommended evaluations)	Urgent labs/procedures: • Blood gas – arterial or venous (e.g., w/i-STAT®), ammonia, lactic acid • Glucose, liver transaminases (AST, ALT) • Electrolytes with bicarbonate, BUN, creatinine • CK • CBC with differential & additional evaluation when infection is suspected • EKG, echocardiography Additional labs to be sent if feasible: • Plasma free & total carnitine • Plasma acylcarnitine profile • Urine organic acids
Metabolic center contact	*[Emergency contact phone/pager of the individual's metabolic center should be provided here.]* Stabilization of the affected individual should be the first priority.

ALT = alanine transaminase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CK = creatine kinase; IV = intravenous; LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; TFP = trifunctional protein

Surveillance

There are no current published guidelines for surveillance. In addition to regular evaluations by a metabolic specialist and metabolic dietician, the evaluations in Table 9 are recommended.

Table 9. Recommended Surveillance for Individuals with LCHAD/TFP Deficiency

Manifestation	Evaluation	Frequency/Comment
Metabolism	Nutritional mgmt	At each visit. Frequency of visits is determined by clinical severity. Follow-up interval can be adjusted based on metabolic control. A rough guideline (by age): • <1 yr: weekly to monthly • 1-7 yrs: every 1-6 mos • >7 yrs: every 6-12 mos
	Comprehensive fatty acid profile to assess for essential fatty acid deficiency [1]	Annually
	Plasma free & total carnitine, acylcarnitine profile, CK, AST, ALT	Recommended frequency (by age): • <1 yr: every 3 mos • 1-7 yrs: every 3-6 mos • >7 yrs: every 6-12 mos
Growth	Measurement of head circumference & growth	At each visit throughout childhood
Development	Monitoring of developmental milestones	
	• Neuropsychological testing using age-appropriate standardized assessment batteries • Standardized quality of life assessment tools for affected persons & parents/caregivers	As needed
Cardiomyopathy	EKG & echocardiography	Annually or more frequently for severe presentation
Peripheral neuropathy	Neurology eval	Annually
	NCV & EMG	As needed
Retinopathy	Ophthalmology eval	Annually
	ERG	Every 2-3 yrs

ALT = alanine transaminase; AST = aspartate aminotransferase; CK = creatine kinase; NCV = nerve conduction velocity test; EMG = electromyography; ERG = electroretinography; LCHAD = long-chain hydroxyacyl-CoA dehydrogenase; TFP = trifunctional protein
1. Affected individuals are at risk of developing essential fatty acid deficiency as a result of a diet restricted in long-chain fat.

Agents/Circumstances to Avoid

Avoid the following:

- Fasting, including periods of preparation and recovery from planned surgery or anesthesia
- Inadequate caloric provision during stressors, especially when fasting is involved (surgery or procedure requiring fasting/anesthesia)
- Inadequate calories following vaccination

  Note: Vaccination is safe.
- Dehydration (risk for rhabdomyolysis and acute renal failure)
- High-fat diet including ketogenic or carbohydrate-restricted diets for the purpose of weight loss, such as Atkins diet

- Administration of intravenous intralipids during an acute metabolic crisis

Anesthetics that contain high doses of long-chain fatty acids (e.g., propofol, etomidate) are avoided in long-chain fatty acid oxidation defects. However, a retrospective analysis revealed no adverse events with propofol for short-duration procedures in individuals with LCHAD/TFP deficiency [Martin et al 2014]. A combination of midazolam, thiopental, fentanyl, and remifentanil was used successfully in an individual with LCHAD deficiency [Steinmann et al 2010].

Evaluation of Relatives at Risk

At-risk sibs of any age. Testing of all at-risk sibs of any age is warranted to identify as early as possible those who would benefit from institution of treatment and preventive measures (see Management, Prevention of Primary Manifestations).

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, obtain a plasma acylcarnitine profile, plasma free and total carnitine, and urine organic acid profile.

Newborn sibs. For at-risk newborn sibs when prenatal testing was not performed: in parallel with newborn screening (NBS)* either test for the familial *HADHA* or *HADHB* pathogenic variants or obtain a plasma acylcarnitine profile, plasma free and total carnitine, and urine organic acid profile.

* The following medical interventions need to begin immediately on receipt of an abnormal NBS result while additional testing is performed to determine whether the abnormal screen represents a true positive NBS result and to establish a definitive diagnosis of LCHAD/TFP deficiency:

- Evaluation of the newborn to ascertain clinical status
- Education of the caregivers to avoid prolonged fasting and to monitor for decreased oral intake, vomiting, or lethargy
- Immediate intervention (to be considered if the newborn is not doing well clinically) possibly including admission to the hospital, fluid resuscitation, infusion of IV dextrose (≥10%), and cardiac evaluation

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

Pregnancy Management

Labor and postpartum periods are catabolic states and place the mother at higher risk for rhabdomyolysis and myoglobinuria. A successful pregnancy in a female with LCHAD deficiency has been reported [van Eerd et al 2017]. Management included increasing MCT intake in the third trimester and high dextrose infusion in the peripartum period.

Maternal complications such as HELLP syndrome and acute fatty liver of pregnancy are seen in an estimated 15%-25% of pregnancies in women carrying a fetus affected with LCHAD/TFP deficiency [den Boer et al 2002, Spiekerkoetter et al 2003, Karall et al 2015]. Pregnant females who are heterozygous for a *HADHA* or *HADHB* pathogenic variant (including suspected carriers) should be monitored for HELLP syndrome and acute fatty liver of pregnancy. Liver function testing should be performed at each prenatal visit during the first two trimesters and more frequently during the third trimester, when the risk for HELLP syndrome and acute fatty liver of pregnancy is the greatest. Management by a team comprising a maternal-fetal medicine specialist and a medical/biochemical geneticist is recommended.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Cardiac transplantation. Favorable outcome after cardiac transplantation in individuals with TFP deficiency has been reported [Bursle et al 2018]. However, it is expected that with timely diagnosis, strict dietary therapy, and MCT or triheptanoin supplementation, cardiac transplantation may not be required.

Bezafibrate is a hypolipidemic drug and an agonist of peroxisome proliferator-activated receptor (PPAR). It increases expression of several enzymes involved in mitochondrial fatty acid oxidation, including TFP [Djouadi et al 2016]. Bezafibrate was reported to have a favorable outcome in two individuals with TFP deficiency [Suyama et al 2020]. Bezafibrate is not available in the United States.

REN001 (Reneo Pharmaceuticals®) is a selective PPAR-δ agonist that increases transcription of genes involved in mitochondrial fatty acid oxidation. It has received orphan drug designation for LCHAD deficiency from the European Medicines Agency.

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

Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency and trifunctional protein (TFP) deficiency are 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 an *HADHA* or *HADHB* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *HADHA* or *HADHB* 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, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are not at risk of developing LCHAD/TFP deficiency. However, pregnant female carriers may be at risk of developing HELLP syndrome and acute fatty liver of pregnancy if the fetus has LCHAD/TFP deficiency (see Pregnancy Management).

Sibs of a proband

- If both parents are known to be heterozygous for an *HADHA* or *HADHB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Significant intrafamilial clinical variability may be observed between sibs who inherit the same biallelic *HADHA* or *HADHB* pathogenic variants. However, this variability is considered to stem primarily from environmental factors such as diet and the severity of infection triggering metabolic decompensation [Tyni & Pihko 1999, Bursle et al 2018, Wei et al 2020].
- Heterozygotes (carriers) are not at risk of developing LCHAD/TFP deficiency. However, pregnant female carriers may be at risk of developing HELLP syndrome and acute fatty liver of pregnancy if the fetus has LCHAD/TFP deficiency (see Pregnancy Management).

Offspring of a proband. The offspring of an individual with LCHAD/TFP deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *HADHA* or *HADHB*.

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

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *HADHA* or *HADHB* pathogenic variants in the family.

Note: Because biochemical analysis is usually normal in carriers, biochemical testing is not reliable for the detection of carriers.

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.
- Pregnant females who are heterozygous for an *HADHA* or *HADHB* pathogenic variant (including suspected carriers) should be monitored for HELLP syndrome and acute fatty liver of pregnancy (see Pregnancy Management).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *HADHA* or *HADHB* 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.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  LCHADD
- **MedlinePlus**
  Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
- **MedlinePlus**
  Mitochondrial trifunctional protein deficiency
- **STAR-G (Screening, Technology and Research in Genetics)**
  Email: info@newbornscreening.info
  LCHADD (Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency)
- **STAR-G (Screening, Technology and Research in Genetics)**
  Email: info@newbornscreening.info
  TFP (Trifunctional protein deficiency)
- **FOD Family Support Group (Fatty Oxidation Disorder)**
  Phone: 517-381-1940
  Email: deb@fodsupport.org; fodgroup@gmail.com
  fodsupport.org
- **International Network for Fatty Acid Oxidation Research and Management**
  www.informnetwork.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state

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. Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HADHA	2p23.3	Trifunctional enzyme subunit alpha, mitochondrial	HADHA database	HADHA	HADHA

Table A. continued from previous page.

HADHB	2p23.3	Trifunctional enzyme subunit beta, mitochondrial	HADHB @ LOVD	HADHB	HADHB

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 Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency (View All in OMIM)

600890	HYDROXYACYL-CoA DEHYDROGENASE/3-KETOACYL-CoA THIOLASE/ENOYL-CoA HYDRATASE, ALPHA SUBUNIT; HADHA
609015	MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY 1; MTPD1
609016	LONG-CHAIN 3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY
620300	MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY 2; MTPD2

Molecular Pathogenesis

Mitochondrial fatty acid oxidation (beta-oxidation) is the primary pathway of energy production from fatty acids. Fatty acid undergoes repeated cycles of four steps inside mitochondria that result in the shortening of fatty acid by two carbon atoms and production of acetyl-coenzyme A (CoA), reduced nicotinamide adenine dinucleotide (NADH), and reduced flavin adenine dinucleotide ($FADH_2$). Acetyl-CoA can either be utilized to make ketone bodies or oxidized via the tricarboxylic acid cycle for energy generation. High-energy electrons in NADH and $FADH_2$ molecules are transferred to the electron transport chain for ATP generation. The first of these four steps are catalyzed by acyl-CoA dehydrogenase, while the last three are catalyzed by the mitochondrial trifunctional protein (TFP) (see Figure 1).

Mitochondrial TFP is an octamer composed of four alpha subunits (encoded by *HADHA*) and four beta subunits (encoded by *HADHB*). The alpha subunit catalyzes long-chain enoyl-CoA hydratase and long-chain 3-hydroxyacyl-CoA dehydrogenase activities, while the beta subunit catalyzes long-chain 3-ketoacyl-CoA thiolase activity.

In addition, the alpha subunit of TFP participates in cardiolipin remodeling, and TFP physically interacts with mitochondrial respiratory chain complex 1 [Taylor et al 2012, Miklas et al 2019, Wang et al 2019]. Resemblance of TFP deficiency to mitochondrial respiratory chain disorders (e.g., elevated lactic acid, cardiomyopathy, polyneuropathy, retinopathy) may be explained by these functional and physical interactions of TFP with the respiratory chain.

Mechanism of disease causation. Loss of function

Table 10. Notable *HADHA* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000182.5 NP_000173.2	c.1528G>C	p.Glu510Gln	Most common *HADHA* pathogenic variant; homozygous persons have LCHAD deficiency [Ijlst et al 1996]. Founder variant in persons of Kashubian ancestry [Piekutowska-Abramczuk et al 2010, Nedoszytko et al 2017].

LCHAD = long-chain hydroxyacyl-CoA dehydrogenase
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

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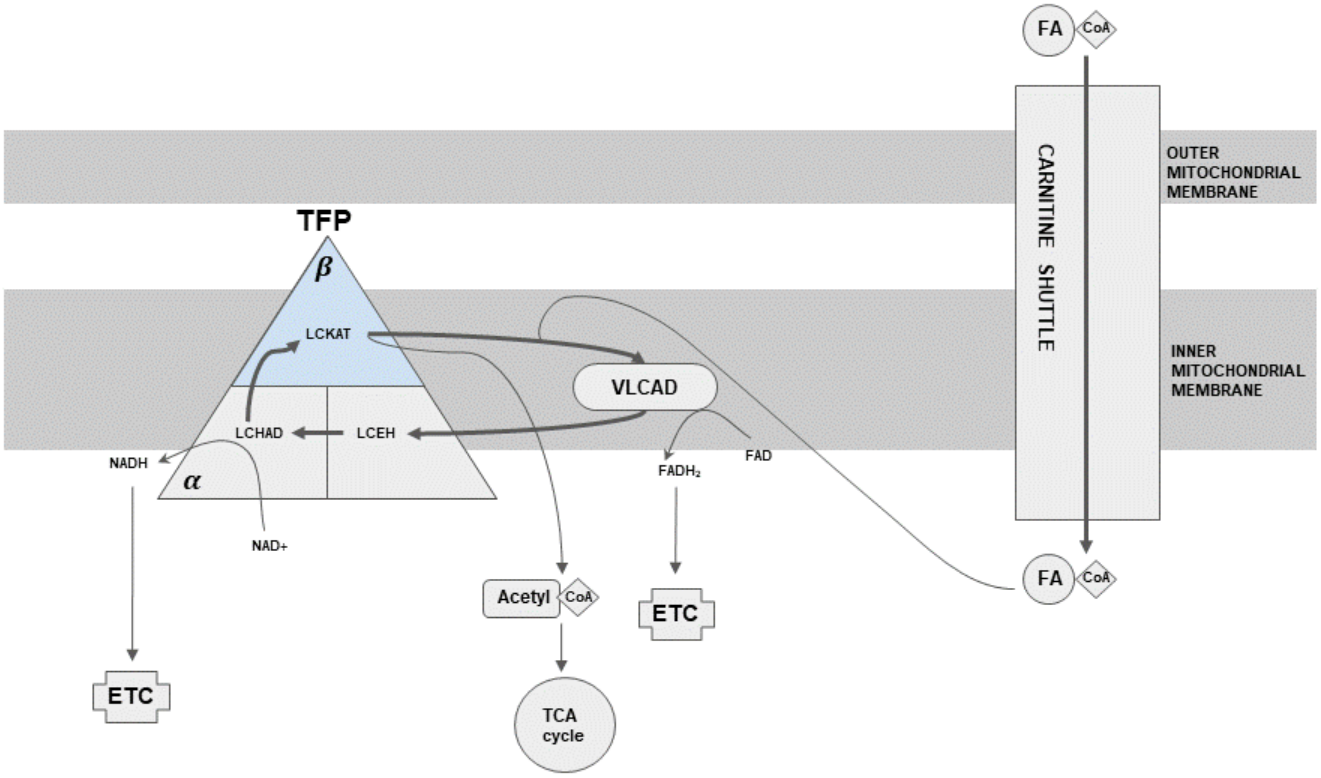

Figure 1. Mitochondrial fatty acid oxidation (beta-oxidation), the primary pathway of energy production from fatty acids

Activated long-chain fatty acyl-coenzyme A (CoA) is transported from the cytoplasm across the mitochondrial membrane by the carnitine shuttle. It then enters the cycle of beta-oxidation with a dehydrogenation reaction by very long-chain acyl-CoA dehydrogenase (VLCAD), producing reduced flavin adenine dinucleotide ($FADH_2$). Trifunctional protein (TFP) catalyzes the remainder of the cycle for long-chain substrates, reducing the fatty acyl-CoA by two carbons, and producing reduced nicotinamide adenine dinucleotide (NADH) and acetyl-CoA. Acetyl-CoA is metabolized by the tricarboxylic acid cycle for energy generation. NADH and $FADH_2$ donate the high-energy electrons captured by the dehydrogenase reaction to the electron transport chain (ETC).

TFP is embedded in the inner mitochondrial membrane and catalyzes the final three of the four steps of long-chain fatty acid beta-oxidation. It comprises four alpha and four beta subunits, encoded by *HADHA* and *HADHB*, respectively. The alpha subunit catalyzes long-chain enoyl-CoA hydratase (LCEH) and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) activities. The beta subunit catalyzes long-chain 3-ketoacyl-CoA thiolase (LCKAT) activity. LCHAD deficiency is associated with specific *HADHA* pathogenic variants where only dehydrogenase activity is impaired, whereas TFP deficiency is associated with either *HADHA* or *HADHB* pathogenic variants leading to instability of the entire complex and thus impairment of all three enzymatic activities.

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