U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Chang IJ, Lam C, Vockley J. Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency. 2000 Apr 20 [Updated 2024 Sep 26]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Synonym: MCAD Deficiency

Irene J Chang, MD, MSc,[1] Christina Lam, MD,[2] and Jerry Vockley, MD, PhD[3]

Created: April 20, 2000; Updated: September 26, 2024.

Summary

Clinical characteristics

Individuals with medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency typically appear normal at birth, and many are diagnosed through newborn screening programs. Symptomatic individuals experience hypoketotic hypoglycemia in response to either prolonged fasting (e.g., weaning the infant from nighttime feedings) or during intercurrent and common infections (e.g., viral gastrointestinal or upper respiratory tract infections), which typically cause loss of appetite and increased energy requirements when fever is present. Untreated severe hypoglycemic episodes can be accompanied by seizures, vomiting, lethargy, coma, and death. Metabolic decompensation during these episodes can result in elevated liver transaminases and hyperammonemia. Individuals with MCAD deficiency who have experienced the effects of uncontrolled metabolic decompensation are also at risk for chronic myopathy. Early identification and avoidance of prolonged fasting can ameliorate these findings. However, children with MCAD deficiency are at risk for obesity after initiation of treatment due to the frequency of feeding.

Diagnosis/testing

The diagnosis of MCAD deficiency is established in a proband through biochemical testing (prominent accumulation of C8-acylcarnitine (octanoylcarnitine) with lesser elevations of C6-, C10-, and C10:1-acylcarnitines and elevated C8/C2 and C8/C10 ratios) AND/OR by identification of biallelic pathogenic variants in *ACADM* by molecular genetic testing OR by significantly reduced activity of MCAD activity in blood or cultured skin fibroblasts. Because of its relatively high sensitivity, *ACADM* molecular genetic testing can obviate the need for enzymatic testing, which is available only in limited academic centers.

Author Affiliations: 1 Assistant Professor, University of California at San Francisco, San Francisco, California; Email: irene.chang@ucsf.edu. 2 Associate Professor, University of Washington; Seattle Children's Hospital, Seattle, Washington; Email: christina.lam@seattlechildrens.org. 3 Professor, University of Pittsburgh, Pittsburgh, Pennsylvania; Email: vockleyg@upmc.edu.

Management

Treatment of manifestations: For routine daily treatment, fasting should be avoided and may require frequent feeding (every 2-3 hours) in infancy, overnight feeding, a bedtime snack, or 2 g/kg of uncooked cornstarch to maintain blood glucose levels during sleep. A normal, healthy diet containing no more than 30% of total energy from fat is recommended. All individuals with MCAD deficiency should avoid skipping meals and weight loss diets that recommend fasting. Prolonged or intense exercise should be covered by adequate carbohydrate intake and hydration. Intravenous glucose is recommended for surgical procedures that require several hours of fasting. Weight control measures such as regular education about proper nutrition and recommended physical exercise should be discussed to help avoid obesity. Standard treatment for developmental delay / aphasia, attention-deficit/hyperactivity disorder, and muscle weakness. For acute inpatient treatment, IV administration of glucose should be initiated immediately with 10% dextrose with appropriate electrolytes at a rate of 1.5 times maintenance rate or at 10-12 mg glucose/kg/minute to achieve and maintain a blood glucose level higher than 5 mmol/L, or between 120 and 170 mg/dL. Address electrolyte and pH imbalances with intravenous fluid management and initiate appropriate treatment for what triggered the metabolic stress.

Surveillance: Infants should establish care with a biochemical genetics clinic including a metabolic dietitian as soon as possible following a positive newborn screen. A metabolic dietician should be involved to ensure proper nutrition in terms of quality and quantity. Affected infants should be seen in team clinic in two to three months, then every six to 12 months if otherwise clinically well; however, the frequency of routine follow-up visits is individualized based on comfort level of the affected persons, their families, and health care providers. Routine assessments for growth, acquisition of developmental milestones, neurobehavioral issues, and secondary carnitine deficiency are recommended.

Agents/circumstances to avoid: Hypoglycemia; infant formulas, coconut oil, and other manufactured foods containing medium-chain triglycerides as the primary source of fat; popular high-fat/low-carbohydrate diets; alcohol consumption, in particular acute alcohol intoxication (e.g., binge drinking), which can elicit metabolic decompensation; aspirin.

Pregnancy management: Pregnant women who have MCAD deficiency must avoid catabolism. This is supported by several case reports describing carnitine deficiency, acute liver failure, and HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets) in pregnant women with MCAD deficiency.

Genetic counseling

MCAD deficiency is inherited in an autosomal recessive manner. At conception, the sibs of an affected individual are at a 25% risk of being affected, a 50% risk of being asymptomatic carriers, and a 25% risk of being unaffected and not carriers. Because of the high carrier frequency for the *ACADM* c.985A>G pathogenic variant in individuals of northern European origin, carrier testing should be discussed with reproductive partners of individuals with MCAD deficiency. Once both *ACADM* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for MCAD deficiency are possible.

Diagnosis

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is the most common inherited fatty acid beta-oxidation disorder; it leaves affected individuals unable to break down medium-chain fats for energy. Fatty acid beta-oxidation produces reducing equivalents and tricarboxylic acid cycle intermediates for energy generation in all tissues during times of physiologic stress and fasting. It also fuels hepatic ketogenesis, a major source of energy for peripheral tissues after glycogen stores are depleted during prolonged fasting and periods of higher energy demands.

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for MCAD deficiency is primarily based on results of a quantitative acylcarnitine profile on dried blood spots (DBS). It is included in most NBS programs worldwide and in every state's NBS program in the United States.

Elevations of C8-acylcarnitine with lesser elevations of C6- and C10-acylcarnitine values above the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing. The cutoff values for C8 differ by NBS program and may be combined with elevated secondary markers (including C0, C2, and C10:1, and the ratios of C8/C2 and C8/C10) in presumptive positive cases to aid in NBS sensitivity.

- The 99th centile values in aggregate North American newborn screening samples are as follows (see Collaborative Laboratory Integrated Reports; subscription required, accessed 3-18-24):
  - C8 of 2.46 nmol/mL (n=1,832); however, due to differences in sample analysis, C8 values may not to be directly comparable to local results.
  - C6 of 2.44 nmol/mL (n=1,832)
  - C10 of 2.38 nmol/mL (n=1,869)
  - C10:1 of 2.44 nmol/mL (n=1,779)
  - C8/C2 ratio of 2.43 (n=1,896)
  - C8/C10 ratio of 2.53 (n=1,879)

  Note: (1) The positive predictive value for elevations of C8-acylcarnitines is currently considered to be very high with the use of tandem mass spectrometry (MS/MS). False positives for elevations of C8-acylcarnitines are not common but can be seen in term infants who are appropriate for gestational age and heterozygous for the common *ACADM* c.985A>G (p.Lys329Glu) pathogenic variant (see Table 1) and premature infants. In one study, individuals with a heterozygous *ACADM* 985A>G pathogenic variant had C8 level >90th centile; in 17 positive samples with concentrations of C8 between 0.5-0.7 µmol/L, 8/17 were heterozygous for this pathogenic variant [Blois et al 2005]. (2) False negatives have been reported in newborns with low free carnitine levels, such as infants born to a mother with low free carnitine levels due to previously undiagnosed maternal MCAD deficiency, maternal carnitine transporter deficiency, or nutritional carnitine deficiency [Leydiker et al 2011, Aksglaede et al 2015].

- Follow-up testing includes (see also Establishing the Diagnosis, Biochemical Testing):
  - Plasma acylcarnitine analysis;
  - Urine organic acid analysis;
  - Urine acylglycine analysis;
  - Plasma free and total carnitine levels.

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

Published reports on NBS outcomes document that individuals identified and treated presymptomatically are protected from metabolic decompensations and relevant sequelae [Catarzi et al 2013, Tal et al 2015]. The following medical interventions need to begin immediately on receipt of an abnormal NBS result while confirmatory testing is performed:

- Avoidance of fasting
- Emergency management that includes supplying enteral or intravenous glucose if normal oral intake is interrupted

Note: A newborn whose blood sample has been submitted for NBS can become symptomatic before screening results are available. Severe and lethal presentations in the first days of life (i.e., before NBS results are available) have been reported [Andresen et al 2012, Lovera et al 2012, Tal et al 2015].

Scenario 2: Symptomatic Individual

A symptomatic individual who was previously healthy OR a person with sudden, unexpected death in whom NBS was not performed or caregivers were not adherent to recommended treatment following a positive NBS result may present with the following supportive – but nonspecific – clinical findings, preliminary laboratory/pathology findings, and family history.

Note: Late-onset presentations have been described in adults after prolonged fasting, including after fasting for surgery or with alcohol intoxication [Lang 2009].

Clinical findings

- Rapid clinical deterioration that is disproportionate in the setting of a common and generally benign infection
- Vomiting that can progress to lethargy, seizures, and coma triggered by a common illness
- Hepatomegaly and acute liver disease (sometimes confused with a diagnosis of Reye syndrome, which is characterized by acute noninflammatory encephalopathy with hyperammonemia, liver dysfunction, and fatty infiltration of the liver).
- Sudden and unexpected death, often with evidence of lethargy, vomiting, and/or fasting in the 48 hours prior to death

Preliminary laboratory/pathology findings

- Hypoketotic hypoglycemia
- Hyperammonemia, more typically in older infants who may have mildly elevated ammonia levels that are in the range of 1.5 to 2 times the normal
- Elevated liver function tests
- Autopsy demonstrating cerebral edema and fatty infiltration of the liver, kidneys, and heart

Note: Postmortem acylcarnitine analysis for MCAD deficiency can be performed on original NBS DBS cards, which can be stored at 4-8 °C for up to at least a decade [Kaku et al 2018].

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

Establishing the Diagnosis

The diagnosis of MCAD deficiency **is established** in a proband by confirmatory biochemical testing AND/OR by identification of biallelic pathogenic (or likely pathogenic) variants in *ACADM* by molecular genetic testing (see Table 1) OR by significantly reduced medium-chain acyl-CoA dehydrogenase enzyme activity in blood or cultured skin fibroblasts. Because of its relatively high sensitivity, *ACADM* molecular genetic testing can obviate the need for enzymatic testing, which is available only in limited academic centers.

Note: (1) Confirmatory postmortem testing is possible in the individual with sudden and unexpected death if MCAD deficiency is suspected. (2) Biochemical and molecular diagnostic methods for MCAD deficiency are sensitive enough to identify asymptomatic affected individuals without using provocative tests. (3) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to

include likely pathogenic variants. (4) Identification of biallelic *ACADM* variants of uncertain significance (or of one known *ACADM* pathogenic variant and one *ACADM* variant of uncertain significance) does not establish or rule out the diagnosis.

Biochemical Testing

Testing should include **plasma acylcarnitine analysis, urine organic acid analysis,** and **urine acylglycine analysis,** ideally collected during an acute episode of metabolic decompensation, as any of these assays can normalize when the individual is not under metabolic stress. Sole reliance on plasma acylcarnitine analysis can lead to a missed diagnosis.

- Plasma acylcarnitine analysis demonstrates:
  - Prominent accumulation of C8-acylcarnitine (octanoylcarnitine);
  - Lesser elevations of C6-, C10-, and C10:1-acylcarnitines;
  - Elevated C8/C2 and C8/C10 ratios.

  Note: Secondary decreased levels of free carnitine (C0) and acetylcarnitine (C2) can be present in carnitine deficiency and cause lower elevations of C8-, C6-, and C10-acylcarnitines, or even normal acylcarnitine profiles [Weiss et al 2023].
- Urine organic acid analysis during an acute episode demonstrates:
  - Elevated medium-chain dicarboxylic acids in a characteristic pattern of hexanoylglycine (C6) > octanoylglycine (C8) > decanoylglycine (C10);
  - Inappropriately low urine or serum ketones by serum beta-hydroxybutyrate analysis or urine organic acid analysis or ketostix;
  - Elevated suberylglycine and dicarboxylic acids (adipic, suberic, sebacic, dodecanedioic, and tetradecanedioic) on urine organic acids.

  Note: (1) Individuals receiving medium-chain triglyceride (MCT) oil supplements or MCT-containing foods (e.g., MCT-supplemented infant formulas, coconut oil) often have elevated concentrations of octanoic acid and decanoic acid in urine but have normal *cis*-4 decenoic acid and should not be interpreted as possibly having MCAD deficiency. (2) Urine organic acid analysis when asymptomatic and clinically stable is often uninformative and typically demonstrates undetectable urinary excretion of the three acylglycines (<10 mmol/mol creatinine).
- Urine acylglycine analysis demonstrates n-hexanoylglycine, 3-phenylpropionylglycine, and suberylglycine.

  Note: This test is more sensitive and specific for the identification of asymptomatic individuals, including newborns and immediately after birth, and those with mild or intermittent biochemical phenotypes that may be missed by organic acid analysis alone.

Molecular Genetic Testing

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

- **Single-gene testing.** Sequence analysis of *ACADM* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **A fatty acid oxidation disorders multigene panel** that includes *ACADM* 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 include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options 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 include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Scenario 2: Symptomatic individual. When the diagnosis of MCAD deficiency has not been considered because the individual was previously healthy OR an individual had sudden, unexpected death in whom NBS was not performed or caregivers were not adherent to recommended treatment following a positive NBS result, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best 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 Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ACADM	Targeted analysis	56%-91% [3]
	Sequence analysis [4]	98% [5]
	Gene-targeted deletion/duplication analysis [6]	Fewer than 10 reported [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. The c.985A>G (p.Lys329Glu) pathogenic variant accounts for between 56% and 91% of MCAD deficiency-causing alleles [Rhead 2006, Gramer et al 2015].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Enzyme Activity Analysis

Analysis of fatty acid beta-oxidation in cultured fibroblasts involves acylcarnitine analysis of culture medium or a mix of culture medium and disrupted cells following the incubation of fibroblast cultures with labeled or non-labeled palmitic acid and non-labeled L-carnitine [Schmidt-Sommerfeld et al 1998]. The accumulation of C6-, C7-, C8-, C9-, and C10-acylcarnitines as described for plasma analysis confirms the diagnosis [Matern 2014].

Noninvasive testing using palmitate in individuals with suspected fatty-acid oxidation defects involves identification of disease-specific acylcarnitine patterns and can help establish the diagnosis [Janzen et al 2017].

Measurement of MCAD enzyme activity in cultured fibroblasts or leukocytes using the electron transfer flavoprotein reduction assay shows <10% of normal exhibit MCAD enzymatic activity. Similar results are reported with a high-performance liquid chromatography method [Wanders et al 2010]. Another study investigating enzyme activity in fibroblasts found <35% activity in individuals with MCAD deficiency [Bouvier et al 2017].

- MCAD enzyme activity is routinely measured in the Netherlands and can guide NBS risk stratification [Jager et al 2019].
- Derks et al [2007] suggested that when residual MCAD enzyme activity in leukocytes is >10% of normal, prevention of fasting is not necessary for otherwise healthy individuals older than age six months [Touw et al 2013].

Confirmatory Postmortem Testing

Molecular genetic testing of *ACADM* using the postmortem blood spot or NBS blood spot retrieved from the screening laboratory can help confirm the diagnosis.

Note: Different screening jurisdictions store leftover DBS samples for variable lengths of time following NBS testing. These samples typically can be retrieved with parent/patient consent for retrospective biochemical or molecular genetic testing.

Clinical Characteristics

Clinical Description

Fatty acid beta-oxidation generates cellular energy in all tissues and fuels hepatic ketogenesis, a major source of energy for peripheral tissues once glycogen stores become depleted during prolonged fasting and/or periods of higher energy demands (see Molecular Genetics). The frequent feeding schedule of infants typically precludes the need for alternative energy sources, but as the interval between feeds increases, reliance on fatty acid catabolism commensurately increases. This can manifest in preprandial hypoglycemia symptoms such as lethargy, irritability, jitteriness, seizures, or hypoglycemic crisis. Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is a known cause of sudden infant death syndrome (SIDS).

MCAD Deficiency

Individuals with MCAD deficiency appear normal at birth and historically have presented between age two and 24 months, although presentations in adulthood have also been reported [Lang 2009]. MCAD deficiency is currently included in newborn screening (NBS) programs in all 50 states of the United States [Lindner et al 2010].

Hypoketotic hypoglycemia. Affected individuals tend to present in response to either prolonged fasting (e.g., weaning the infant from nighttime feedings) or during intercurrent and common infections (e.g., viral gastrointestinal or upper respiratory tract infections), which typically cause loss of appetite and increased energy requirements when fever is present.

- Hypoglycemic episodes can be accompanied by seizures.
- In a cohort of non-diabetic adults, MCAD deficiency was diagnosed in some individuals presenting with fasting hypoglycemia [Douillard et al 2012].
- Such instances of metabolic stress lead to vomiting and lethargy, which may quickly progress to coma and death.

- The presence of low levels of ketones on urinalysis, urine organic acids, or serum beta-hydroxybutyrate analysis should not be taken as evidence against MCAD deficiency ("hypoketotic" as compared to nonketotic), as ketones can be present during times of acute metabolic decompensation due to long-chain fatty acid oxidation.

Hepatomegaly can arise during an acute decompensation, which is also characterized by hypoketotic hypoglycemia, elevated liver transaminases, and hyperammonemia.

Sudden death. Sudden and unexpected death was historically common as the first manifestation of MCAD deficiency and still can occur as late as adulthood (e.g., precipitated by times of increased metabolic stress such as surgery or prolonged fasting).

- Historically, if the diagnosis of MCAD deficiency has not been previously established, between 18% to 25% of affected individuals died during their first metabolic crisis [Iafolla et al 1994].
- The advent of NBS has dramatically decreased the mortality of MCAD deficiency in the neonatal period to 0.6%-2.4% in screened populations [Mütze et al 2022].
- Early death due to severe hypoglycemia before the return of NBS results still occurs [Mütze et al 2022].
- Findings at autopsy include cerebral edema and fatty infiltration of the liver, kidneys, and heart.

Free carnitine deficiency can occur during acute decompensation or chronically due to renal excretion of free carnitine bound to the excess acylcarnitines that accumulate in MCAD deficiency.

Neurologic findings. Individuals with MCAD deficiency typically have no neurologic disease. However, individuals who have experienced the effects of an uncontrolled metabolic decompensation are at risk of losing developmental milestones and acquiring aphasia and attention-deficit/hyperactivity disorder, which are thought to be secondary to brain injury sustained during the acute metabolic event.

Muscular concerns. Individuals with MCAD deficiency who have experienced the effects of uncontrolled metabolic decompensation are also at risk for chronic myopathy, as observed in 18% of individuals who had several episodes of metabolic decompensation [Iafolla et al 1994]. In a long-term study of individuals with MCAD deficiency diagnosed prior to NBS, many reported fatigue, muscle pain, and reduced exercise tolerance. No abnormality in cardiac function was identified to explain these symptoms [Derks et al 2006]. Additionally, exertion-induced myalgias, progressive proximal limb muscle weakness, and dropped head syndrome have been reported in affected individuals [Vengalil et al 2017]. Muscle MRI showed moderate fibrofatty infiltration and variable myoedema.

Growth. Children with MCAD deficiency are at risk for obesity after initiation of treatment due to the frequency of feeding (rather than the inherent nature of the condition itself).

Arrhythmia. Cardiac symptoms in MCAD deficiency are rare but have been reported occasionally. The causality has not been definitively linked.

- Prolongation of the QTc interval has been reported in an affected infant and ventricular tachyarrhythmias in another [Yusuf et al 2010, Wiles et al 2014].
- A 16-year-old female presented with hepatic, renal, and cardiac failure after an alcoholic binge and subsequent period of starvation [Mayell et al 2007].
- An adult with MCAD deficiency also developed supraventricular tachycardia, ventricular tachycardia, and ultimately ventricular fibrillation resulting in cardiac arrest after presenting with vomiting and headaches in the setting of hyperammonemia and hypoglycemia [Feillet at al 2003].

Renal disease. Some studies have suggested that individuals with MCAD deficiency and other fatty acid disorders are at risk for chronic kidney disease as they age because renal proximal tubules contain a high concentration of mitochondria that express fatty acid enzymes. Autopsy findings associated with MCAD

deficiency have identified fatty infiltration of the kidney [Boles et al 1998]. However, frank kidney disease has not been reported in individuals with MCAD deficiency. Those with tubulointerstitial fibrosis have also been found to have lower expression of some fatty acid oxidation enzymes, leading to adenosine triphosphate depletion, apoptosis, and intracellular lipid deposition [Kang et al 2015].

"Mild" MCAD Deficiency

Often referred to as "asymptomatic" MCAD deficiency, this designation is not entirely accurate. The expansion of NBS programs using tandem mass spectrometry (MS/MS) led to the identification of affected individuals with milder abnormalities in their acylcarnitine profiles (see Genotype-Phenotype Correlations).

- Individuals with MCAD deficiency can remain asymptomatic, although whether this is attributable to early awareness of the condition, early initiation of treatment and resulting prevention of symptoms, or to a higher residual MCAD enzymatic activity remains to be determined.
- Individuals with a "milder" biochemical phenotype can still develop life-threatening symptoms [Fingerhut et al 2017].
- All individuals with MCAD deficiency should be considered at risk of developing clinical manifestations and should receive long-term follow up and management.

Genotype-Phenotype Correlations

A collaborative retrospective analysis of a cohort of 221 affected individuals identified by NBS in the United States showed that C8 level and genotype were significant predictors of neonatal symptoms. Individuals with neonatal symptoms had significantly higher C8 values [Bentler et al 2016]. While it appears that residual enzyme activity levels better correlate with phenotype [Touw et al 2013], it is reasonable to assume that environmental factors (e.g., diet, stress, or intercurrent illnesses) are critical in determining the natural history of this condition.

Several other genotype-phenotype correlations have been described:

- **c.199T>C (p.Tyr67His)** (previously known as Tyr42His). This pathogenic variant has an allele frequency of approximately 6% in MCAD-deficient newborns [Andresen et al 2001, Maier et al 2005, Waddell et al 2006, Nichols et al 2008] and is associated with some residual MCAD enzymatic activity [Andresen et al 2001]. People homozygous for this pathogenic variant, however, are probably not at risk to develop disease. Individuals who are heterozygous for the c.199T>C pathogenic variant and another pathogenic variant have lower acylcarnitine levels and are at risk for metabolic crisis [Gramer et al 2015].
- **c.600-18G>A (IVS7 as G-A -18).** Individuals with the compound heterozygous pathogenic variants c.600-18G>A and c.985A>G have a mild phenotype and may not be detected by NBS due to residual MCAD enzyme activity [Grünert et al 2015].
- **c.985A>G (p.Lys329Glu)** (previously known as p.Lys304Glu)
  - Individuals homozygous for the common European *ACADM* c.985A>G (p.Lys329Glu) pathogenic variant have the highest C8 NBS values and are most likely to have neonatal symptoms [Arnold et al 2010, Bentler et al 2016].
  - Those with less pronounced abnormalities in their acylcarnitine profiles are more likely to be compound heterozygotes either for the common pathogenic variant c.985A>G (p.Lys329Glu) and another pathogenic variant, or for two non-c.985A>G pathogenic variants [Maier et al 2005, Smith et al 2010].
  - Individuals homozygous for c.985A>G (p.Lys329Glu) had a mean C8 level of 13.8 µmol/L (range: 9-22 µmol/L), and compound heterozygotes had a mean C8 level of 2.6 µmol/L (range: 1.9-3.2 µmol/L) [Zytkovicz et al 2001, Blois et al 2005, Weiss et al 2023]. In another study, individuals homozygous for c.985A>G had higher NBS C8-carnitine (23.4 ± 19.6 vs 6.6 ± 3.0 µmol/L) and

lifetime plasma C8-carnitine levels (6.2 ± 5 vs 3.6 ± 1.9 µmol/L) compared to those with at least one other pathogenic variant ($p<0.001$ for both calculations) [Anderson et al 2020].

Note: Historically, variant nomenclature designated the first amino acid at p.1 of the mature protein, whereas current nomenclature designates the first amino acid at p.1 of the pro-protein.

Nomenclature

MCAD deficiency was first described in individuals presenting with a Reye-like phenotype and urine organic acid analysis that revealed overexcretion of medium-chain dicarboxylic acids and hexanoylglycine in the absence of significant ketosis [Kølvraa et al 1982, Roe et al 1986, Bzduch et al 2001]. Accordingly, it is likely that prior to MCAD deficiency having been delineated, affected individuals were misdiagnosed as having Reye syndrome.

Prevalence

The overall prevalence of MCAD deficiency is 5.3 (range: 4.1-6.7; 99% CI) in 100,000 births across a variety of populations [Feuchtbaum et al 2012] and one in 17,759 in the United States [Therrell et al 2014, Maier 2015]. MCAD deficiency is prevalent in individuals of (especially northern) European ancestry. The carrier frequency for the c.985A>G pathogenic variant in *ACADM* is between 1:40 and 1:100 in those of northern European ancestry, suggestive of a founder effect [Gregersen et al 1993, Tanaka et al 1997]. A similar prevalence has been observed among Portuguese individuals with Roma ancestry [Rocha et al 2014] and Native Americans of California [Feuchtbaum et al 2012].

The number of newborns detected with MCAD deficiency through NBS programs exceeds that expected based on the population frequency of the common c.985A>G pathogenic variant [Andresen et al 2001, Maier et al 2005, Wilcken et al 2009, Vilarinho et al 2010, Andresen et al 2012, Touw et al 2012].

The *ACADM* c.449_452delCTGA deletion is more prevalent in Asian (i.e., Taiwanese, Japanese, and Korean) populations [Woo et al 2011, Chien et al 2013, Hara et al 2016, Tajima et al 2016].

Based on NBS programs or pilot studies worldwide, the incidence of MCAD deficiency has been determined as follows:

- **Asia**
  - Japan. One in 51,000 live births [Shigematsu et al 2002]. There has also been a significant increase in the diagnosis of MCAD deficiency in Japanese individuals, with most having at least one novel pathogenic variant [Hara et al 2016, Tajima et al 2016].
  - Saudi Arabia. One in 18,000 live births [Al-Hassnan et al 2010]
  - Taiwan. One in 263,500 live births [Chien et al 2013]
- **Australia.** One in 19,000 live births (New South Wales) [Wilcken et al 2009]
- **Europe.** The prevalence of MCAD deficiency in Europe has ranged from a high of 1:4,900 live births in northern Germany [Sander et al 2001] to a low of 1:24,900 in Austria [Kasper et al 2010] and 1:23,000 in central Italy.
- **North America.** Prevalence has ranged from 1:23,400 live births in Canada [Prasad et al 2012] to a range of 1:13,000-19,000 in various states aross the United States [Chace et al 2002, Frazier et al 2006, Hsu et al 2008, Nichols et al 2008, Anderson et al 2012, Feuchtbaum et al 2012, Therrell et al 2014, Maier 2015].

Historically, MCAD deficiency was considered less common in the Hispanic, African American, and Native American populations in the US. More recent analysis of data from California demonstrated that MCAD deficiency may be as prevalent in Native Americans (1:7,500 live births) as in northern Europeans. Prevalences are similar among newborns of Hispanic, Black, and Middle Eastern origin (1:23,000 live births) [Feuchtbaum et al 2012].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

All causes of a Reye-like syndrome (i.e., acute noninflammatory encephalopathy with hyperammonemia, liver dysfunction, and fatty infiltration of the liver) need to be considered in the differential diagnosis of medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency, including other disorders of fatty acid beta-oxidation, defects in ketogenesis, urea cycle disorders, organic acidurias, respiratory chain defects, and inborn errors of carbohydrate metabolism (e.g., hereditary fructose intolerance).

Disorders of fatty acid beta-oxidation. Because of the nonspecific clinical presentation of MCAD deficiency, distinguishing it from other mitochondrial fatty acid beta-oxidation disorders requires biochemical and molecular testing.

Carnitine transport disorders. The carnitine transport disorders are very closely related to the fatty acid beta-oxidation disorders, as they are involved in long-chain fatty acid transport across the mitochondrial inner membrane. These disorders clinically present with a similar combination of hypoketotic hypoglycemia and liver dysfunction as seen in MCAD deficiency. Recurrent rhabdomyolysis, skeletal myopathy, and cardiomyopathy may also develop.

Genes of interest in the differential diagnosis of MCAD deficiency are listed in Table 2.

Table 2. Genes of Interest in the Differential Diagnosis of Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Gene(s)	Disorder	MOI	Features of Disorder	
			Clinical characteristics	Laboratory findings
Disorders of fatty acid beta-oxidation				
ACADS	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	AR	Clinically benign biochemical phenotype [1]	Acylcarnitines demonstrate ↑ of C4-acylcarnitines (butyrylcarnitine), distinguishing this disorder from MCAD deficiency.
ACADVL	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	AR	May present similarly to MCAD deficiency w/hypoketotic hypoglycemia, liver dysfunction, & liver failure, but is clinically distinct w/presence of significant rhabdomyolysis & cardiomyopathy not seen in MCAD deficiency.	Plasma acylcarnitines demonstrate ↑ of C14-, C14:1-, C16-, & C16:1-acylcarnitines, distinguishing this disorder from MCAD deficiency.

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Clinical characteristics	Laboratory findings
EFTA *EFTB* *ETFDH*	Multiple acyl-CoA dehydrogenase deficiency (MADD)	AR	Complex disorder w/presentations ranging from neonatal w/complex congenital abnormalities & dysmorphism to hypoketotic hypoglycemia, cardiomyopathy, & rhabdomyolysis in later-onset presentations.	• Acylcarnitines demonstrate variable ↑ of C4-, C5-, C5DC-, C6-, C8-, C10:1-, C12-, C14-, C14:1-, C16-, C16:1-, C16-OH-, C16:1-OH-, C18-, C18:1-, C18-OH-, & C18:1-OH-acylcarnitines. • ↑ of diagnostic biochemical markers may incl glutaric acid, 3-hydroxyisovaleric acid, lactic acid, medium- & long-chain dicarboxylic acids, & glycine species such as isovalerylglycine, isobutyrylglycine, & 2-methylbutyrylglycine. • Ketone bodies incl acetoacetic acid & 3-hydroxybutyric acids are minimal or undetectable, distinguishing this disorder from MCAD deficiency.
HADHA *HADHB*	Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency / trifunctional protein (TFP) deficiency	AR	May present similarly to MCAD deficiency w/hypoketotic hypoglycemia, liver dysfunction, & liver failure, but are clinically distinct w/presence of significant rhabdomyolysis & cardiomyopathy as well as peripheral neuropathy & retinopathy not seen in MCAD deficiency.	Plasma acylcarnitines demonstrate ↑ of C16-OH-, C16:1-OH-, C18-OH-, & C18:1-OH-acylcarnitines, distinguishing these disorders from MCAD deficiency.
Carnitine transport disorders				
SLC22A5	Systemic primary carnitine deficiency (carnitine uptake defect)	AR	Broad clinical spectrum; may present w/decompensation similar to MCAD deficiency (hypoketotic hypoglycemia, poor feeding, irritability, lethargy, hepatomegaly, ↑ liver transaminases, & hyperammonemia triggered by fasting or common illnesses) or w/ childhood myopathy, pregnancy-related low stamina, cardiac arrythmia, or fatigue	Plasma total & free carnitine levels are low, distinguishing this disorder from MCAD deficiency.
CPT1A	Carnitine palmitoyltransferase (CPT) 1A deficiency	AR	Does not present w/cardiomyopathy or skeletal myopathy	Plasma total & free carnitine levels are ↑, w/↓ levels of long-chain acylcarnitines & an ↑ C0/(C16+C18) ratio, distinguishing this disorder from MCAD deficiency.
CPT2	Carnitine palmitoyltransferase (CPT) II deficiency	AR	In addition to the more commonly known adult form, persons may develop a severe infantile hepatocardiomuscular form of the disorder.	Plasma acylcarnitine analysis demonstrate ↑ of C16-OH-, C16:1-, C18-, & C18:1-acylcarnitines, distinguishing this disorder from MCAD deficiency.

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Clinical characteristics	Laboratory findings
SLC25A20	Carnitine-acylcarnitine translocase (CACT) deficiency	AR	May be clinically indistinguishable from CPT II deficiency	May be biochemically indistinguishable from CPT II deficiency; CACT deficiency & CPT II deficiency have identical ↑ of C16-OH-, C16:1-, C18-, & C18:1-acylcarnitines, distinguishing both from MCAD deficiency.
Other causes of a Reye-like syndrome (selected examples)				
ALDOB	Hereditary fructose intolerance	AR	Following dietary exposure to fructose, sucrose, or sorbitol, symptoms of nausea, vomiting, & abdominal distress as well as chronic growth restriction / failure to thrive manifest.	Following dietary exposure to fructose, sucrose, or sorbitol, hypoglycemia, lactic acidemia, hypophosphatemia, hyperuricemia, hypermagnesemia, & hyperalaninemia can present.
ARG1 *ASL* *ASS1* *CPS1* *NAGS* *OTC* *SLC25A13* *SLC25A15*	Urea cycle disorders (NAGS, CPS1, OTC, ASS1, ASL, ARG1, ORNT1, & citrin deficiencies)	AR XL [2]	Can be assoc w/acute neonatal encephalopathy w/hyperventilation & hypothermia, Reye-like syndrome, migraines, recurrent vomiting, protein avoidance, or unexplained "cerebral palsy"	More significant hyperammonemia & normal plasma acylcarnitine profile, distinguishing this disorder from MCAD deficiency.

AR = autosomal recessive; ARG1 = arginase; ASL deficiency = argininosuccinic aciduria; ASS1 deficiency = citrullinemia type I deficiency; CPS1 = carbamoylphosphate synthetase I; MCAD = medium-chain acyl-coenzyme A dehydrogenase; MOI = mode of inheritance; NAGS = N-acetylglutamate synthase; ORNT1 = ornithine translocase; OTC = ornithine transcarbamylase; XL = X-linked

1. Most infants with SCAD deficiency identified through newborn screening have remained well, and asymptomatic relatives who meet diagnostic criteria have been reported. Thus, SCAD deficiency is now viewed as a clinically benign biochemical phenotype rather than a disease.

2. OTC deficiency is inherited in an X-linked manner; deficiencies of NAGS, CPS1, ASS1, ASL, ARG1, ORNT1, and citrin are inherited in an autosomal recessive manner.

Management

Management guidelines for acute illness in individuals with medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency have been published [McGregor et al 2021] (full text).

When MCAD deficiency is suspected during the diagnostic evaluation, including on newborn screening (i.e., due to highly elevated C8-, C6-, C10-, and C10:1-acylcarnitines, elevated C8/C10 ratio, and urine hexanoylglycine elevation), metabolic 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 (e.g., childhood obesity due to frequent feeding) require a multidisciplinary approach 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 MCAD deficiency, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Medium-Chain Acyl-Co A Dehydrogenase Deficiency: Recommended Evaluations Following Initial Diagnosis

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian [1]	**In a symptomatic individual,** consider obtaining the following additional laboratory studies, where clinically appropriate: • Blood glucose concentration • Liver function tests (i.e., AST, ALT, alkaline phosphatase, prothrombin time, partial thromboplastin time, total bilirubin, albumin) • Blood gas analysis • Ammonia concentration (collected in a sodium-heparin tube, placed on ice immediately, & sent STAT to lab on ice) • Lactic acid concentration • CBC w/differential • Electrolytes • Blood culture (in case of fever)
	In an asymptomatic individual: • Laboratory testing or imaging is obtained as clinically indicated. • Free and total carnitine level are checked routinely in some but not all practices.
Developmental/neurobehavioral assessment	• Consider referral to developmental pediatrician, depending on age & current developmental achievement. • For persons age >12 mos: screening for concerns incl ADHD if there is history of recurrent metabolic decompensations or severe hypoglycemic episodes
Assessment for muscle weakness	Consider referral for PT if present.
Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assess parental / affected person's coping skills & resources
Genetic counseling by genetics professionals [2]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of MCAD deficiency to facilitate medical & personal decision making

ADHD = attention-deficit/hyperactivity disorder; ALT = alanine transaminase; AST = aspartate transaminase; CBC = complete blood count; MCAD = medium-chain acyl-coenzyme A dehydrogenase; MOI = mode of inheritance; PT = physical therapy; STAT = short turnaround time

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

2. Clinical geneticist and/or clinical biochemical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for MCAD deficiency. However, routine dietary therapy (see Table 4) can ameliorate and/or prevent symptoms of this condition.

Table 4. Medium-Chain Acyl-Co A Dehydrogenase Deficiency: Routine Daily Treatment

Principle/Manifestation	Treatment	Considerations/Other
Avoidance of fasting	• In infants, frequent feeding (every 2-3 hrs). Breastmilk or standard infant formulas typically meet nutritional needs during infancy. • Overnight feeding, a bedtime snack, or 2 g/kg of uncooked cornstarch [1, 2] • Normal, healthy diet containing no more than 30% of total energy from fat • Extra calories are not needed, & overfeeding can lead to obesity. • All persons w/MCAD deficiency should avoid skipping meals & weight loss diets that recommend fasting. • Prolonged or intense exercise should be covered by adequate carbohydrate intake & hydration. • IV glucose is recommended for surgical procedures that require several hours of fasting.	General rules for length of time of fasting in asymptomatic affected persons: [3] • Birth to age 4 mos: no more than 4 hrs of fasting during day or night • Age 5-12 mos: an additional hr of fasting for each month of life up to age 12 mos (i.e., 5 hrs fasting at age 5 mos, 6 hrs fasting at age 6 mos, etc., until max of 12 hrs at age 1 yr) • Age >1 yr: no fasting longer than 12 hrs for life, [4] although persons w/certain genotypes predicted to result in milder disease or who have >10% residual enzyme activity may not require restriction on fasting past early childhood when clinically well [5]
Secondary carnitine deficiency	Initial oral dosage of 25-50 mg L-carnitine/kg/day divided into 3-4 doses is commonly used, although not all centers recommend correcting secondary carnitine deficiency. [6, 7]	• To eliminate toxic metabolites • Persons who are homozygous for c.985A>G may need higher doses of L-carnitine supplementation. [8]
Obesity	Weight control measures such as regular education about proper nutrition & recommended physical exercise	Long-term outcome studies revealed that persons treated for MCAD deficiency are prone to excessive weight gain. [9]
Developmental delay / aphasia	Standard treatment per neurodevelopmental specialist	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
ADHD	Standard treatment per neurodevelopment or psychiatry / behavioral health	
Muscle weakness	Physical medicine & rehab / PT & OT eval & treatment	To incl assessment of: • Gross motor & fine motor skills • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

ADHD = attention-deficit/hyperactivity disorder; IV = intravenous; MCAD = medium-chain acyl-coenzyme A dehydrogenase; OT = occupational therapy; PT = physical therapy

1. As a source of complex carbohydrates at bedtime to ensure sufficient glucose supply overnight

2. If an individual does not have an illness, this supplementary feeding may not be necessary.

3. See Genetic Metabolic Dietitians International (accessed 9-16-24).

4. Some centers liberalize fasting requirements after age two to three years.

5. Touw et al [2012]

6. Controversy exists whether L-carnitine supplementation is necessary in MCAD deficiency, even in those with low free carnitine levels [Weiss et al 2023].

7. Two exercise studies of individuals with MCAD deficiency before and after L-carnitine supplementation suggested improved exercise tolerance with supplementation of 100 mg/kg/day [Lee et al 2005] and statistically insignificant benefit with supplementation of 50 mg/kg/day [Huidekoper et al 2006].

8. Couce et al [2013]

9. Prepubertal children may become overweight given the frequent feeding as part of treatment, especially with the increasing incidence of obesity in pediatric and general populations worldwide.

Table 5. Medium-Chain Acyl-Co A Dehydrogenase Deficiency: Emergency Outpatient Treatment

Manifestation	Treatment	Consideration/Other
Mildly ↑ catabolism [1]	• Carbohydrate supplementation orally or via enteral feed [2] • ↑ of carnitine supplementation [3]	• Trial of outpatient treatment at home for up to 12 hrs • Reassessment (~every 2 hrs) for clinical changes [4]
Fever	Administration of antipyretics (acetaminophen, ibuprofen) for fever	
Occasional vomiting	Antiemetics [5]	

1. Fever <38.5 °C (101 °F); enteral or gastrostomy tube feeding is tolerated without recurrent vomiting or diarrhea; absence of neurologic symptoms (altered consciousness, irritability, hypotonia, dystonia)
2. Stringent guidelines to quantify carbohydrate/caloric requirements are available to guide nutritional arrangements in the outpatient setting, with some centers recommending frequent provision of carbohydrate-rich, protein-free beverages every two hours, with frequent reassessment.
3. Controversy exists whether L-carnitine supplementation is necessary in MCAD deficiency.
4. Alterations in mentation/alertness, fever, enteral feeding tolerance, and/or any new or evolving clinical features should be discussed with the designated center of expertise for inherited metabolic diseases.
5. Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to hospital.

An acute illness places the infant with MCAD deficiency at high risk for metabolic crisis. Metabolic crisis should be considered a medical emergency and implementation of treatment is essential (see Table 6). Consultation with a biochemical geneticist should be obtained as soon as possible.

Table 6. Medium-Chain Acyl-Co A Dehydrogenase Deficiency: Acute Inpatient Treatment

Manifestation/Concern	Treatment	Consideration/Other
↑ catabolism (due to fever, perioperative/peri-interventional fasting periods, repeated vomiting/diarrhea)	• Administration of simple carbohydrates by mouth (e.g., glucose tablets or sweetened, non-diet beverages) or IV fluids • IV administration of glucose should be initiated immediately w/10% dextrose w/appropriate electrolytes at rate of 1.5x maintenance rate or 10-12 mg glucose/kg/min to achieve & maintain blood glucose level >5 mmol/L, or between 120 & 170 mg/dL. • Address electrolytes & pH imbalances w/IV fluid mgmt.	To reverse catabolism & prevent hypoglycemia [1]
Early initiation of investigation of underlying cause of metabolic stress	Initiation of appropriate treatment for what triggered metabolic stress	
Consider L-carnitine supplementation	It is common practice to supplement based on theoretical postulation that carnitine supplementation may prevent metabolic decompensation. However, a beneficial effect has not been proven clinically. [2]	

IV = intravenous
1. See New England Consortium of Metabolic Programs and Genetic Metabolic Dietitians International (accessed 9-16-24).
2. Weiss et al [2023]

Transitional care from pediatric to adult-centered multidisciplinary care settings. As a lifelong disorder with varying implications according to age, smooth transition of care from the pediatric setting is essential for long-term management and should be organized as a well-planned, continuous, multidisciplinary process integrating resources of all relevant subspecialties. Standardized procedures for transitional care do not exist for MCAD deficiency due to the absence of multidisciplinary outpatient departments.

- Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with MCAD deficiency together with pediatric metabolic experts, dietitians, psychologists, and social workers.
- As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise with metabolic diseases with sufficient resources is essential.

Prevention of Primary Manifestations

Avoidance of fasting remains the cornerstone of MCAD deficiency treatment. Although management of any given affected individual is nuanced and managed on a case-by-case basis, minor illnesses, where caloric needs are increased or provision of adequate calories is compromised, should be observed closely and promptly treated with a low threshold for hospital admission. An emergency management protocol should be in place and parents or caregivers should be given an emergency letter.

A clinical geneticist or clinical biochemical geneticist or similarly qualified metabolic specialist should be consulted immediately during concurrent illness, especially when it involves fever and/or poor caloric intake.

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 (see also Tables 5 and 6).

Individuals with MCAD deficiency are at risk for a secondary free carnitine deficiency, as accumulated acylcarnitine species cause depletion of carnitine stores by renal excretion. Accumulated acylcarnitine species are also thought to inhibit organic cation/carnitine transporter 2 (OCTN2), which lowers the renal excretion threshold for free carnitine and further depletes carnitine stores in the body [Jager et al 2022]. However, controversy exists whether free carnitine level should be monitored routinely and if L-carnitine supplementation is necessary or clinically beneficial.

Table 7. Medium-Chain Acyl-Co A Dehydrogenase Deficiency: Prevention of Secondary Manifestations

Manifestation/Situation	Prevention	Considerations/Other
Hypoglycemia due to ↑ catabolism &/or fasting	• Intense & ongoing education of affected persons & caregivers re natural history, maintenance, & emergency treatment • Treatment protocols & provision of emergency letters [1] or cards that are frequently updated & emphasize importance of preventive measures (e.g., IV glucose regardless of "normal" laboratory results, overnight in-hospital observation) to incl guidance for care in event of illness while on holiday/vacation. • MedicAlert® bracelet/pendants or car seat stickers • Adequate supplies of specialized dietary products (carbohydrate-only formulas or other caloric sources); Lys-free, Trp-reduced amino acid formula; and medication required for maintenance & emergency treatment (carnitine, antipyretics) should always be maintained at home.	• Written protocols for maintenance & emergency treatment should be provided to parents & primary care providers / pediatricians, & to teachers & school staff. [2, 3] • Emergency letters/cards should be provided summarizing key information & principles of emergency treatment for MCAD deficiency & containing contact information for primary treating metabolic center. • For any planned travel or vacations, consider contacting center of expertise near destination prior to travel dates.

Table 7. continued from previous page.

Manifestation/Situation	Prevention	Considerations/Other
Surgery or procedure (incl dental procedures)	• Notify designated metabolic center in advance of procedure to discuss perioperative mgmt w/ surgeons & anesthesiologists. [3] • Emergency surgeries/procedures require planning input from physicians w/expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional mgmt).	Consider placing "flag" in affected person's medical record such that all care providers are aware of diagnosis & need to solicit opinions & guidance from designated metabolic specialists in setting of certain procedures.

IV = intravenous; MCAD = medium-chain acyl-coenzyme A dehydrogenase
1. The New England Metabolic Consortium of Metabolic Programs website provides an example of a post-emergency management letter for MCAD deficiency (see Acute Illness Protocol, page 4 [pdf]).
2. Essential information including written treatment protocols should be provided before inpatient emergency treatment might be necessary.
3. Parents or local hospitals should immediately inform the designated metabolic center if: (1) temperature rises >38.5 °C; (2) vomiting/diarrhea or other symptoms of intercurrent illness develop; or (3) new neurologic symptoms occur.

Surveillance

Infants should establish care with a biochemical genetics clinic including a metabolic dietitian as soon as possible following a positive newborn screen. A metabolic dietician (see gmdi.org) should be involved to ensure proper nutrition in terms of quality and quantity. After the baseline visit and confirmatory testing, affected infants should be seen in team clinic in two to three months, then every six to 12 months if otherwise clinically well. Affected individuals can be seen more frequently by a metabolic dietitian or in clinic as needed to ensure that families understand and are comfortable with treatment while the infant is otherwise well.

The frequency of routine follow-up visits is individualized based on comfort level of the affected persons, their families, and health care providers.

In addition to regular evaluations by a metabolic specialist and metabolic dietician, the evaluations summarized in Table 8 are recommended to monitor existing manifestations, the individual's response to care, and the emergence of new manifestations.

Table 8. Medium-Chain Acyl-Co A Dehydrogenase Deficiency: Recommended Surveillance

Manifestation	Evaluation	Frequency/Comment
Abnormal growth, incl poor growth or excessive weight gain [1]	Measurement of growth & head circumference	At each visit
Delayed acquisition of developmental milestones [2]	Monitoring of developmental progress & educational needs	
	• Neuropsychological testing using age-appropriate standardized assessment batteries • Standardized quality-of-life assessment tools for affected persons & parents/caregivers	As needed
Neurobehavioral issues	Behavioral assessment for ADHD	
Secondary carnitine deficiency	Free carnitine level may be considered.	Annually [3]

ADHD = attention-deficit/hyperactivity disorder
1. Prepubertal children may become overweight given the frequent feeding as part of treatment, especially with the increasing incidence of obesity in pediatric and general populations worldwide.
2. Although development is typically normal for individuals treated prospectively, those who experience metabolic decompensations requiring hospitalization often demonstrate developmental and neurologic disabilities.
3. Not routinely checked at all metabolic centers

Agents/Circumstances to Avoid

Hypoglycemia must be avoided by frequent feedings early in life to avoid catabolism – if necessary, by intravenous administration of glucose.

Infant formulas, coconut oil, and other manufactured foods containing medium-chain triglycerides as the primary source of fat are not recommended in MCAD deficiency; however, ingesting small amounts is not contraindicated.

Popular high-fat/low-carbohydrate diets are not appropriate for individuals with MCAD deficiency.

Alcohol consumption, in particular acute alcohol intoxication (e.g., binge drinking), often elicits metabolic decompensation in individuals with MCAD deficiency [Lang 2009].

Aspirin has been demonstrated to exacerbate MCAD deficiency by increasing mitochondrial fatty acid oxidation and long-chain fatty acid flux and inhibiting peroxisomal fatty acid oxidation, which normally serves as a lipitoxic buffer [Uppala et al 2017].

Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger sibs and offspring of a proband in order to identify as early as possible those who would benefit from treatment and preventive measures.

- If the *ACADM* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs and offspring of a proband.
- If the *ACADM* pathogenic variants in the family are not known, plasma acylcarnitine and urine acylglycine analysis can be used to clarify the disease status of at-risk sibs and offspring of a proband.

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

Pregnancy Management

Pregnant women who have MCAD deficiency must avoid catabolism. This is supported by several case reports describing carnitine deficiency, acute liver failure, and HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets) in pregnant women with MCAD deficiency [Nelson et al 2000, Santos et al 2007, Leydiker et al 2011].

Therapies Under Investigation

A Phase II dose-escalating clinical trial examining the use of glycerol phenylbutyrate (Ravicti®) in the prevention of hypoglycemia in affected individuals age ≥16 years is currently ongoing (NCT06067802).

A previous Phase I clinical trial for the use of glycerol phenylbutyrate at 2, 4, and 6 g/m^2/day in four adults with MCAD deficiency who had at least one copy of the common *ACADM* c.985A>G (p.Lys329Glu) pathogenic variant was completed in 2017 (NCT01881984). The primary outcome was changes in the assessment of metabolic stress pre- and post-dosing with Ravicti®. There were no serious adverse events. Other adverse events included gastrointestinal disorders (e.g., dry mouth, nausea, vomiting), elevated phenylbutyrate level, neck pain, decreased reflexes, and thromboembolic event. Previous molecular modeling has suggested that the MCAD enzyme may be able to utilize phenylbutyryl-coenzyme A as a substrate [Kormanik et al 2012].

A Phase II, open-label, fixed-dose study evaluating the use of sodium phenylbutyrate (ACER-001) in the treatment of adult and pediatric patients with MCAD deficiency due to the common *ACADM* c.985 A>G (p.Lys329Glu) pathogenic variant is ongoing as of June 2024 (NCT06069375).

A Phase II, escalating-dose, open-label study of triheptanoin to prevent hypoglycemia in individuals with MCAD deficiency is ongoing as of June 2024 (NCT06067802).

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

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

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

Sibs of a proband

- If both parents are known to be heterozygous for an *ACADM* 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.
- Given that a clear genotype-phenotype correlation does not exist for MCAD deficiency and that individuals with biallelic *ACADM* pathogenic variants may remain asymptomatic until late adulthood, apparently unaffected sibs should be tested for MCAD deficiency (see Management, Evaluation of Relatives at Risk).
- 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 MCAD deficiency or is a carrier (see Clinical Characteristics, Prevalence and **Family planning**), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ACADM*.

- Given the high carrier frequency in the general population, it is appropriate to test the offspring of an individual with MCAD deficiency for the disorder (see Management, Evaluation of Relatives at Risk).

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

Carrier Detection

Molecular genetic testing to determine genetic status is possible if both *ACADM* pathogenic variants have been identified in an affected family member.

Note: Biochemical screening tests such as acylcarnitine, organic acid, or acylglycine analyses are not useful in determining carrier status.

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.
- The carrier frequency for the *ACADM* c.985A>G pathogenic variant is between 1:40 and 1:100 in those of northern European ancestry. Analysis of data from California demonstrated that MCAD deficiency may be as prevalent in Native Americans (1:7,500 live births) as in northern Europeans (see Clinical Characteristics, Prevalence). Founder variants have been identified in the Mennonite and Amish populations (see Table 9).
- The ACMG includes MCAD deficiency among those disorders for which expanded carrier screening should be offered to all pregnant individuals and individuals planning a pregnancy [Gregg et al 2021]. Of note, because of the inherent detection limitations of ancestry-based targeted variant testing, sequence analysis (rather than targeted variant analysis) is recommended in the National Society of Genetic Counselors practice guidelines for expanded carrier screening [Sagaser et al 2023].

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].

Note: States store leftover dried blood spot samples for variable lengths of time following newborn screening (NBS) testing. These samples may be retrievable with parent/patient consent for retrospective biochemical or molecular genetic testing.

Prenatal Testing and Preimplantation Genetic Testing

Once both *ACADM* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for MCAD deficiency are possible.

Prompt postnatal testing by NBS, plasma acylcarnitines, and urine acylglycines and consultation with a biochemical geneticist are indicated.

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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
  MCADD
- **Genetic Metabolic Dietitians International**
  MCAD
- **Medical Home Portal**
  MCADD
- **MedlinePlus**
  Medium-chain acyl-coenzyme A dehydrogenase deficiency
- **New England Consortium of Metabolic Programs**
  A Guide for Parents of Babies Recently Screened for MCADD
- **NewbornScreening.Info - Disorder Fact Sheets**
  Medium chain acyl-CoA dehydrogenase deficiency
- **FOD Family Support Group (Fatty Oxidation Disorder)**
  Phone: 517-381-1940
  Email: deb@fodsupport.org; fodgroup@gmail.com
  fodsupport.org
- **INFORM**
  International Network for Fatty Acid Oxidation Research and Management
  Phone: 412-692-5099
  informnetwork.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **MitoAction**
  Phone: 888-648-6228
  Email: support@mitoaction.org
  mitoaction.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. Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ACADM	1p31.1	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	CCHMC - Human Genetics Mutation Database (ACADM)	ACADM	ACADM

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 Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency (View All in OMIM)

201450	ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN, DEFICIENCY OF; ACADMD
607008	ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN; ACADM

Molecular Pathogenesis

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is a disorder of mitochondrial fatty acid beta-oxidation. Medium- and short-chain fatty acids passively diffuse across the mitochondrial membrane independent of carnitine transport and are activated to coenzyme A (CoA) esters in the mitochondrial matrix. Fatty acid beta-oxidation consists of four sequential reactions catalyzed by two sets of chain length-specific enzymes. Medium- and short-chain enzymes are located in the mitochondrial matrix. MCAD is responsible for the initial dehydrogenation of acyl-CoAs with a chain length between four and 12 carbon atoms. Each turn of the beta-oxidation spiral pathway shortens the acyl-CoA chain by two carbons and produces a molecule each of acetyl-CoA, $FADH^+$, and $NADH_2$.

The mature MCAD protein is a homotetramer encoded by a nuclear gene; it is active within the mitochondria. The leading 25 amino acids of the precursor protein are cleaved off once the MCAD protein has reached the mitochondria. Heat shock protein 60 (HSP60) then aids in the folding of the monomer (42.5 kd). The assembled, mature homotetramer is flavin dependent, with each subunit containing one flavin adenine dinucleotide (FAD) molecule. Electron transfer flavoprotein (ETF) functions as the enzyme's electron acceptor, which explains why MCAD metabolites are also present in individuals with glutaric acidemia type II.

Individuals with MCAD deficiency have reduced mitochondrial MCAD enzyme functioning and cannot convert medium-chain fatty acids (those with 6-10 carbons) into acetyl-CoA for ATP synthesis, ketogenesis, and Krebs (i.e., tricarboxylic acid) cycle use. MCAD deficiency impairs the energy supply to peripheral tissues through reduction of oxidative phosphorylation substrates and ketogenesis, thus increasing glucose dependency and utilization. This results in hypoketotic hypoglycemia, metabolic acidosis, liver disease, and lethargy, which progress to coma and death when glycogen stores are depleted. Metabolites detectable in body fluids (blood, urine, bile) include medium-chain fatty acids, corresponding fatty acylglycine and acylcarnitine esters, and dicarboxylic acids. Accumulation of these metabolites may cause oxidative damage [Derks et al 2014]. When well, individuals with MCAD deficiency are able to compensate for decreased energy production by using glycogen stores for free fatty acids. However, during times of illness and fasting, hepatic glycogen stores are rapidly depleted and affected individuals with MCAD deficiency are unable to utilize fatty acids for energy; therefore, they can rapidly progress to lethal hypoglycemia.

Mitochondrial complex I-III dysfunction in liver and skeletal muscles has also been postulated as a pathomechanism of disease in murine models of MCAD deficiency [Amaral & Wajner 2020].

Mechanism of disease causation. Loss of function

Table 9. *ACADM* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change [2]	Comments [Reference]
NM_000016.5 NP_000007.1	c.199T>C	p.Tyr67His	Folding pathogenic variant assoc w/milder biochemical & clinical phenotype; commonly identified in persons of European descent & in the Amish from Lancaster Co, PA [Maier et al 2009, Koster et al 2014, Hara et al 2016, Puffenberger 2021, Lynch et al 2022] [3]
NM_000016.5	c.287-30A>G (IVS4-30A>G)	--	Founder variant in persons of Mennonite (Weaverland & Groffdale) ancestry [Strauss & Puffenberger 2009]
NM_000016.5 NP_000007.1	c.449_452delCTGA	p.Thr150ArgfsTer4	More prevalent in Asian (Taiwanese, Japanese, & Korean) populations [4]
NM_000016.5	c.600-18G>A	--	Persons w/the compound heterozygous pathogenic variants c.985A>G & c.600-18G>A have a mild phenotype & may not be detected by NBS due to residual MCAD enzyme activity [Grünert et al 2015].
NM_000016.5 NP_000007.1	c.985A>G	p.Lys329Glu	Commonly identified in persons of European descent [Rhead 2006, Gramer et al 2015] [4]

NBS = newborn screening
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.
1. Variant designation that does not conform to current naming conventions
2. Historically, variant nomenclature designated the first amino acid at p.1 of the mature protein, whereas current nomenclature designates the first amino acid at p.1 of the pro-protein.
3. Affected individuals who are compound heterozygous for c.199T>C (p.Tyr67His) and a second pathogenic variant are at risk for developing clinical symptoms [Maier et al 2009, Koster et al 2014, Hara et al 2016].
4. This pathogenic variant has been shown to destabilize the quaternary structure of the enzyme due to misfolding, resulting in loss of function with rapid degradation of the mutated protein [Maier et al 2009].

Chapter Notes

Author Notes

Dr Jerry Vockley (vockleyg@upmc.edu) is actively involved in clinical research regarding individuals with MCAD deficiency and other fatty acid oxidation disorders. He would be happy to communicate with persons who have any questions regarding diagnosis of MCAD deficiency or other considerations.

Author History

Irene J Chang, MD (2019-present)
Christina Lam, MD (2024-present)
Dietrich Matern, MD, PhD; Mayo Clinic College of Medicine (1999-2019)
J Lawrence Merritt 2nd, MD; University of Washington (2019-2024)
Piero Rinaldo, MD, PhD; Mayo Clinic College of Medicine (1999-2019)
Jerry Vockley, MD, PhD (2024-present)

Revision History

- 26 September 2024 (ma) Comprehensive update posted live

- 27 June 2019 (ha) Comprehensive update posted live
- 5 March 2015 (me) Comprehensive update posted live
- 19 January 2012 (me) Comprehensive update posted live
- 3 February 2005 (me) Comprehensive update posted live
- 27 January 2003 (me) Comprehensive update posted live
- 20 April 2000 (me) Review posted live
- 16 December 1999 (dm) Original submission

References

Literature Cited

Aksglaede L, Christensen M, Olesen JH, Duno M, Olsen RK, Andresen BS, Hougaard DM, Lund AM. Abnormal newborn screening in a healthy infant of a mother with undiagnosed medium-chain Acyl-CoA dehydrogenase deficiency. JIMD Rep. 2015;23:67-70. PubMed PMID: 25763512.

Al-Hassnan ZN, Imtiaz F, Al-Amoudi M, Rahbeeni Z, Al-Sayed M, Al-Owain M, Al-Zaidan H, Al-Odaib A, Rashed MS. Medium-chain acyl-CoA dehydrogenase deficiency in Saudi Arabia: incidence, genotype, and preventive implications. J Inherit Metab Dis. 2010;33 Suppl 3 :S263-7. PubMed PMID: 20567907.

Amaral AU, Wajner M. Recent advances in the pathophysiology of fatty acid oxidation defects: secondary alterations of bioenergetics and mitochondrial calcium homeostasis caused by the accumulating fatty acids. Front Genet. 2020;11:598976. PubMed PMID: 33329744.

Anderson DR, Viau K, Botto LD, Pasquali M, Longo N. Clinical and biochemical outcomes of patients with medium-chain acyl-CoA dehydrogenase deficiency. Mol Genet Metab. 2020;129:13-9. PubMed PMID: 31836396.

Anderson S, Botti C, Li B, Millonig JH, Lyon E, Millson A, Karabin SS, Brooks SS. Medium chain acyl-CoA dehydrogenase deficiency detected among Hispanics by New Jersey newborn screening. Am J Med Genet A. 2012;158A:2100-5. PubMed PMID: 22848008.

Andresen BS, Dobrowolski SF, O'Reilly L, Muenzer J, McCandless SE, Frazier DM, Udvari S, Bross P, Knudsen I, Banas R, Chace DH, Engel P, Naylor EW, Gregersen N. Medium-chain acyl-CoA dehydrogenase (MCAD) mutations identified by MS/MS-based prospective screening of newborns differ from those observed in patients with clinical symptoms: identification and characterization of a new, prevalent mutation that results in mild MCAD deficiency. Am J Hum Genet. 2001;68:1408-18. PubMed PMID: 11349232.

Andresen BS, Lund AM, Hougaard DM, Christensen E, Gahrn B, Christensen M, Bross P, Vested A, Simonsen H, Skogstrand K, Olpin S, Brandt NJ, Skovby F, Nørgaard-Pedersen B, Gregersen N. MCAD deficiency in Denmark. Mol Genet Metab. 2012;106:175-88. PubMed PMID: 22542437.

Arnold GL, Saavedra-Matiz CA, Galvin-Parton PA, Erbe R, Devincentis E, Kronn D, Mofidi S, Wasserstein M, Pellegrino JE, Levy PA, Adams DJ, Nichols M, Caggana M. Lack of genotype-phenotype correlations and outcome in MCAD deficiency diagnosed by newborn screening in New York State. Mol Genet Metab. 2010;99:263-8. PubMed PMID: 20036593.

Bentler K, Zhai S, Elsbecker SA, Arnold GL, Burton BK, Vockley J, Cameron CA, Hiner SJ, Edick MJ, Berry SA, et al. 221 newborn-screened neonates with medium-chain acyl-coenzyme A dehydrogenase deficiency: findings from the Inborn Errors of Metabolism Collaborative. Mol Genet Metab. 2016;119:75-82. PubMed PMID: 27477829.

Blois B, Riddell C, Dooley K, Dyack S. Newborns with C8-acylcarnitine level over the 90th centile have an increased frequency of the common MCAD 985A>G mutation. J Inherit Metab Dis. 2005;28:551-6. PubMed PMID: 15902558.

Boles RG, Buck EA, Blitzer MG, Platt MS, Cowan TM, Martin SK, Yoon H, Madsen JA, Reyes-Mugica M, Rinaldo P. Retrospective biochemical screening of fatty acid oxidation disorders in postmortem livers of 418 cases of sudden death in the first year of life. J Pediatr. 1998;132:924-33. PubMed PMID: 9627580.

Bouvier D, Vianey-Saban C, Ruet S, Acquaviva C. Development of a tandem mass spectrometry method for rapid measurement of medium- and very-long-chain acyl-CoA dehydrogenase activity in fibroblasts. JIMD Rep. 2017;35:71-8. PubMed PMID: 27943070.

Bzduch V, Behulova D, Lehnert W, Fabriciova K, Kozak L, Salingova A, Hrabincova E, Benedekova M. Metabolic cause of Reye-like syndrome. Bratisl Lek Listy. 2001;102:427-9. PubMed PMID: 11763681.

Catarzi S, Caciotti A, Thusberg J, Tonin R, Malvagia S, la Marca G, Pasquini E, Cavicchi C, Ferri L, Donati MA, Baronio F, Guerrini R, Mooney SD, Morrone A. Medium-chain acyl-CoA deficiency: outlines from newborn screening, in silico predictions, and molecular studies. ScientificWorldJournal. 2013;2013:625824. PubMed PMID: 24294134.

Chace DH, Kalas TA, Naylor EW. The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism. Annu Rev Genomics Hum Genet. 2002;3:17-45. PubMed PMID: 12142359.

Chien YH, Lee NC, Chao MC, Chen LC, Chen LH, Chien CC, Ho HC, Suen JH, Hwu WL. Fatty acid oxidation disorders in a chinese population in taiwan. JIMD Rep. 2013;11:165-72. PubMed PMID: 23700290.

Couce ML, Sánchez-Pintos P, Diogo L, Leão-Teles E, Martins E, Santos H, Bueno MA, Delgado-Pecellín C, Castiñeiras DE, Cocho JA, García-Villoria J, Ribes A, Fraga JM, Rocha H. Newborn screening for medium-chain acyl-CoA dehydrogenase deficiency: regional experience and high incidence of carnitine deficiency. Orphanet J Rare Dis. 2013;8:102. PubMed PMID: 23842438.

Derks TG, Reijngoud DJ, Waterham HR, Gerver WJ, Van Den Berg MP, Sauer PJ, Smit GP. The natural history of medium-chain acyl CoA dehydrogenase deficiency in the Netherlands: clinical presentation and outcome. J Pediatr. 2006;148:665-70. PubMed PMID: 16737882.

Derks TG, Touw CM, Ribas GS, Biancini GB, Vanzin CS, Negretto G, Mescka CP, Reijngoud DJ, Smit GP, Wajner M, Vargas CR. Experimental evidence for protein oxidative damage and altered antioxidant defense in patients with medium-chain acyl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2014;37:783-9. PubMed PMID: 24623196.

Derks TG, Van Spronsen FJ, Rake JP, Van Der Hilst CS, Span MM, Smit GP. Safe and unsafe duration of fasting for children with MCAD deficiency. Eur J Pediatr. 2007;166:5-11. PubMed PMID: 16788829.

Douillard C, Mention K, Dobbelaere D, Wemeau JL, Saudubray JM, Vantyghem MC. Hypoglycaemia related to inherited metabolic diseases in adults. Orphanet J Rare Dis. 2012;7:26. PubMed PMID: 22587661.

Feillet F, Steinmann G, Vianey-Saban C, de Chillou C, Sadoul N, Lefebvre E, Vidailhet M, Bollaert PE. Adult presentation of MCAD deficiency revealed by coma and severe arrythmias. Intensive Care Med. 2003;29:1594-7. PubMed PMID: 12897989.

Feuchtbaum L, Carter J, Dowray S, Currier RJ, Lorey F. Birth prevalence of disorders detectable through newborn screening by race/ethnicity. Genet Med. 2012;14:937-45. PubMed PMID: 22766612.

Fingerhut R, Joset P, Rupp NJ, Girsberger M, Sluka SHM, Herget T, Azzarello-Burri SM, Rauch A, Baumgartner M. MCAD-deficiency with severe neonatal onset, fatal outcome and normal acylcarnitine profile. Int J Neonatal Screen. 2017;3:21.

Frazier DM, Millington DS, McCandless SE, Koeberl DD, Weavil SD, Chaing SH, Muenzer J. The tandem mass spectrometry newborn screening experience in North Carolina: 1997-2005. J Inherit Metab Dis. 2006;29:76-85. PubMed PMID: 16601872.

Gramer G, Haege G, Fang-Hoffmann J, Hoffmann GF, Bartram CR, Hinderhofer K, Burgard P, Lindner M. Medium-chain acyl-CoA dehydrogenase deficiency: evaluation of genotype-phenotype correlation in patients detected by newborn screening. JIMD Rep. 2015;23:101-12. PubMed PMID: 25940036.

Gregersen N, Winter V, Curtis D, Deufel T, Mack M, Hendrickx J, Willems PJ, Ponzone A, Parrella T, Ponzone R, Ding J-H, Zhang W, Chen YT, Kahler S, Roe CR, Kølvraa S, Schneiderman K, Andresen BS, Bross P, Bolund L. Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency: the prevalent mutation G985 (K304E) is subject to a strong founder effect from northwestern Europe. Hum Hered. 1993;43:342-50. PubMed PMID: 7904584.

Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, Chen E, Sparks TN, Reddi HV, Rajkovic A, Dungan JS; ACMG Professional Practice and Guidelines Committee. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23:1793-806. PubMed PMID: 34285390.

Grünert SC, Wehrle A, Villavicencio-Lorini P, Lausch E, Vetter B, Schwab KO, Tucci S, Spiekerkoetter U. Medium-chain acyl-CoA dehydrogenase deficiency associated with a novel splice mutation in the ACADM gene missed by newborn screening. BMC Med Genet. 2015;16:56. PubMed PMID: 26223887.

Hara K, Tajima G, Okada S, Tsumura M, Kagawa R, Shirao K, Ohno Y, Yasunaga S, Ohtsubo M, Hata I, Sakura N, Shigematsu Y, Takihara Y, Kobayashi M. Significance of ACADM mutations identified through newborn screening of MCAD deficiency in Japan. Mol Genet Metab. 2016;118:9-14. PubMed PMID: 26947917.

Hsu HW, Zytkovicz TH, Comeau AM, Strauss AW, Marsden D, Shih VE, Grady GF, Eaton RB. Spectrum of medium-chain acyl-CoA dehydrogenase deficiency detected by newborn screening. Pediatrics. 2008;121:e1108-14. PubMed PMID: 18450854.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Huidekoper HH, Schneider J, Westphal T, Vaz FM, Duran M, Wijburg FA. Prolonged moderate-intensity exercise without and with L-carnitine supplementation in patients with MCAD deficiency. J Inherit Metab Dis. 2006;29:631–6. PubMed PMID: 16972171.

Iafolla AK, Thompson RJ Jr, Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. J Pediatr. 1994;124:409–15. PubMed PMID: 8120710.

Jager EA, Kuijpers MM, Bosch AM, Mulder MF, Rubio-Gozalbo ME, Visser G, de Vries M, Williams M, Waterham HR, van Spronsen FJ, Schielen PCJI, Derks TGJ. A nationwide retrospective observational study of population newborn screening for medium-chain acyl-CoA dehydrogenase (MCAD) deficiency In the Netherlands. J Inherit Metab Dis. 2019;42:890-7. PubMed PMID: 31012112.

Jager EA, Schaafsma M, van der Klauw MM, Heiner-Fokkema MR, Derks TGJ. Plasma carnitine concentrations in Medium-chain acyl-CoA dehydrogenase deficiency: lessons from an observational cohort study. J Inherit Metab Dis. 2022;45:1118-29. PubMed PMID: 35778950.

Janzen N, Hofmann AD, Schmidt G, Das AM, Illsinger S. Non-invasive test using palmitate in patients with suspected fatty acid oxidation defects: disease-specific acylcarnitine patterns can help to establish the diagnosis. Orphanet J Rare Dis. 2017;12:187. PubMed PMID: 29268767.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Kaku N, Ihara K, Hirata Y, Yamada K, Lee S, Kanemasa H, Motomura Y, Baba H, Tanaka T, Sakai Y, Maehara Y, Ohga S. Diagnostic potential of stored dried blood spots for inborn errors of metabolism: a metabolic

autopsy of medium-chain acyl-CoA dehydrogenase deficiency Journal of Clinical Pathology 2018;71:885-9. PubMed PMID: 29720407.

Kang HM, Ahn SH, Choi P, Ko YA, Han SH, Chinga F, Park AS, Tao J, Sharma K, Pullman J, Bottinger EP, Goldberg IJ, Susztak K. Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development. Nat Med. 2015;21:37–46. PubMed PMID: 25419705.

Kasper DC, Ratschmann R, Metz TF, Mechtler TP, Möslinger D, Konstantopoulou V, Item CB, Pollak A, Herkner KR. The national Austrian newborn screening program - eight years experience with mass spectrometry. past, present, and future goals. Wien Klin Wochenschr. 2010;122:607-13. PubMed PMID: 20938748.

Kølvraa S, Gregersen N, Christensen E, Hobolth N. In vitro fibroblast studies in a patient with C6-C10-dicarboxylic aciduria: evidence for a defect in general acyl-CoA dehydrogenase. Clin Chim Acta. 1982;126:53-67. PubMed PMID: 7172449.

Kormanik K, Kang H, Cuebas D, Vockley J, Mohsen AW. Evidence for involvement of medium chain acyl-CoA dehydrogenase in the metabolism of phenylbutyrate. Mol Genet Metab. 2012;107:684-9. PubMed PMID: 23141465.

Koster KL, Sturm M, Herebian D, Smits SH, Spiekerkoetter U. Functional studies of 18 heterologously expressed medium-chain acyl-CoA dehydrogenase (MCAD) variants. J Inherit Metab Dis. 2014;37:917-28. PubMed PMID: 24966162.

Lang TF. Adult presentations of medium-chain acyl-CoA dehydrogenase deficiency (MCADD). J Inherit Metab Dis. 2009;32:675-83. PubMed PMID: 19821147.

Lee PJ, Harrison EL, Jones MG, Jones S, Leonard JV, Chalmers RA. L-carnitine and exercise tolerance in medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency: a pilot study. J Inherit Metab Dis. 2005;28:141-52. PubMed PMID: 15877203.

Leydiker KB, Neidich JA, Lorey F, Barr EM, Puckett RL, Lobo RM, Abdenur JE. Maternal medium-chain acyl-CoA dehydrogenase deficiency identified by newborn screening. Mol Genet Metab. 2011;103:92-5. PubMed PMID: 21354840.

Lindner M, Hoffmann GF, Matern D. Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. J Inherit Metab Dis. 2010;33:521–6 PubMed PMID: 20373143.

Lovera C, Porta F, Caciotti A, Catarzi S, Cassanello M, Caruso U, Gallina MR, Morrone A, Spada M. Sudden unexpected infant death (SUDI) in a newborn due to medium chain acyl CoA dehydrogenase (MCAD) deficiency with an unusual severe genotype. Ital J Pediatr. 2012;38:59. PubMed PMID: 23095120.

Lynch MT, Maloney KA, Pollin TI, Streeten EA, Puffenberger EG, Strauss KA; Regeneron Genetics Center; Shuldiner AR, Mitchell BD. Impact of parental relatedness on reproductive outcomes among the Old Order Amish of Lancaster County. Am J Med Genet A. 2022;188:2119-28. PubMed PMID: 35442562.

Maier EM. Neonatal screening for medium-chain acyl-coA deficiency—insights and unexpected challenges. Int J Neonatal Screen. 2015;1:79-88.

Maier EM, Liebl B, Roschinger W, Nennstiel-Ratzel U, Fingerhut R, Olgemoller B, Busch U, Krone N, Kries RV, Roscher AA. Population spectrum of ACADM genotypes correlated to biochemical phenotypes in newborn screening for medium-chain acyl-CoA dehydrogenase deficiency. Hum Mutat. 2005;25:443-52. PubMed PMID: 15832312.

Maier EM, Pongratz J, Muntau AC, Liebl B, Nennstiel-Ratzel U, Busch U, Fingerhut R, Olgemoller B, Roscher AA, Roschinger W. Validation of MCADD newborn screening. Clin Genet. 2009;76:179-87. PubMed PMID: 19780764.

Matern D. Acylcarnitines. In: Blau N, Duran M, Gibson KM, Dionisi-Vici C eds. *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases.* Heidelberg, Gemany: Springer Verlag; 2014:775-84

Mayell SJ, Edwards L, Reynolds FE, Chakrapani AB. Late presentation of medium-chain acyl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2007;30:104. PubMed PMID: 17143576.

McGregor TL, Berry SA, Dipple KM, Hamid R; Council on Genetics. Management principles for acute illness in patients with medium-chain acyl-coenzyme A dehydrogenase deficiency. Pediatrics. 2021;147:e2020040303. PubMed PMID: 33372121.

Mütze U, Nennstiel U, Odenwald B, Haase C, Ceglarek U, Janzen N, Garbade SF, Hoffmann GF, Kölker S, Haas D. Sudden neonatal death in individuals with medium-chain acyl-coenzyme A dehydrogenase deficiency: limit of newborn screening. Eur J Pediatr. 2022;181:2415-22. PubMed PMID: 35294644.

Nelson J, Lewis B, Walters B. The HELLP syndrome associated wiht fetal medium-chain acyl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2000;23:518-9. PubMed PMID: 10947209.

Nichols MJ, Saavedra-Matiz CA, Pass KA, Caggana M. Novel mutations causing medium chain acyl-CoA dehydrogenase deficiency: under-representation of the common c.985 A > G mutation in the New York state population. Am J Med Genet A. 2008;146A:610-9. PubMed PMID: 18241067.

Prasad C, Speechley KN, Dyack S, Rupar CA, Chakraborty P, Kronick JB. Incidence of medium-chain acyl-CoA dehydrogenase deficiency in Canada using the Canadian Paediatric Surveillance Program: role of newborn screening. Paediatr Child Health. 2012;17:185-9. PubMed PMID: 23543005.

Puffenberger EG. Mendelian disease research in the Plain populations of Lancaster County, Pennsylvania. Am J Med Genet A. 2021;185:3322-33. PubMed PMID: 34532947.

Rhead WJ. Newborn screening for medium-chain acyl-CoA dehydrogenase deficiency: a global perspective. J Inherit Metab Dis. 2006;29:370-7. PubMed PMID: 16763904.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rocha H, Castiñeiras D, Delgado C, Egea J, Yahyaoui R, González Y, Conde M, González I, Rueda I, Rello L, Vilarinho L, Cocho J. Birth prevalence of fatty acid β-oxidation disorders in Iberia. JIMD Rep. 2014;16:89-94. PubMed PMID: 25012579.

Roe CR, Millington DS, Maltby DA, Kinnebrew P. Recognition of medium-chain acyl-CoA dehydrogenase deficiency in asymptomatic siblings of children dying of sudden infant death or Reye-like syndromes. J Pediatr. 1986;108:13–8. PubMed PMID: 3944676.

Sagaser KG, Malinowski J, Westerfield L, Proffitt J, Hicks MA, Toler TL, Blakemore KJ, Stevens BK, Oakes LM. Expanded carrier screening for reproductive risk assessment: An evidence-based practice guideline from the National Society of Genetic Counselors. J Genet Couns. 2023;32:540-57. PubMed PMID: 36756860.

Sander S, Janzen N, Janetzky B, Scholl S, Steuerwald U, Schafer J, Sander J. Neonatal screening for medium chain acyl-CoA deficiency: high incidence in Lower Saxony (northern Germany). Eur J Pediatr. 2001;160:318–9. PubMed PMID: 11388605.

Santos L, Patterson A, Moreea SM, Lippiatt CM, Walter J, Henderson M. Acute liver failure in pregnancy associated with maternal MCAD deficiency. J Inherit Metab Dis. 2007;30:103. PubMed PMID: 17186412.

Schmidt-Sommerfeld E, Bobrowski PJ, Penn D, Rhead WJ, Wanders RJ, Bennett MJ. Analysis of carnitine esters by radio-high performance liquid chromatography in cultured skin fibroblasts from patients with mitochondrial fatty acid oxidation disorders. Pediatr Res. 1998;44:210–4. PubMed PMID: 9702916.

Shigematsu Y, Hirano S, Hata I, Tanaka Y, Sudo M, Sakura N, Tajima T, Yamaguchi S. Newborn mass screening and selective screening using electrospray tandem mass spectrometry in Japan. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;776:39–48. PubMed PMID: 12127323.

Smith EH, Thomas C, McHugh D, Gavrilov D, Raymond K, Rinaldo P, Tortorelli S, Matern D, Highsmith WE, Oglesbee D. Allelic diversity in MCAD deficiency: the biochemical classification of 54 variants identified during 5 years of ACADM sequencing. Mol Genet Metab. 2010;100:241–50. PubMed PMID: 20434380.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Strauss KA, Puffenberger EG. Genetics, medicine, and the Plain people. Annu Rev Genomics Hum Genet. 2009;10:513-36. PubMed PMID: 19630565.

Tajima G, Hara K, Tsumura M, Kagawa R, Okada S, Sakura N, Hata I, Shigematsu Y, Kobayashi M. Screening of MCAD deficiency in Japan: 16 years' experience of enzymatic and genetic evaluation. Mol Genet Metab. 2016;119:322-8. PubMed PMID: 27856190.

Tal G, Pitt J, Morrisy S, Tzanakos N, Boneh A. An audit of newborn screening procedure: Impact on infants presenting clinically before results are available. Mol Genet Metab. 2015;114:403-8. PubMed PMID: 25604974.

Tanaka K, Gregersen N, Ribes A, Kim J, Kølvraa S, Winter V, Eiberg H, Martinez G, Deufel T, Leifert B, Santer R, Francois B, Pronicka E, Laszlo A, Kmoch S, Kremensky I, Kalaydjicva L, Ozalp I, Ito M. A survey of the newborn populations in Belgium, Germany, Poland, Czech Republic, Hungary, Bulgaria, Spain, Turkey, and Japan for the G985 variant allele with haplotype analysis at the medium chain Acyl-CoA dehydrogenase gene locus: clinical and evolutionary consideration. Pediatr Res. 1997;41:201–9. PubMed PMID: 9029639.

Therrell BL Jr, Lloyd-Puryear MA, Camp KM, Mann MY. Inborn errors of metabolism identified via newborn screening: Ten-year incidence data and costs of nutritional interventions for research agenda planning. Mol Genet Metab. 2014;113:14-26. PubMed PMID: 25085281.

Touw CM, Smit GP, de Vries M, de Klerk JB, Bosch AM, Visser G, Mulder MF, Rubio-Gozalbo ME, Elvers B, Niezen-Koning KE, Wanders RJ, Waterham HR, Reijngoud DJ, Derks TG. Risk stratification by residual enzyme activity after newborn screening for medium-chain acyl-CoA dehyrogenase deficiency: data from a cohort study. Orphanet J Rare Dis. 2012;7:30. PubMed PMID: 22630369.

Touw CM, Smit GP, Niezen-Koning KE, Bosgraaf-de Boer C, Gerding A, Reijngoud DJ, Derks TG. In vitro and in vivo consequences of variant medium-chain acyl-CoA dehydrogenase genotypes. Orphanet J Rare Dis. 2013;8:43. PubMed PMID: 23509891.

Uppala R, Dudiak B, Beck ME, Bharathi SS, Zhang Y, Stolz DB, Goetzman ES. Aspirin increases mitochondrial fatty acid oxidation. Biochem Biophys Res Commun. 2017;482:346–51. PubMed PMID: 27856258.

Vengalil S, Preethish-Kumar V, Polavarapu K, Christopher R, Gayathri N, Natarajan A, Manjunath M, Nashi S, Prasad C, Nalini A. Fatty acid oxidation defects presenting as primary myopathy and prominent dropped head syndrome. Neuromuscul Disord. 2017;27:986-96. PubMed PMID: 28927828.

Vilarinho L, Rocha H, Sousa C, Marcão A, Fonseca H, Bogas M, Osório RV. Four years of expanded newborn screening in Portugal with tandem mass spectrometry. J Inherit Metab Dis. 2010;33 Suppl 3 :S133-8. PubMed PMID: 20177789.

Waddell L, Wiley V, Carpenter K, Bennetts B, Angel L, Andresen BS, Wilcken B. Medium-chain acyl-CoA dehydrogenase deficiency: genotype-biochemical phenotype correlations. Mol Genet Metab. 2006;87:32–9. PubMed PMID: 16291504.

Wanders RJ, Ruiter JP, Ijlst L, Waterham HR, Houten SM. The enzymology of mitochondrial fatty acid beta-oxidation and its application to follow-up analysis of positive neonatal screening results. J Inherit Metab Dis. 2010;33:479–94. PubMed PMID: 20490924.

Weiss KJ, Berger U, Haider M, Wagner M, Märtner EMC, Regenauer-Vandewiele S, Lotz-Havla A, Schuhmann E, Röschinger W, Maier EM. Free carnitine concentrations and biochemical parameters in medium-chain acyl-CoA dehydrogenase deficiency: genotype-phenotype correlation. Clin Genet. 2023;103:644-54. PubMed PMID: 36840705.

Wilcken B, Haas M, Joy P, Wiley V, Bowling F, Carpenter K, Christodoulou J, Cowley D, Ellaway C, Fletcher J, Kirk EP, Lewis B, McGill J, Peters H, Pitt J, Ranieri E, Yaplito-Lee J, Boneh A. Expanded newborn screening: outcome in screened and unscreened patients at age 6 years. Pediatrics. 2009;124:e241–8. PubMed PMID: 19620191.

Wiles JR, Leslie N, Knilans TK, Akinbi H. Prolonged QTc interval in association with medium-chain acyl-coenzyme A dehydrogenase deficiency. Pediatrics. 2014;133:e1781-6. PubMed PMID: 24799540.

Woo HI, Park HD, Lee YW, Lee DH, Ki CS, Lee SY, Kim JW. Clinical, biochemical and genetic analyses in two Korean patients with medium-chain acyl-CoA dehydrogenase deficiency. Korean J Lab Med. 2011;31:54-60. PubMed PMID: 21239873.

Yusuf K, Jirapradittha J, Amin HJ, Yu W, Hasan SU. Neonatal ventricular tachyarrhythmias in medium chain acyl-CoA dehydrogenase deficiency. Neonatology. 2010;98:260-4. PubMed PMID: 20414003.

Zytkovicz TH, Fitzgerald EF, Marsden D, Larson CA, Shih VE, Johnson DM, Strauss AW, Comeau AM, Eaton RB, Grady GF. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: a two-year summary from the New England Newborn Screening Program. Clin Chem. 2001;47:1945-55. PubMed PMID: 11673361.

License