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Multiple Acyl-CoA Dehydrogenase Deficiency

Synonyms: Electron Transfer Flavoprotein Dehydrogenase Deficiency, Glutaric Acidemia II, Glutaric Aciduria II, MADD

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Summary

Clinical characteristics

Multiple acyl-CoA dehydrogenase deficiency (MADD) represents a clinical spectrum in which presentations can be divided into type I (neonatal onset with congenital anomalies), type II (neonatal onset without congenital anomalies), and type III (late onset).

Individuals with type I or II MADD typically become symptomatic in the neonatal period with severe metabolic acidosis, which may be accompanied by profound hypoglycemia and hyperammonemia. Many affected individuals die in the newborn period despite metabolic treatment. In those who survive the neonatal period, recurrent metabolic decompensation resembling Reye syndrome and the development of hypertrophic cardiomyopathy can occur. Congenital anomalies may include dysmorphic facial features, large cystic kidneys, hypospadias and chordee in males, and neuronal migration defects (heterotopias) on brain MRI.

Individuals with type III MADD, the most common presentation, can present from infancy to adulthood. The most common symptoms are muscle weakness, exercise intolerance, and/or muscle pain, although metabolic decompensation with episodes of rhabdomyolysis can also be seen. Rarely, individuals with late-onset MADD (type III) may develop severe sensory neuropathy in addition to proximal myopathy.

Diagnosis/testing

The diagnosis of MADD is established in a proband with elevation of several acylcarnitine species in blood in combination with increased excretion of multiple organic acids in urine and/or by identification of biallelic pathogenic variants in *ETFA*, *ETFB*, or *ETFDH*.

Management

Treatment of manifestations: Routine daily treatment includes limitation of protein and fat in the diet, avoidance of prolonged fasting, high-dose riboflavin (100-300 mg daily), carnitine supplementation (50-100 mg/kg daily in 3 divided doses) in those with carnitine deficiency, and coenzyme Q_{10} supplements (60-240 mg daily in 2

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divided doses). Further treatments include feeding therapy with consideration of gastrostomy tube for those with failure to thrive, as well as standard treatment for developmental delay, cardiac dysfunction, and sensory neuropathy. Emergency outpatient treatment for mild decompensation includes decreasing the fasting interval, administration of antipyretics for fever, and antiemetics for vomiting. Acute treatment includes hospitalization with intravenous fluid containing at least 10% dextrose, and bicarbonate therapy depending on the metabolic status.

Prevention of primary manifestations: Avoidance of fasting and supplementation with riboflavin, L-carnitine, and coenzyme Q_{10}; a diet restricted in fat and protein is prescribed for some affected individuals based on the severity of the disorder.

Prevention of secondary complications: Education of parents and caregivers such that diligent observation and management can be administered expediently in the setting of intercurrent illness or other catabolic stressors. Prompt initiation of dextrose containing intravenous fluids is essential to avoid complications such as liver failure, rhabdomyolysis, encephalopathy, and coma. Written protocols for emergency treatment should be provided to parents and primary care providers/pediatricians, and to teachers and school staff.

Surveillance: Measurement of plasma free and total carnitine, acylcarnitine profile, serum creatine kinase (CK), urine organic acids, head circumference (in infants and children), and growth and developmental milestones at each visit; neuropsychological testing and standardized quality-of-life assessment tools for affected individuals and parents/caregivers as needed; EKG and echocardiogram annually for individuals with severe forms of MADD and less frequently for individuals with milder presentations.

Agents/circumstances to avoid: Inadequate caloric provision during stressors (including following vaccination); prolonged fasting; dehydration; high-fat, high-protein diet; volatile anesthetics and those that contain high doses of long-chain fatty acids; administration of intravenous intralipids during an 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 in parallel with plasma acylcarnitine profile, plasma free and total carnitine, and urine organic acid assay) to allow for early diagnosis and treatment of MADD.

Pregnancy management: Successful pregnancy with low-fat, high-carbohydrate diet in late-onset MADD has been published. There is no evidence to suggest that taking supplemental carnitine during pregnancy leads to adverse fetal effects. Riboflavin is a B vitamin and is considered an essential nutrient that is likely eliminated through feces and urine and does not result in excessive tissue absorption.

Genetic counseling

MADD is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% change of being affected, a 50% chance of being unaffected and a carrier, and a 25% change of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants have been identified in an affected family member.

Diagnosis

Formal clinical diagnostic criteria for multiple acyl-CoA dehydrogenase deficiency (MADD) have not been established.

Suggestive Findings

Scenario 1. Abnormal Newborn Screening (NBS) Result

NBS for MADD is primarily based on quantification of the analytes C4, C5, and C8 with or without other higher acylcarnitine species on dried blood spots.

Multiple acylcarnitine species (C4, C5, C8, and other higher acylcarnitine) 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 (see Supportive Laboratory Findings, **Specific findings**).

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

Medical interventions (see Management) need to begin immediately on receipt of an abnormal NBS result while additional testing is being performed to confirm the diagnosis.

Note: The most severe neonatal-onset form of MADD presents in the newborn period despite initiation of treatment. A newborn may become symptomatic before NBS is sent or resulted.

Scenario 2. Symptomatic Individual

Supportive – but often nonspecific – clinical findings, supportive laboratory findings, and other studies can include the following.

Clinical Findings

Neonatal onset

- Encephalopathy
- Tachypnea
- Hepatomegaly
- Hypotonia

Neonatal-onset form can present with or without congenital anomalies. When present, the main congenital anomalies are:

- Dysmorphic facial features (See Clinical Characteristics.)
- Dysplastic kidneys
- Rocker-bottom feet
- Hypospadias with or without chordee in males

Late onset (onset of signs and/or symptoms at any age beyond the neonatal period)

- Episodic vomiting with hypoglycemia and metabolic acidosis
- Muscle weakness and/or exercise intolerance
- Reye syndrome-like illness
- Rhabdomyolysis
- Acute respiratory failure

Supportive Laboratory Findings

Nonspecific findings

- Hypoglycemia (nonketotic or hypoketotic) with blood glucose often less than 45 mg/dL
- Urinalysis that demonstrates the absence of ketones in the setting of hypoglycemia

- Metabolic acidosis
- Hyperammonemia; blood ammonia level may be more than 200 µmol/L in newborns and more than 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 (range 1,000-100,000 IU/L) is suggestive of rhabdomyolysis.
  - A CK value of greater than 15,000 IU/L at presentation increases the risk for acute kidney injury [Bosch et al 2009].

Specific findings. The elevation of multiple acylcarnitine species of different length size in blood in combination with increased excretion of multiple organic acids in urine is highly suggestive of MADD.

- **Plasma acylcarnitine profile** typically shows elevations of C4, C5, C5DC, C6, C8, C10, C12, C14:1, C16, and C18:1.
- **Urine organic acid analysis** shows elevations of multiple organic acids, including:
  - Lactic acid
  - Glutaric acid
  - 2-hydroxyglutaric acid
  - 2-hydroxybutyric acid
  - 2-hydroxyisocaproic acid
  - 3-hydroxyisovaleric acid
  - 5-hydroxyhexanoic acid
  - Ethylmalonic acid
  - Adipic acid
  - Suberic acid
  - Sebacic acid
  - Other dicarboxylic acids
- **Urine acylglycine assay** shows elevations of:
  - Isobutyrylglycine
  - Isovalerylglycine
  - Hexanoylglycine
  - Suberylglycine

Note: Because elevations of these metabolites individually are not entirely specific to MADD and can be intermittent, follow-up testing is required to establish the diagnosis of MADD (see Establishing the Diagnosis).

Other Studies

Brain MRI may show increased signal intensity of periventricular white matter, basal ganglia, and corpus callosum in T_2-weighted images [Nyhan et al 2012, Vieira et al 2017]. In the most severe neonatal forms, subcortical heterotopias may be seen.

Muscle imaging, biopsy, and enzymology

- MRI of affected muscle group typically shows fatty infiltration and edema [Zhao et al 2018].
- Muscle biopsy outside an episode of rhabdomyolysis, in the late-onset form with myopathic presentation, shows extramitochondrial lipid accumulation characteristic of lipid storage myopathy, which may be accompanied by coenzyme Q_{10} deficiency [Liang & Nishino 2011, Whitaker et al 2015].
- Diminished activity of mitochondrial respiratory chain complexes has also been reported [Angelini et al 2018].

Note: Muscle imaging, biopsy, and enzymology are not required to establish the diagnosis of MADD.

Establishing the Diagnosis

The diagnosis of MADD **is established** in a proband with elevation of several acylcarnitine species in blood in combination with increased excretion of multiple organic acids in urine AND/OR by identification of biallelic pathogenic (or likely pathogenic) variants in *ETFA*, *ETFB*, or *ETFDH* (see Table 1).

Note: 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.

Molecular Genetic Testing Approaches

Scenario 1. Abnormal NBS result. When NBS results and other laboratory findings suggest the diagnosis of MADD, molecular genetic testing approaches can include **serial 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.
    1. Perform sequence analysis of *ETFDH* first. If only one pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
    2. Perform sequence analysis of *ETFA* or *ETFB* second. If only one pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
    3. Lastly, perform sequence analysis of the remaining gene. If only one pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *ETFA*, *ETFB*, *ETFDH*, 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.

Scenario 2. Symptomatic individual

- For a symptomatic individual who has findings associated with late-onset MADD OR neonatal-onset MADD 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 MADD 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 Multiple Acyl-CoA Dehydrogenase Deficiency

Gene [1, 2]	Proportion of MADD Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3, 4] Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
ETFA	5% [7]	~90% [8]	1 reported [9]
ETFB	2% [7]	~90% [10]	None reported [4]
ETFDH	93% [7]	~94% [11]	3 reported [12]
Unknown [13]	NA		

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 allelic variants detected in these genes.
4. Of note, many studies of *ETFA*, *ETFB*, and *ETFDH* did not include analysis for large deletions or duplications; therefore, deletions and duplications may be more common than reported. Sequencing studies do not routinely test for pathogenic variants deep in introns or in the promoter region.
5. 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. Although sequence analysis is sensitive in detecting the pathogenic variants mentioned here, it is important to remember that often only one pathogenic variant is detected, suggesting deep intronic or promoter region variants. For issues to consider in interpretation of sequence analysis results, click here.
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. The proportion of pathogenic variants listed here are specific for late-onset variant MADD (type III) (see also Phenotype Correlations by Gene). There is no database to determine what percentage of MADD is attributable to pathogenic variants in each gene. In a few case series, pathogenic variants in *ETFDH* accounted for approximately half of MADD cases, while those in *ETFA* and *ETFB* accounted for the remaining half with almost equal shares [Olsen et al 2003, Yotsumoto et al 2008].
8. Freneaux et al [1992], Purevjav et al [2002], Olsen et al [2003], Schiff et al [2006], Yotsumoto et al [2008], Stals et al [2018]
9. A deletion of exon 11 has been reported [Stals et al 2018].
10. Curcoy et al [2003], Olsen et al [2003], Schiff et al [2006], Yotsumoto et al [2008], Sudo et al [2015], Alfares et al [2017], Navarrete et al [2019]
11. Goodman et al [2002], Wen et al [2010], Wen et al [2013], Xi et al [2014]
12. A 312-bp deletion and two multiexon deletions have been reported [Wen et al 2010, Kim et al 2018].
13. Sometimes no pathogenic variant is found after sequencing all three genes, which may indicate other unidentified genetic etiologies for MADD.

Clinical Characteristics

Clinical Description

Multiple acyl-CoA dehydrogenase deficiency (MADD) represents a clinical spectrum in which individuals at the most severe end present with severe decompensation in the neonatal period either with or without congenital anomalies. Those on the milder end may present anytime beyond the neonatal period. They may present with metabolic decompensations when challenged by metabolic stressors, or with chronic symptoms of myopathy and exercise intolerance. Newborn screening (NBS) has enabled identification of asymptomatic newborns with late-onset forms. Early diagnosis and treatment may prevent complications in such cases. The clinical presentation can be divided into three categories according to severity – from most to least severe:

- **Type I.** Neonatal onset with congenital anomalies and metabolic decompensation
- **Type II.** Neonatal onset with metabolic decompensation without congenital anomalies
- **Type III.** Late onset with progressive or fluctuating muscle weakness and episodes of rhabdomyolysis

Neonatal Onset with Congenital Anomalies (Type I)

This group represents the most severe spectrum of MADD.

Metabolic decompensation. Newborns become symptomatic within a few hours after birth, often before NBS has been sent or results have become available. The most common presentation is severe metabolic acidosis leading to tachypnea and respiratory distress. This may be accompanied by profound hypoglycemia and hyperammonemia. Other features may include hypotonia and hepatomegaly. Often, there is a "sweaty feet" odor. The clinical condition typically deteriorates despite intervention and prognosis is very poor: most of these affected newborns have died in the first week of life.

Dysmorphic facial features. Often there are associated dysmorphic facial features. The most typical features:

- High anterior hairline
- Wide nasal bridge
- Short nose with anteverted nares and long philtrum
- Tented upper lip
- Midface retrusion
- Low-set ears

Renal. The characteristic renal malformation seen in affected newborns is large cystic kidneys. The kidneys may be huge and easily palpable. Antenatal oligohydramnios leading to Potter sequence may also be seen.

Genital. Both hypospadias and chordee have been described in affected males.

Musculoskeletal. Some affected infants have been found to have single palmar creases and/or rocker-bottom feet.

Neurologic. Affected newborns present with metabolic encephalopathy. Seizures secondary to profound hypoglycemia, electrolyte imbalances, or hyperammonemia may occur. Neuronal migration defects manifesting as heterotopia may be seen on brain MRI or autopsy.

Neonatal Onset Without Congenital Anomalies (Type II)

Newborns usually present within a few days after birth with metabolic decompensation as described above. The prognosis is very poor: most affected individuals do not survive the initial episode. Those who do survive usually die later in infancy either due to hypertrophic cardiomyopathy or recurrence of metabolic decompensation resembling Reye syndrome.

Late Onset (Type III)

This is the most common presentation. Signs and symptoms of late-onset MADD may become apparent any time from infancy to adulthood. In a cohort of 350 individuals with late-onset MADD, the mean age at diagnosis was 17.6 years with a range of 0.13 years to 69 years [Grünert 2014]. In this cohort, 33.1% of affected individuals had acute metabolic decompensation and 85.3% had chronic musculoskeletal symptoms consisting of muscle weakness, exercise intolerance, or muscle pain. About 20% of affected individuals had both acute metabolic decompensation episodes and chronic symptoms. Individuals with late-onset MADD frequently are detected as asymptomatic newborns through NBS. However, they may not have a known diagnosis of MADD at presentation because either NBS was not performed or was falsely negative.

Metabolic decompensation. Affected individuals may present with recurrent episodes of vomiting accompanied by nonketotic hypoglycemia, metabolic acidosis, and liver dysfunction, which is usually precipitated by metabolic stressors such as infection or fasting. Liver dysfunction, which manifests as liver enzyme elevations, hyperbilirubinemia, and coagulopathy, is reversible. If untreated, individuals may become encephalopathic.

Musculoskeletal. A majority of affected individuals develop chronic muscular symptoms such as muscle weakness, fatigue, myalgia, and exercise intolerance that responds to riboflavin treatment (see Management).

- The most common myopathic presentation is progressive or fluctuating proximal myopathy. Weakness of neck muscles and masseter is also commonly seen [Xi et al 2014].
- Progressive weakness may involve respiratory muscles leading to acute or subacute respiratory failure [Ersoy et al 2015].
- Rapidly progressive proximal myopathy and respiratory failure may mimic Guillain-Barre syndrome (GBS) [Hong et al 2018]. It is important to consider MADD in such scenarios, as early initiation of treatment with riboflavin may lead to complete resolution of symptoms in individuals with MADD.

  Electrophysiologic studies such as electromyography and nerve conduction velocity (NCV) are helpful in differentiating MADD from GBS, as these studies typically show evidence of peripheral nerve demyelination in GBS. However, further differentiation by plasma acylcarnitine profile and urine organic acid assay should be done promptly.
- Individuals with MADD are at risk of developing rhabdomyolysis, which may manifest during the acute episode of metabolic decompensation [Prasad & Hussain 2015].
- Bent spine syndrome characterized by progressive forward flexion of the trunk caused by selective involvement of paravertebral muscles has also been reported [Peng et al 2015].

Cardiac. Hypertrophic cardiomyopathy is seen in the severe neonatal-onset presentation. However, cardiac arrhythmias and diastolic dysfunction may occur during the metabolic decompensation in late-onset forms and can be fatal [Angle & Burton 2008, Xi et al 2014].

Neurologic. Rarely, individuals with late-onset MADD may develop severe sensory neuropathy in addition to proximal myopathy [Wang et al 2016]. The main symptoms of neuropathy are numbness of the extremities and sensory ataxia. NCV in these individuals shows severe axonal sensory neuropathy. Sensory neuropathy is not reversible with riboflavin treatment.

Biochemical Features

Elevations of several acylcarnitine species in blood in combination with increased exertion of multiple organic acids in urine are highly suggestive of MADD, as summarized in Supportive Laboratory Findings.

Plasma acylcarnitine profile. Individuals with the late-onset milder form may show a less dramatic profile with elevation of only C6, C8, C10, and C12. Additionally, the acylcarnitine profile may be normal if performed during an asymptomatic phase in individuals with the late-onset form.

Plasma carnitine assay may show a very low free carnitine. In this setting the acylcarnitine profile may be falsely normal. Hence, in the setting of very low plasma free carnitine, the plasma acylcarnitine profile should be repeated after carnitine supplementation [Wen et al 2015].

Urine organic acid profile in those with the late-onset form may be less dramatic, with elevations of only ethylmalonic and adipic acids associated with mild dicarboxylic aciduria. Urine organic acid profile may be normal if performed during the asymptomatic phase in those with the late-onset form.

In vitro probe analysis. An individual's fibroblasts are incubated with palmitic acid and culture medium is assayed for acylcarnitine after 96 hours of incubation. There is substantial accumulation of C16 in severe forms, while the downstream acylcarnitines C14, C12, C10, and C8 are not increased. In contrast, C14, C12, C10, and C8 are increased in milder forms, while C16 is relatively lower [Endo et al 2010].

Phenotype Correlations by Gene

ETFDH. The majority of individuals with late-onset MADD (type III) have pathogenic variants in this gene [Grünert 2014].

ETFA* and *ETFB pathogenic variants are relatively more common in individuals with a neonatal presentation of MADD (types I and II) [Olsen et al 2003, Yotsumoto et al 2008].

Genotype-Phenotype Correlations

Genotype-phenotype correlation is seen in the three known genes that lead to MADD (*ETFA*, *ETFB*, and *ETFDH*) [Olsen et al 2003]. The information provided here applies to pathogenic variants in all three genes.

- Biallelic pathogenic null variants or pathogenic variants that severely affect mRNA expression or stability and result in total lack of protein cause the most severe form of MADD (i.e., neonatal onset with congenital malformations [type I]).
- Pathogenic variants that affect the active site and/or pathogenic splice site variants giving rise to very low residual enzyme activity more often lead to neonatal presentation without congenital anomalies (type II).
- Affected individuals who have at least one pathogenic missense variant that does not affect the active site, mRNA expression, or mRNA stability typically have relatively high residual enzyme activity with resulting late onset and milder disease (type III).

Nomenclature

MADD was first described in 1976 in an infant with nonketotic hypoglycemia, metabolic acidosis, and strong "sweaty feet" odor [Przyrembel et al 1976]. Urine organic acid analysis revealed excretion of several organic acids including massive amounts of glutaric and lactic acids. This disorder was suspected to be due to abnormal metabolism of several acyl-CoA compounds and was named glutaric aciduria type 2 to distinguish it from glutaric aciduria type 1 due to glutaryl-CoA dehydrogenase deficiency, which was described a year before.

Prevalence

MADD is very rare. Exact prevalence is not known. Incidence at birth is estimated at 1:250,000 [Schulze et al 2003]. It is more common in China, where it is the most common cause of lipid storage myopathy [Xi et al 2014]. The carrier frequency of the pathogenic c.250G>A variant in Han Chinese is estimated at 1.35%, implying a disease prevalence of 1:22,000 in this population [Wang et al 2011].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ETFA*, *ETFB*, or *ETFDH*.

Differential Diagnosis

Disorders of Riboflavin Metabolism

Disorders of riboflavin metabolism can mimic multiple acyl-CoA dehydrogenase deficiency (MADD) (both biochemically and clinically) or have overlapping phenotypic features with MADD and should be considered as the primary differential diagnoses. With frequent use of exome sequencing, it is postulated that many individuals diagnosed with MADD of unknown genetic etiology will be identified as having a genetic alteration associated with a disorder of riboflavin metabolism.

Cellular uptake of riboflavin is mediated by the transmembrane proteins hRFVT1, hRFVT2, and hRFVT3 (encoded by *SLC52A1*, *SLC52A2*, and *SLC52A3*, respectively). Riboflavin is then converted to the coenzyme flavin mononucleotide by riboflavin kinase and then to flavin adenine dinucleotide (FAD) by FAD synthase (encoded by *FLAD1*).

FAD is a cofactor for electron transfer by the ETF/ETFDH complex from oxidations of fatty acids and some amino acids to the electron transport chain in the inner mitochondrial membrane [Watmough & Frerman 2010]. If FAD biogenesis is deficient, electron transfer by the ETF/ETFDH complex is compromised, which can result in a clinical presentation mimicking that of MADD (as MADD is caused by impairment of the ETF-ETFDH complex itself; see Molecular Genetics).

Table 2 summarizes disorders of riboflavin metabolism presenting as MADD or with overlapping phenotypic features with MADD that should be considered in the differential diagnosis.

Table 2. Riboflavin Metabolism Disorders to Consider in the Differential Diagnosis of MADD

Gene(s)	Disorder	MOI	Clinical Features	
			Overlapping w/MADD	Distinguishing from MADD
FLAD1	MADD-like illness (OMIM 255100)	AR	Presentation is similar to late-onset MADD w/lipid storage myopathy & similar biochemical abnormalities. [1]	• Assoc swallowing & speech difficulties usually seen • Respiratory difficulties → respiratory arrest is the usual outcome.
SLC52A1	Transient MADD-like illness in neonates (OMIM 615026)	AD	• Neonatal presentation w/poor feeding, lethargy, hypotonia, hypoglycemia, & hyperammonemia similar to neonatal-onset MADD [2] • Biochemical profile similar to MADD	• Transient presentation & dramatic improvement w/riboflavin supplementation • May be secondary to maternal heterozygous pathogenic variant → maternal riboflavin deficiency & secondary neonatal riboflavin deficiency [3]
SLC52A2 *SLC52A3*	Brown-Vialetto-Van Laere syndrome (See Riboflavin Transporter Deficiency Neuronopathy.)	AR	Biochemical profile similar to MADD	• Can present in infancy w/progressive neurologic deterioration, hypotonia, respiratory insufficiency, & early death, or later in life w/deafness & cranial nerve palsies • Riboflavin supplementation may improve symptoms.

AD = autosomal dominant; AR = autosomal recessive; MADD = multiple acyl-CoA dehydrogenase deficiency; MOI = mode of inheritance

1. Olsen et al [2016]

2. Mosegaard et al [2017]

3. Ho et al [2011]

Note: Many other inborn errors of metabolism (in additional to disorders of riboflavin metabolism) can have a very similar clinical presentation to MADD and should be considered in the differential diagnosis.

Neonatal-Onset MADD

Inborn errors of metabolism with neonatal onset and clinical similarities with MADD are summarized in Table 3.

Congenital anomalies. The severe neonatal-onset form of carnitine palmitoyltransferase II deficiency is the only disorder in Table 3 that is associated with congenital anomalies.

Table 3. Disorders with Neonatal Onset to Consider in the Differential Diagnosis of Multiple Acyl-CoA Dehydrogenase Deficiency

Gene	Disorder	MOI	Biochemical Profile / Comment
ACADVL	Very long-chain acyl-CoA dehydrogenase deficiency	AR	Profound nonketotic hypoglycemia mimics other FAO defects.
ASL	Argininosuccinate lyase deficiency	AR	Marked hyperammonemia mimics urea cycle defects.
ASS1	Citrullinemia type I	AR	
CPS1	Carbamoylphosphate synthetase I deficiency (See Urea Cycle Disorders Overview.)	AR	
CPT1A	Carnitine palmitoyltransferase 1A deficiency	AR	Profound nonketotic hypoglycemia mimics other FAO defects.
CPT2	Carnitine palmitoyltransferase II deficiency	AR	• Lethal neonatal form: hypoglycemia, hyperammonemia, & congenital anomalies (cystic kidney dysplasia & neuronal migration defects) • Severe infantile hepatocardiomuscular form: profound nonketotic hypoglycemia mimicking other FAO defects; not assoc w/congenital anomalies
HADHA	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	AR	Profound nonketotic hypoglycemia mimics other FAO defects.
HADHB	Trifunctional protein deficiency	AR	
OTC	Ornithine transcarbamylase deficiency	XL	Marked hyperammonemia mimics urea cycle defects.
SLC22A5	Systemic primary carnitine deficiency [1]	AR	Profound nonketotic hypoglycemia mimics other FAO defects.
SLC25A20	Carnitine-acylcarnitine translocase deficiency	AR	

AR = autosomal recessive; FAO = fatty acid oxidation; MADD = multiple acyl-CoA dehydrogenase deficiency; MOI = mode of inheritance; XL = X-linked

1. Acylcarnitine profile and urine organic acid profile are helpful in differentiating systemic primary carnitine deficiency and MADD; these tests are more useful during acute episodes and after carnitine supplementation.

Late-Onset MADD

Inborn errors of metabolism with late onset and clinical similarities with MADD are summarized in Table 4.

Table 4. Disorders with Late Onset to Consider in the Differential Diagnosis of MADD

Gene	Disorder	Associated Clinical Presentation(s)	
		Recurrent episodes of vomiting, nonketotic hypoglycemia, & liver dysfunction [1]	Exercise intolerance & muscle weakness
ACADM	Medium-chain acyl-coenzyme A dehydrogenase deficiency	+	
ACADVL	Very long-chain acyl-CoA dehydrogenase deficiency	+	+ [2]
ALDOA	GSD XII (OMIM 611881)		
CPT1A	Carnitine palmitoyltransferase 1A deficiency	+	

Table 4. continued from previous page.

Gene	Disorder	Associated Clinical Presentation(s)	
		Recurrent episodes of vomiting, nonketotic hypoglycemia, & liver dysfunction [1]	Exercise intolerance & muscle weakness
CPT2	Carnitine palmitoyltransferase II deficiency	+	+ [2]
ENO3	GSD XIII (OMIM 612932)		
LDHA	GSD XI (OMIM 612933)		
PFKM	GSD VII (OMIM 232800)		
PGAM2	GSD X (OMIM 261670)		
PGM1	GSD XIV (OMIM 614921)		
PYGM	GSD V		
SLC22A5	Systemic primary carnitine deficiency [3]	+	+
SLC25A20	Carnitine-acylcarnitine translocase deficiency	+	

All disorders in Table 4 are inherited in an autosomal recessive manner.
GSD = glycogen storage disease
1. Usually precipitated by infection or fasting
2. With recurrent rhabdomyolysis
3. Acylcarnitine profile and urine organic acid profile are helpful in differentiating systemic primary carnitine deficiency and MADD; these tests are more useful during acute episodes and after carnitine supplementation.

Lipid storage myopathy. Late-onset MADD is often diagnosed after muscle biopsy, which shows lipid storage myopathy (LSM). The differential diagnosis of LSM includes MADD, systemic primary carnitine deficiency (see Table 3 and Table 4), neutral lipid storage disease with ichthyosis, and neutral lipid storage disease with myopathy (see Table 5).

Table 5. Lipid Storage Myopathies to Consider in the Differential Diagnosis of MADD

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/MADD	Distinguishing from MADD
ABHD5	Neutral lipid storage disease with ichthyosis (OMIM 275630)	AR	Muscle weakness, exercise intolerance	Congenital ichthyosis; variable multisystemic presentation w/ID, cataract, & hepatic steatosis
PNPLA2	Neutral lipid storage disease with myopathy (OMIM 610717)	AR	Muscle weakness, exercise intolerance, muscle cramps	Acyl carnitine profile & urine organic acid profile are helpful in differentiating these conditions; these tests are more useful during acute episodes & after carnitine supplementation.

AR = autosomal recessive; ID = intellectual disability; MADD = multiple acyl-CoA dehydrogenase deficiency; MOI = mode of inheritance

Other

Inflammatory myopathies. Apart from genetic conditions, inflammatory myopathies, particularly polymyositis, mimic late-onset MADD with muscular presentation.

Management

When multiple acyl-CoA dehydrogenase deficiency (MADD) is suspected during the diagnostic evaluation (i.e., due to abnormal acylcarnitine profile and urine organic acids profile following a positive newborn screening, or evaluation of exercise intolerance and/or muscle weakness in adults), treatment should be initiated immediately.

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a multidisciplinary approach including multiple subspecialists, with oversight and expertise from a specialized metabolic center.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MADD, the evaluations in Tables 6 and 7 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis of MADD in a Neonate

System/Concern	Evaluation	Comment
Metabolic decompensation	Consult w/metabolic physician / biochemical geneticist & specialist metabolic dietitian. [1]	Transfer to specialist center w/experience in management of inherited metabolic diseases strongly recommended
	• STAT blood gas (arterial or venous), ammonia & lactic acid • Glucose, liver transaminases (AST, ALT) • Electrolytes w/bicarbonate, BUN, creatinine • CK • CBC w/differential & additional eval if infection suspected	Urgent labs to be obtained if acute metabolic crisis suspected
	Plasma free & total carnitine, plasma acylcarnitine profile, & urine organic acids	Obtain during a period of acute metabolic decompensation if possible.
Renal	Consider renal ultrasound.	To assess for renal cysts or malformations
Genital	Assessment for hypospadias & chordee	In males
Neurologic	Consider neurology consult.	Consider brain MRI to assess for brain malformations.
Cardiologic	Consider cardiology consult & echocardiography.	For eval of cardiomyopathy
Miscellaneous/ Other	Consult w/psychologist &/or social worker.	To ensure understanding of diagnosis & assess parental coping skills & resources

BUN = blood urea nitrogen; CBC = complete blood counts; CK = creatine kinase

1. After a new diagnosis of MADD in an infant, the closest hospital and local pediatrician should also be informed.

Table 7. Recommended Evaluations Following Initial Diagnosis of MADD in an Older Child, Adolescent, or Adult with Later-Onset Disease

System/Concern	Evaluation	Comment
Metabolic decompensation	Consult w/metabolic physician/biochemical geneticist & specialist metabolic dietitian.	Consider short hospitalization at center of expertise for inherited metabolic conditions to provide detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute metabolic crises) for caregivers.
	• STAT blood gas (arterial or venous), ammonia & lactic acid • Glucose, liver transaminases (AST, ALT) • Electrolytes w/bicarbonate, BUN, creatinine • CK • CBC w/differential & additional eval when infection is suspected.	Urgent labs to be obtained if acute metabolic crisis suspected
	Plasma free & total carnitine, plasma acylcarnitine profile, & urine organic acids	Obtain during a period of acute metabolic decompensation if possible.
	Assessment of feeding schedule	To avoid fasting (See Table 8.)
Development	Developmental assessment	To incl: • Motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Neurologic	Consider neurologist consult.	For eval of myopathy & sensory neuropathy
Cardiologic	Consider cardiologist consult & echocardiography.	For baseline cardiac eval & to rule out cardiomyopathy
Miscellaneous/ Other	Consult w/psychologist &/or social worker.	To ensure understanding of diagnosis & assess parents' / affected person's coping skills & resources

BUN = blood urea nitrogen; CBC = complete blood counts; CK = creatine kinase

Treatment of Manifestations

Table 8. Routine Daily Treatment in Individuals with MADD

Principle/Manifestation	Treatment	Remarks
Limitation of protein & fat	A diet high in carbohydrates & low in protein & fat is recommended.	• Diet should be started in consultation w/metabolic dietitian to ensure adequate metabolic control & appropriate growth in infants, children, & adolescents. • Late-onset MADD w/milder presentation may not require specialized diet.
Avoidance of fasting [1]	Between birth & age 3 mos: frequent feeds (every 2-3 hrs)	Feeding interval can be ↑ to 4 hrs if tolerated at 4 mos & by 1 hr every 2 mos after that, up to 8 hrs by 1 yr.
	• Between ages 1 & 2 yrs: fasting up to 10 hrs may be attempted. • After 2 yrs: fasting up to 12 hrs may be attempted.	• If hypoglycemia remains an issue, overnight feedings or 2 g/kg of uncooked cornstarch [2] at bedtime may be considered. • Decrease feeding interval by 50% during periods of illness (see Table 9).
Stabilization of ETF/ETFDH complex [3]	High-dose riboflavin (100-300 mg/day)	• Riboflavin supplementation should be tried in all persons w/MADD irrespective of the molecular genetic cause. • ~98% of persons w/late-onset MADD respond to riboflavin. [4]

Table 8. continued from previous page.

Principle/Manifestation	Treatment	Remarks
Carnitine deficiency	L-carnitine 50-100 mg/kg/day in 3 divided doses	
Secondary coenzyme Q_{10} deficiency [5]	Coenzyme Q_{10} supplement of 60-240 mg/day in 2 divided doses	• Coenzyme Q is the electron acceptor from ETF/ETFDH complex. • Like riboflavin, coenzyme Q_{10} supplementation should be tried in all persons w/MADD. • The antioxidant properties of coenzyme Q_{10} are also beneficial.
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Developmental delay / Intellectual disability	Interventions per developmental pediatrician / neurodevelopmental specialist	Incl PT, OT, & speech therapy as indicated
Cardiac dysfunction	Standard treatment per cardiologist	
Sensory neuropathy	Standard treatment per neurologist	Sensory neuropathy usually does not respond to riboflavin treatment.

MADD = multiple acyl-CoA dehydrogenase deficiency; OT = occupational therapy; PT = physical therapy
1. These represent general recommendations; no consensus guidelines on duration of fasting are available.
2. To ensure sufficient glucose supply overnight
3. Riboflavin is converted to FAD, which is a cofactor for both ETF and ETFDH. By increasing the FAD level, riboflavin supplementation in late-onset forms stabilizes the ETFDH enzyme and hence enhances its activity.
4. Grünert [2014]
5. Secondary coenzyme Q_{10} deficiency in persons with MADD has been documented [Cornelius et al 2013].

Table 9. Emergency Outpatient Treatment in Individuals with MADD

Manifestation/Concern	Treatment	Consideration/Other
Metabolic decompensation/ hypoglycemia [1]	Decrease fasting interval by 50% of non-sick-day duration.	See Table 8 for recommended maximal fasting intervals at baseline.
Fever	Administration of antipyretics (acetaminophen, ibuprofen) if temperatures rises >38.5°C	• If ↓ PO intake, vomiting, or lethargy: start emergency inpatient treatment (see Table 10). • There should be low threshold for starting inpatient management for infants & young children.
Occasional vomiting	Antiemetics	Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food & beverages at home or w/transfer to hospital.

PO = oral
1. Parents or local hospitals should immediately inform the designated metabolic center if: (a) temperature rises above 38.5°C; (b) persistent vomiting/diarrhea or other symptoms of intercurrent illness develop; or (c) new neurologic symptoms occur.

Acute manifestations (e.g., lethargy, encephalopathy, intractable vomiting, seizures, or progressive coma) often occur in the setting of intercurrent illness and/or inadequate caloric intake due to poor appetite or prolonged fasting. These should be managed with generous caloric support in a hospital setting. Identification and treatment of any suspected or proven infection should be done simultaneously.

Table 10. Acute Inpatient Treatment in Individuals with MADD

Manifestation/Concern	Treatment	Consideration/Other
Hypoglycemia	IV fluid should be started w/high-dose glucose (8-12 mg/kg/min for young patients) to maintain blood glucose >100 mg/dL [1]	• High-dose glucose needed to avoid catabolism • If hyperglycemia: start insulin infusion rather than ↓ glucose infusion rate.
Metabolic acidosis	• For severe metabolic acidosis (pH <7.10): initiate bicarbonate therapy. • A common formula for bicarbonate dose is: bicarbonate (mEq) = 0.5 x weight (kg) x [desired bicarbonate - measured bicarbonate] • Give half of calculated dose as slow bolus & remaining half 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. • If severe hyperammonemia & altered mental status persists after above measures, consider extracorporeal toxin removal procedures (e.g., hemodialysis, hemofiltration).	Although IV sodium benzoate w/sodium phenylacetate has been used in such circumstances, utility is doubtful.
Rhabdomyolysis	• Start IV fluid containing 10% dextrose & electrolytes as necessary at 1.5-2x maintenance to provide adequate hydration & calories, & ensure a urine output of >3 mL/kg/hr to prevent acute renal failure. • If there is acute renal failure at presentation, a nephrologist should be consulted for hemodialysis.	• Avoid treating rhabdomyolysis w/ glucose-free IV fluid such as 0.45% normal saline, as it will promote catabolism & worsening of rhabdomyolysis. • If hyperglycemia develops due to high dextrose infusion, start insulin infusion.
Carnitine deficiency	If severe carnitine deficiency or carnitine depletion: start IV levocarnitine at 50-100 mg/kg/day in 4 divided doses.	In less severe carnitine deficiency: start oral levocarnitine once affected person is stable because of concern for cardiac arrhythmias due to accumulation of long-chain acylcarnitines during acute metabolic crisis.

Note: For late-onset MADD, oral riboflavin should be initiated as soon as possible (see Table 8).
IV = intravenous; mEq = milliequivalent
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.

Prevention of Primary Manifestations

Avoidance of fasting and supplementation with riboflavin remains the mainstay of treatment. In addition, L-carnitine supplementation to maintain normal carnitine level and coenzyme Q_{10} supplementation is beneficial. A diet restricted in fat and protein is prescribed for some affected individuals based on the severity of the disorder (see Treatment of Manifestations).

Prevention of Secondary Complications

One of the most important components of management (as it relates to prevention of secondary complications) is education of parents and caregivers such that diligent observation and management can be administered expediently in the setting of intercurrent illness or other catabolic stressors. Prompt initiation of dextrose-

containing intravenous fluids is essential to avoid complications such as liver failure, rhabdomyolysis, encephalopathy, and coma.

Written protocols for emergency treatment (see Table 11) should be provided to parents, primary care providers/pediatricians, and teachers and school staff. Emergency letters should summarize key information and principles of emergency treatment for MADD 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 11. Sample Emergency Management Protocol for Individuals with MADD

Patient identification details	Name: _____ Date of birth: _____ Medical record number: _____
Diagnosis	This individual has been diagnosed with multiple acyl-CoA dehydrogenase deficiency (MADD). MADD is an inherited disorder of fatty acid and amino acid metabolism.
Warning signs/ symptoms	Intercurrent infections, poor oral intake, vomiting, or diarrhea can precipitate metabolic decompensation leading to vomiting, lethargy, metabolic acidosis, lactic acidosis, and coma. Prompt provision of adequate calories (reversal of catabolism) and intravenous fluids are essential. If not adequately treated, patients can develop severe hypoglycemia, liver failure, muscle breakdown, kidney failure, and permanent neurologic damage. Severe morbidity and even death can occur.
Emergency room management	• Start intravenous fluid immediately even if not clinically dehydrated with 10% dextrose and appropriate electrolytes at 1.5 times 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 <10 mEq/L). • Do not wait for results of laboratory evaluation before starting intravenous fluids with glucose. • Monitor blood glucose levels every 1-2 hours initially and maintain glucose levels above 100 mg/dL.
Laboratory evaluation	Urgent labs: • STAT blood gas (arterial or venous), ammonia, and lactic acid • Glucose, liver transaminases (AST, ALT) • Electrolytes with bicarbonate, blood urea nitrogen (BUN), creatinine • Creatine kinase (CK) • Complete blood counts (CBC) with differential and additional evaluation when infection is suspected. Additional labs to be sent if feasible: • Plasma free and total carnitine, plasma acylcarnitine profile, urine organic acids
Metabolic center contact	Emergency contact phone or pager of the patient's metabolic center should be provided here. Stabilization of the patient should be the first priority.

Surveillance

Published guidelines for surveillance are not currently available. In addition to regular evaluations by a metabolic specialist and metabolic dietician, the evaluations in Table 12 are recommended.

Table 12. Recommended Surveillance for Individuals with MADD

Manifestation/Concern	Evaluation	Frequency/Comment
Metabolic control	Plasma free & total carnitine, acylcarnitine profile, CK, & urine organic acid	At each visit
Poor growth	Measurement of head circumference [1] & growth	
Delayed acquisition of developmental milestones	Monitor developmental milestones.	
	Neuropsychological testing using age-appropriate standardized assessment batteries	As needed
	Standardized quality-of-life assessment tools for affected persons & parents/caregivers	
Cardiomyopathy	EKG, echocardiography	Annually for severe forms; less frequently for milder presentations

CK = creatine kinase
1. In infants and children

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. Vaccination is safe.
- Dehydration (risk for rhabdomyolysis and acute renal failure)
- High-fat, high-protein diet, including ketogenic or carbohydrate-restricted diets for the purpose of weight loss, such as Atkins diet
- Volatile anesthetics and those that contain high doses of long-chain fatty acids such as propofol and etomidate. However, a combination of low-dose propofol, fentanyl, and nitrous oxide was used successfully in an individual with MADD [Lilitsis et al 2017].
- Administration of intravenous intralipids during an acute metabolic crisis

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of MADD. For at-risk newborn sibs when prenatal testing was not performed: in parallel with newborn screening either test for the familial *ETFA*, *ETFB*, or *ETFDH* pathogenic variants (if known) or obtain plasma acylcarnitine profile, plasma free and total carnitine, and urine organic acid assay.

Acylcarnitine profile may be normal in the setting of low plasma free carnitine and should be repeated after carnitine supplementation in such cases.

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

Pregnancy Management

Successful pregnancy with a low-fat, high-carbohydrate diet in late-onset MADD has been published [Creanza et al 2018]. Protein intake was increased during the second and third trimesters to ensure adequate fetal growth. In addition, a higher dose of levocarnitine was needed. Supplementation with the pre-pregnancy riboflavin dose was continued throughout pregnancy.

No evidence suggests that taking supplemental carnitine during pregnancy leads to adverse fetal effects.

Riboflavin is a B vitamin and is considered an essential nutrient. There is limited published information on adverse pregnancy or fetal outcome with excessive riboflavin intake, although Rivlin [1978] reported that excess riboflavin was most likely eliminated through feces and urine and did not result in excessive tissue absorption.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

There are few experimental therapies for MADD. Only a few case reports are available to support their utility:

- **Sodium D,L-3 hydroxybutyrate (NaHB).** Favorable outcome after ketone body treatment has been reported [Van Hove et al 2003, Van Rijt et al 2014]. Ketone bodies not only replace the missing endogenous energy supply but also provide building blocks for myelin synthesis in the brain. Hence, it may be helpful in re-myelination as well as cardiomyopathy [Gautschi et al 2015].
- **Bezafibrate.** Bezafibrate is a hypolipidemic drug and an agonist of peroxisome proliferating activator receptor. It increases expression of several enzymes involved in mitochondrial fatty acid oxidation. Bezafibrate was reported to have favorable outcome on acylcarnitine profile in one affected individual and on skin fibroblasts from 12 people with MADD [Shioya et al 2014, Yamada et al 2017].

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.

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

Multiple acyl-CoA dehydrogenase deficiency (MADD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *ETFA*, *ETFB*, or *ETFDH* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ETFA*, *ETFB*, or *ETFDH* pathogenic variant and allow reliable recurrence risk assessment. (Although a *de novo* pathogenic variant has not been reported in MADD to date, *de novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *ETFA*, *ETFB*, or *ETFDH* 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 being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has MADD or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ETFA*, *ETFB*, or *ETFDH*.

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

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *ETFA*, *ETFB*, or *ETFDH* pathogenic variants in the family.

Biochemical testing. Biochemical testing for carrier detection is not useful, as there is no abnormal biochemical pattern in 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, clarification of carrier status, 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.

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

Molecular genetic testing. Once the *ETFA*, *ETFB*, or *ETFDH* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Biochemical testing. Biochemical testing for prenatal diagnosis is not reliable.

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.

- **STAR-G (Screening, Technology and Research in Genetics)**
  Glutaric Acidemia 2
- **FOD Family Support Group (Fatty Oxidation Disorder)**
  Phone: 517-381-1940

Email: deb@fodsupport.org; fodgroup@gmail.com
fodsupport.org

- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org

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. Multiple Acyl-CoA Dehydrogenase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ETFA	15q24.2-q24.3	Electron transfer flavoprotein subunit alpha, mitochondrial	ETFA database	ETFA	ETFA
ETFB	19q13.41	Electron transfer flavoprotein subunit beta	ETFB database	ETFB	ETFB
ETFDH	4q32.1	Electron transfer flavoprotein-ubiquinone oxidoreductase, mitochondrial	ETFDH database	ETFDH	ETFDH

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 Multiple Acyl-CoA Dehydrogenase Deficiency (View All in OMIM)

130410	ELECTRON TRANSFER FLAVOPROTEIN, BETA POLYPEPTIDE; ETFB
231675	ELECTRON TRANSFER FLAVOPROTEIN DEHYDROGENASE; ETFDH
231680	MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY; MADD
608053	ELECTRON TRANSFER FLAVOPROTEIN, ALPHA POLYPEPTIDE; ETFA

Molecular Pathogenesis

ETF is a heterodimer protein in the mitochondrial matrix composed of alpha (ETFA) and beta (ETFB) subunits. It accepts electrons from several acyl-coA dehydrogenases involved in fatty acid oxidation and also some dehydrogenases involved in amino acid and choline metabolism pathways. The electrons are then transferred to ETFDH, located in the inner mitochondrial membrane, which then transfers electrons to ubiquinone (coenzyme Q) in the electron transport chain. Hence, impairment of the ETF-ETFDH complex leads to multiple acyl-coA dehydrogenase deficiency (MADD) as well as impairment of the metabolism of several amino acids and choline. Some of the enzymes indirectly affected because of ETF-ETFDH complex impairment:

- Fatty acid oxidation
  - Short-chain acyl-CoA dehydrogenase
  - Medium-chain acyl-CoA dehydrogenase

- Very long-chain acyl-CoA dehydrogenase
- Amino acid metabolism
  - Isovaleryl CoA dehydrogenase (leucine metabolism)
  - Short-/branched-chain acyl-CoA dehydrogenase (isoleucine metabolism)
  - Isobutyryl CoA dehydrogenase (valine metabolism)
  - Alpha ketoadipic acid dehydrogenase, glutaryl CoA dehydrogenase (lysine and tryptophan metabolism)
- Choline metabolism
  - Dimethylglycine dehydrogenase
  - Sarcosine dehydrogenase

Mechanism of disease causation. MADD is caused by loss-of-function variants. Homozygous or compound heterozygous null pathogenic variants or pathogenic variants that severely affect mRNA expression or stability result in total lack of protein and cause the most severe form of MADD: neonatal onset with congenital malformations (type I). Pathogenic variants involving the active site and/or pathogenic splice site variants give rise to very low residual enzyme activity, leading to neonatal onset without congenital malformations (type II). Affected individuals who harbor at least one pathogenic missense variant not affecting the active site, mRNA expression, or stability have relatively high residual activity, and subsequently milder, late-onset disease (type III) [Olsen et al 2003].

Table 13. MADD: Notable Pathogenic Variants by Gene

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
ETFA	NM_000126.3 NP_000117.1	c.797C>T	p.Thr266Met	A common pathogenic variant [Freneaux et al 1992]; assoc w/neonatal-onset MADD
ETFDH	NM_004453.4 NP_004444.2	c.250G>A	p.Ala84Thr	A common pathogenic variant in southern China, considered a founder variant in Han Chinese population [Xi et al 2014]; assoc w/ late-onset MADD
		c.770A>G	p.Tyr257Cys	Common pathogenic variants in China [Xi et al 2014]; assoc w/late-onset MADD
		c.1227A>C	p.Leu409Phe	

Variants listed in the table have been provided by the author. *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

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