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Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Synonym: MCAD Deficiency

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Summary

Clinical characteristics

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) is one of the enzymes involved in mitochondrial fatty acid β-oxidation. Fatty acid β-oxidation fuels hepatic ketogenesis, which provides a major source of energy once hepatic glycogen stores become depleted during prolonged fasting and periods of higher energy demands. MCAD deficiency is the most common disorder of fatty acid β-oxidation and one of the most common inborn errors of metabolism. Most children are now diagnosed through newborn screening. Clinical symptoms in a previously apparently healthy child with MCAD deficiency include hypoketotic hypoglycemia and vomiting that may progress to lethargy, seizures, and coma triggered by a common illness. Hepatomegaly and liver disease are often present during an acute episode. Children appear normal at birth and – if not identified through newborn screening – typically present between age three and 24 months, although presentation even as late as adulthood is possible. The prognosis is excellent once the diagnosis is established and frequent feedings are instituted to avoid any prolonged periods of fasting.

Diagnosis/testing

The diagnosis of MCAD deficiency is established in a proband with confirmatory biochemical testing results and biallelic pathogenic variants in *ACADM* identified on molecular genetic testing. Diagnostic testing is typically initiated after either a positive newborn screening result or suggestive biochemical testing in a previously healthy individual who develops symptoms. Biochemical and molecular diagnostic methods for MCAD deficiency are sensitive enough to identify asymptomatic affected individuals without needing provocative tests. Assays to determine residual enzyme activity are possible but not routinely necessary and not clinically available in many regions.

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Management

Treatment of manifestations: The most important intervention is giving simple carbohydrates by mouth (e.g., glucose tablets or sweetened, non-diet beverages) or IV if needed to reverse catabolism and sustain anabolism.

Prevention of primary manifestations: The mainstay is avoidance of fasting: infants require frequent feedings; toddlers could be placed on a relatively low-fat diet (e.g., <30% of total energy from fat) and could receive 2 g/kg of uncooked cornstarch at bedtime to ensure sufficient glucose overnight.

Agents/circumstances to avoid: Hypoglycemia (e.g., from excessive fasting); infant formulas that contain medium-chain triglycerides as the primary source of fat.

Evaluation of relatives at risk: 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 the 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.

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 fatty acid β-oxidation disorder. Fatty acid β-oxidation 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

MCAD deficiency **should be suspected** in:

- An infant with a positive newborn screening result;
- A previously healthy individual who becomes symptomatic and has supportive clinical and laboratory findings; or
- A case of sudden and unexpected death.

Positive Newborn Screening (NBS) Result

NBS for MCAD deficiency is primarily based on the results of a quantitative acylcarnitine profile on dried blood spot (DBS) cards.

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 cut-off 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 (Mayo Clinic CLIR, accessed 7-26-23).

Follow-up testing includes: plasma acylcarnitine analysis, urine organic acid analysis, and urine acylglycine analysis. If the test results support the likelihood of MCAD deficiency, additional testing is required to establish the diagnosis (see Establishing the Diagnosis).

The American College of Medical Genetics and Genomics ACT Sheet and Diagnostic Algorithm (pdfs) for follow up of an abnormal NBS result suggestive of MCAD deficiency should be reviewed.

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 c.985A>G pathogenic variant (see Table 1), and premature infants [McCandless et al 2013]. False negatives have been reported in newborns with low free carnitine levels, such as infants born to a mother with low free carnitine levels, including previously undiagnosed mothers with MCAD deficiency, maternal carnitine transporter deficiency, or nutritional carnitine deficiency [Leydiker et al 2011, Aksglaede et al 2015].

Note: A newborn whose blood sample has been submitted for NBS may become symptomatic before the screening results are available. Severe lethal presentations in the first week of life (i.e., before NBS results are available) have been reported [Ensenauer et al 2005, Wilcken et al 2007, Lindner et al 2011, Andresen et al 2012, Lovera et al 2012, Tal et al 2015].

Published reports on NBS outcomes document that individuals identified and treated presymptomatically can be saved from metabolic decompensations and relevant sequelae [Wilcken et al 2007, Lindner et al 2011, Catarzi et al 2013, Tal et al 2015]. However, these reports also show that some individuals with MCAD deficiency present (sometimes fatally) within the first few days of life, making it impossible to obtain NBS results prior to their initial clinical manifestation [McCandless et al 2013] Implementation of NBS has seen improvements in mortality rates from >20% to 3.5%-10% [Nennstiel-Ratzel et al 2005, Grosse et al 2006, Wilcken et al 2007, Feuchtbaum et al 2018].

A Previously Healthy Individual Who Becomes Symptomatic

Symptoms in a previously healthy individual may include:

- Hypoketotic hypoglycemia and vomiting that may 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).

Historically, prior to NBS, the first acute episode would typically occur before age two years; however, affected individuals may present at any age including adulthood [Raymond et al 1999, Schatz & Ensenauer 2010]. Late-onset presentations have been described in adults after prolonged fasting, including after fasting for surgery, or with alcohol intoxication [Lang 2009].

Rapid clinical deterioration that is disproportionate in the setting of a common and generally benign infection should raise the suspicion of MCAD deficiency or other fatty acid β-oxidation disorders, and should prompt initiation of treatment simultaneously with additional diagnostic testing.

Sudden and Unexpected Death

Most FAO disorders including MCAD deficiency frequently manifest with sudden and unexpected death [Rinaldo et al 2002]. The following information supports the possibility of MCAD deficiency:

- Evidence of lethargy, vomiting, and/or fasting in the 48 hours prior to death
- Breast-fed infant (rather than bottle-fed) [Ahrens-Nicklas et al 2016]

- Adult following an episode of fasting or alcohol consumption [Lang 2009]
- A family history of sudden death or Reye syndrome in sibs [Bzduch et al 2001]
- Findings at autopsy of cerebral edema and fatty infiltration of the liver, kidneys, and heart [Boles et al 1998]

Note: Postmortem acylcarnitine analysis for MCAD deficiency may 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].

Establishing the Diagnosis

The diagnosis of MCAD deficiency **is established** in a proband with Suggestive Findings (see above) by confirmatory biochemical testing and biallelic pathogenic variants in *ACADM* identified by molecular genetic testing (see Table 1). Biochemical and molecular diagnostic methods for MCAD deficiency are sensitive enough to identify asymptomatic affected individuals without using provocative tests. Assays to determine residual enzyme activity are possible but not routinely necessary and not clinically available in many regions.

Note: Confirmatory postmortem testing is possible in the individual with sudden and unexpected death if MCAD deficiency is suspected.

Biochemical Testing

Testing should include **plasma acylcarnitine analysis** with proper interpretation. **Urine organic acid analysis** and **urine acylglycine analysis** may provide supporting evidence and have been used for diagnosis prior to the advent of widely available molecular testing, or when molecular testing is not readily available.

Plasma acylcarnitine analysis. The acylcarnitine profile of individuals with MCAD deficiency is characterized by the prominent accumulation of C8- (octanoylcarnitine), with lesser elevations of C6-, C10-, and C10:1-acylcarnitines [Millington et al 1990, Chace et al 1997, Smith et al 2010]. Secondary decreased levels of free carnitine (C0) and acetylcarnitine (C2) may be seen with carnitine deficiency. The C8/C2 and C8/C10 ratios have also been used for interpretation of primary elevations of C8.

Sole reliance on plasma acylcarnitine analysis may not be sufficient, and either urine organic acids or acylglycines (ideally collected during an acute episode of metabolic decompensation as these, as well as acylcarnitines, could normalize when the individual is not under metabolic stress) should be analyzed to reach a correct biochemical diagnosis.

Note: When clinical suspicion of MCAD deficiency remains high and plasma acylcarnitine testing is not diagnostic, low free carnitine levels should be considered during the evaluation. Secondary carnitine deficiency may cause lower elevations of C8-, C6-, and C10 -acylcarnitines, or even normal acylcarnitine profiles [Clayton et al 1998; Leydiker et al 2011]. Some laboratories report acylcarnitine profiles with low C0 and C2-acylcarnitines, and while nonspecific, these findings may indicate an underlying metabolic disorder such as maternal MCAD deficiency, maternal carnitine transporter deficiency, or nutritional carnitine deficiency [Aksglaede et al 2015; Leydiker et al 2011].

Urine organic acid analysis. In symptomatic individuals, medium-chain dicarboxylic acids are elevated with a characteristic pattern – hexanoylglycine (C6) > octanoylglycine (C8) > decanoylglycine (C10) – while ketones are inappropriately low. During acute episodes, suberylglycine and dicarboxylic acids (adipic, suberic, sebacic, dodecanedioic, and tetradecanedioic) may be elevated, and represent additional biochemical markers of MCAD deficiency [Niwa 1995, Rinaldo et al 1998].

- Standard urine organic acid profiles are often uninformative in individuals with MCAD deficiency who are clinically stable and not fasting [Rinaldo et al 2001]. Under these conditions, the urinary excretion of

the three acylglycines is often <10 mmol/mol creatinine – levels not readily detectable by routine organic acid analysis.
- Individuals receiving medium-chain triglyceride (MCT) oil supplements or MCT-containing foods (e.g., MCT-supplemented infant formulas, coconut oil) may demonstrate elevated concentrations of octanoic acid and decanoic acid, but have normal *cis*-4 decenoic acid and should not be interpreted as possibly having MCAD deficiency.
- Low levels of ketones may be seen (see Clinical Description, **Hypoketotic hypoglycemia**).

Urine acylglycine analysis will detect urinary n-hexanoylglycine, 3-phenylpropionylglycine, and suberylglycine. This test is more sensitive and specific for the identification of asymptomatic individuals and those with mild or intermittent biochemical phenotypes that may be missed by organic acid analysis alone [Rinaldo et al 1988, Rinaldo et al 2001].

- During acute episodes, large amounts of hexanoylglycine and suberylglycine are present (which are also readily detectable by urine organic acid analysis).
- Acylglycine analysis is informative in newborns and is the preferred test in persons who are clinically asymptomatic or who have mild or intermittent biochemical phenotypes.
- The test, requiring only a random urine sample from asymptomatic individuals and no provocative tests, is informative immediately after birth [Bennett et al 1991].

Note: Integrated analysis, post-analytic interpretation, and differential diagnosis of acylcarnitine and acylglycine results deemed to be abnormal could be aided by tools developed through the Collaborative Laboratory Integrated Reports (CLIR) project.

Molecular Genetic Testing

Molecular genetic testing approaches, which are determined by the clinical findings, can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (typically exome sequencing and exome array).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Infants with positive NBS and confirmatory follow-up testing are likely to be diagnosed using gene-targeted testing (see Option 1), whereas symptomatic individuals with nonspecific supportive clinical and laboratory findings (who had not undergone NBS or had normal NBS results in the past) in whom the diagnosis of MCAD deficiency has not been considered are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

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* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon-level or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- Targeted analysis for common northern European pathogenic variants may be performed first in individuals of northern European background:
  - c.985A>G (p.Lys329Glu)
  - c.199T>C (p.Tyr67His)

- Targeted analysis for common Japanese pathogenic variants may be performed first in individuals of Japanese ancestry. These variants account for about 60% of alleles examined in the Japanese population [Tajima et al 2016]:
  - c.449_452delCTGA (p.Thr150ArgfsTer4)
  - c.50G>A (p.Arg17His)
  - c.1085G>A (p.Gly362Glu)
  - c.157C>T (p.Arg53Cys)
  - c.843A>T (p.Arg281Ser)

A 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 may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of MCAD deficiency has not been considered, **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.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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]	4 reported [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. 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. HGMD (accessed 7-26-23)
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. [Morris et al [1995], Arnold et al [2010], Searle et al [2013], Abulí et al [2016]

Enzyme Activity Analysis

Analysis of fatty acid β-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-C10 acylcarnitines as described for plasma analysis confirms the diagnosis [Matern 2014].

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

Measurement of MCAD enzyme activity (currently not available in the United States) in cultured fibroblasts or other tissues (leukocytes, liver, heart, skeletal muscle, or amniocytes) by the ETF reduction assay reveals that individuals with MCAD deficiency usually exhibit MCAD enzymatic activity that is <10% of normal [Hale et al 1990]. Similar enzyme deficiency was seen in a different assay using an HPLC method [Wanders et al 2010]. Another study investigating enzyme activity in fibroblasts found <35% activity in individuals with MCAD deficiency [Bouvier et al 2017].

- 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]. According to Sturm et al [2012], however, residual MCAD enzyme activity <30% requires treatment and follow up.
- It is uncertain whether variability in MCAD enzyme activity assays plays a role in these different conclusions.
- MCAD enzyme activity is routinely measured in the Netherlands and may guide NBS risk stratification [Jager et al 2019].

Confirmatory Postmortem Testing

Collect postmortem blood [Chace et al 2001] and bile [Rashed et al 1995] spots on filter paper cards of the type used for NBS for subsequent acylcarnitine analysis. Collection of both specimens provides a better chance of detecting affected individuals and independently confirming the diagnosis.

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

Note: Although postmortem biochemical and/or molecular genetic testing of tissues and cultured skin fibroblasts is possible [Rinaldo et al 2002], it is logistically impractical and thus rarely performed.

Clinical Characteristics

Clinical Description

Fatty acid β-oxidation 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 Pathophysiology). 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 may manifest in preprandial hypoglycemia symptoms such as lethargy, irritability, jitteriness, seizures, or hypoglycemic crisis. MCAD deficiency is a known cause of sudden infant death syndrome (SIDS) [Roe et al 1986].

MCAD Deficiency

Individuals with MCAD deficiency appear normal at birth and historically have presented between age three and 24 months; presentations in adulthood have also been reported [Duran et al 1986, Raymond et al 1999, Lang 2009].

Hypoketotic hypoglycemia. Affected individuals tend to present in response to either prolonged fasting (e.g., weaning the infant from nighttime feedings) or 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 may also begin with or 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 should not be taken as evidence against MCAD deficiency ("hypoketotic" as compared to nonketotic), as ketones may be detected during times of acute metabolic decompensation.

Hepatomegaly may be present during an acute decompensation, which is also characterized by hypoketotic hypoglycemia, increased anion gap, hyperuricemia, elevated liver transaminases, and hyperammonemia.

Sudden death. Sudden and unexpected death was historically common as the first manifestation of MCAD deficiency [Iafolla et al 1994, Rinaldo et al 1999, Chace et al 2001] and still may occur as late as adulthood (e.g., precipitated by times of increased metabolic stress such as surgery or prolonged fasting) [Raymond et al 1999].

- If the diagnosis of MCAD has not been previously established, at least 18% and up to 25% of affected individuals die during their first metabolic crisis [Iafolla et al 1994].
- Early death before the return of newborn screening (NBS) results still occurs.
- Findings at autopsy include cerebral edema and fatty infiltration of the liver, kidneys, and heart [Boles et al 1998].

Neurologic findings. Individuals with MCAD deficiency who have suffered the effects of an uncontrolled metabolic decompensation are at risk of losing developmental milestones and acquiring aphasia and attention-deficit disorder, which are thought to be secondary to brain injury sustained during the acute metabolic event.

Muscular concerns. Individuals with MCAD deficiency who have suffered the effects of uncontrolled metabolic decompensation may be at risk for chronic muscle weakness, as observed in 18% of individuals who experienced 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].

Growth. Children with MCAD deficiency are at risk for obesity after initiation of treatment, likely due to the frequency of feeding.

Arrhythmia. Cardiac symptoms in MCAD deficiency are rare but have been reported in sporadic case reports. Prolongation of the QTc interval has been reported in an infant with MCAD deficiency [Wiles et al 2014]. A girl age 16 years 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 may be at risk for chronic kidney disease as they age. Renal proximal tubules contain high concentration of mitochondria that express fatty acid enzymes, which may be affected in individuals with fatty acid oxidation defects. Autopsy findings associated with MCAD deficiency have identified fatty infiltration of the kidney [Boles et al 1998]. Individuals with tubulointerstitial fibrosis have also been demonstrated to have lower expression of some fatty acid oxidation enzymes, leading to ATP 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 may remain asymptomatic, although whether this is attributable to early awareness of the disease, early initiation of treatment and resulting prevention of symptoms, or to a higher residual MCAD enzymatic activity remains to be determined [Zschocke et al 2001].
- Individuals with a "milder" biochemical phenotype can still develop life-threatening symptoms [Dessein et al 2010].
- All individuals with MCAD deficiency should be considered at risk of developing clinical manifestations and should receive long-term follow up and management [Arnold et al 2010].

Pathophysiology

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is a disorder of mitochondrial fatty acid β-oxidation. Fatty acid β-oxidation releases energy and provides acetyl-CoA for hepatic ketogenesis. Once glycogen stores are depleted during prolonged fasting and periods of higher energy demands, peripheral tissues switch to using energy from fatty acid oxidation to preserve glucose for utilization by the brain. The brain can also use ketone bodies derived from fatty acids.

Medium- and short-chain fatty acids passively diffuse across the mitochondrial membrane independent of carnitine transport and are activated to CoA esters in the mitochondrial matrix. Fatty acid β-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 β-oxidation spiral pathway shortens the acyl-CoA chain by two carbons and produces a molecule each of acetyl-CoA, $FADH^+$, and $NADH_2$.

MCAD deficiency impairs the energy supply to peripheral tissues through ketogenesis and increases 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].

Genotype-Phenotype Correlations

Inclusion of MCAD deficiency in NBS programs has led to the identification of individuals with less pronounced abnormalities in their acylcarnitine profiles who are compound heterozygotes either for the common European *ACADM* pathogenic variant c.985A>G (p.Lys329Glu), previously known as p.Lys304Glu), and another pathogenic variant, or for two non-c.985A>G pathogenic variants [Albers et al 2001, Andresen et al 2001, Zschocke et al 2001, Maier et al 2005, Smith et al 2010].

- Most individuals are compound heterozygous for the c.985A>G pathogenic variant and another deletion or pathogenic variant, or homozygous for c.985A>G.
- Individuals homozygous for the common c.985A>G variant had the highest C8 newborn screen values and were most likely to have neonatal symptoms [Waddell et al 2006, Arnold et al 2010, Bentler et al 2016].
- Individuals with compound heterozygous pathogenic variants c.985A>G and c.600-18G>A have a mild phenotype and may not be detected by NBS due to residual MCAD enzyme activity [Grünert et al 2015].
- 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].

The c.199T>C 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]. Individuals who are heterozygous for the c.199T>C variant and another pathogenic variant may have lower acylcarnitine levels but still be at risk for metabolic crisis [Gramer et al 2015].

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 disorder.

For several presumably mild pathogenic variants identified only presymptomatically through NBS, expression studies that may aid in risk assessment have also been conducted to evaluate the effect of the variant on protein folding, temperature sensitivity, and enzyme activity [Jank et al 2014, Koster et al 2014].

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 better delineated, affected individuals were misdiagnosed as having Reye syndrome.

Note that historical nomenclature begins amino acid numbering at p.1 of the mature protein, whereas current nomenclature begins amino acid numbering at p.1 of the pro-protein. Therefore, the common pathogenic variant encoded by c.985A>G (p.Lys329Glu) was historically known as p.Lys304Glu.

Prevalence

The overall prevalence of MCAD deficiency is 5.3 (4.1-6.7, 99% CI) per 100,000 births across a variety of populations [Feuchtbaum et al 2012]. MCAD deficiency is prevalent in individuals of (especially northern) European descent. The carrier frequency for the c.985A>G pathogenic variant in *ACADM* is between 1:40 and 1:100 in northern Europeans, suggestive of a founder effect [Gregersen et al 1993, Tanaka et al 1997]. A similar prevalence has been observed among Portuguese 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 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. 1:51,000 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. 1:18,000 live births [Al-Hassnan et al 2010]
  - Taiwan. 1:263,500 live births [Chien et al 2013]
- **Australia.** New South Wales. 1:19,000 live births [Wilcken et al 2009]
- **Europe.** The prevalence in live births in Europe has ranged from a high of 1:4,900 in northern Germany [Sander et al 2001] to a low of 1:24,900 in Austria [Kasper et al 2010] or 1:23,000 in central Italy.
- **North America.** Prevalence has ranged from 1:23,400 live births in Canada [Prasad et al 2012] to ranges of 1:13,000 to 1:19,000 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].

Historically, MCAD deficiency was considered less common in the Hispanic, African American, and Native American populations in the USA. 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 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 MCAD deficiency, including other disorders of fatty acid β-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 β-oxidation. Because of the nonspecific clinical presentation of MCAD deficiency, distinguishing it from other mitochondrial fatty acid β-oxidation disorders requires biochemical and molecular testing.

Medium-chain acyl-coenzyme A dehydrogenase belongs to the acyl-CoA dehydrogenase (ACAD) gene family, which includes three other dehydrogenases involved in the fatty acid β-oxidation pathway [Swigonová et al 2009]: short-chain-specific acyl-CoA dehydrogenase (SCAD) encoded by *ACADS*, long-chain-specific acyl-CoA dehydrogenase (LCAD) encoded by *ACADL*, and very long-chain-specific acyl-CoA dehydrogenase (VLCAD) encoded by *ACADVL*, long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD), and trifunctional protein (TFP) encoded by *HADHA* and *HADHB*.

Additional enzymes with homology to MCAD are isovaleryl-CoA dehydrogenase encoded by *IVD* (see Classic Isovaleric Acidemia), short-/branched-chain-specific acyl-CoA dehydrogenase encoded by *ACADSB* [Alfardan et al 2010], isobutyryl-CoA dehydrogenase encoded by *ACAD8* [Pedersen et al 2006], and mitochondrial acyl-CoA dehydrogenase family member 9 encoded by *ACAD9* [Haack et al 2010].

Disorders to consider in the differential diagnosis:

- **Multiple acyl-CoA dehydrogenase deficiency** (also known as MADD or glutaric acidemia type II [GA II]) is a complex disorder with presentations ranging from neonatal with complex congenital abnormalities and dysmorphism to hypoketotic hypoglycemia, cardiomyopathy, and rhabdomyolysis in later-onset presentations. Acylcarnitines demonstrate variable elevations 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-, and C18:1-OH-acylcarnitines. Additionally, elevations of diagnostic biochemical markers may include glutaric acid, 3-hydroxyisovaleric acid, lactic acid, medium- and long-chain dicarboxylic acids, and glycine species such as isovalerylglycine, isobutyrylglycine, and 2-methylbutyrylglycine. However, ketone bodies including acetoacetic acid and 3-hydroxybutyric acids will be minimal or undetectable, distinguishing GA II from MCAD deficiency. MADD is associated with biallelic pathogenic variants in one of three genes: *EFTA*, *EFTB*, or *ETFDH*.
- **Short-chain acyl-CoA dehydrogenase (SCAD) deficiency** (SCAD deficiency) is associated with biallelic pathogenic variants in *ACADS*. Most infants with SCAD deficiency identified through newborn screening programs 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. Acylcarnitines will demonstrate elevations of C4-acylcarnitines (butyrylcarnitine), distinguishing SCAD deficiency from MCAD deficiency.
- **Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency** may present similarly to MCAD deficiency with hypoketotic hypoglycemia, liver dysfunction, and liver failure, but VLCAD deficiency is clinically distinct with the presence of significant rhabdomyolysis and cardiomyopathy not seen in MCAD deficiency. Plasma acylcarnitines demonstrate elevations of C14-, C14:1-, C16- and C16:1-acylcarnitines, distinguishing VLCAD deficiency from MCAD deficiency. VLCAD deficiency is caused by biallelic pathogenic variants in *ACADVL*.
- **Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency** and **trifunctional protein (TFP) deficiency** may present similarly to MCAD deficiency with hypoketotic hypoglycemia, liver dysfunction, and liver failure, but LCHAD and TFP deficiencies are clinically distinct with the presence of significant rhabdomyolysis and cardiomyopathy as well as peripheral neuropathy and retinopathy not seen in MCAD deficiency. Plasma acylcarnitines demonstrate elevations of C16-OH-, C16:1-OH-, C18-OH-, and C18:1-OH-acylcarnitines, distinguishing LCHAD deficiency and TFP deficiency from MCAD deficiency. LCHAD and TFP deficiencies are caused by biallelic variants in *HADHA* and *HADHB*, respectively.

- The **carnitine transport disorders** are very closely related to the fatty acid β-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. These disorders include the following.
  - **Systemic primary carnitine deficiency** (also known as carnitine uptake defect) is caused by biallelic pathogenic variants in *SLC22A5*. Plasma total and free carnitine levels are low, distinguishing systemic primary carnitine deficiency from MCAD deficiency.
  - **Carnitine palmitoyltransferase 1A (CPT 1A) deficiency** is caused by biallelic pathogenic variants in *CPT1A* and does not present with cardiomyopathy or skeletal myopathy. Plasma total and free carnitine levels are elevated, with decreased levels of long-chain acylcarnitines and an elevated C0/(C16+C18) ratio, distinguishing CPT 1A deficiency from MCAD deficiency.
  - **Carnitine palmitoyltransferase II (CPT II) deficiency** is caused by biallelic pathogenic variants in *CPT2*, and in addition to the more commonly known adult form, individuals may develop a severe infantile hepatocardiomuscular form of the disorder. Plasma acylcarnitine analysis will demonstrate elevations of C16-OH-, C16:1-, C18-, and C18:1-acylcarnitines, distinguishing CPT II deficiency from MCAD deficiency.
  - **Carnitine-acylcarnitine translocase (CACT) deficiency** is caused by biallelic pathogenic variants in *SLC25A20*. CACT deficiency may be indistinguishable from CPT II deficiency clinically and biochemically. CACT deficiency and CPTII have identical elevations on plasma acylcarnitines of C16-OH-, C16:1-, C18-, and C18:1-acylcarnitines, distinguishing both from MCAD deficiency.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an **asymptomatic** individual with a diagnosis of medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency or an **abnormal newborn screen**, the following evaluations are recommended:

- Plasma acylcarnitine analysis
- Plasma free and total carnitine levels
- Urine acylglycine analysis
- Urine organic acid analysis
- Consultation with a biochemical geneticist, clinical geneticist, and/or genetic counselor

In a **symptomatic** individual diagnosed with MCAD deficiency, the following additional laboratory studies should be considered when 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 (collected in a sodium-heparin tube, placed on ice immediately, and sent STAT to the lab on ice)
- Lactic acid
- CBC with differential
- Electrolytes
- Blood cultures (in case of fever)

Treatment of Manifestations

The 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. Consultation with a biochemical geneticist should be obtained as soon as possible.

- Early initiation of investigation of the underlying cause of the metabolic stress and initiation of appropriate treatment is necessary.
- Treatment recommendations are available but should be implemented in consultation with a biochemical geneticist [Aldubayan et al 2017]. See New England Consortium of Metabolic Programs and Genetic Metabolic Dietitians International.

The most important aspect of treating symptomatic individuals is reversal of catabolism and prevention of hypoglycemia by providing simple carbohydrates by mouth (e.g., glucose tablets or sweetened, non-diet beverages) or intravenous fluids if the individual is unable to receive sufficient oral intake to maintain anabolism.

IV administration of glucose should be initiated immediately with a bolus of 2 mL/kg 25% dextrose, followed by 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 [Saudubray et al 1999].

Emergency letter. All affected individuals should have a frequently updated "emergency" letter that may be given, if needed, to health care providers who may not be familiar with MCAD deficiency. This letter should include a detailed explanation of the management of acute metabolic decompensation, emphasizing the importance of preventive measures (e.g., intravenous glucose regardless of "normal" laboratory results, overnight in-hospital observation), and the telephone numbers of the individual's metabolic specialist.

- A MedicAlert® bracelet may be helpful.
- The New England Metabolic Consortium of Metabolic Programs website provides an example of a post-emergency management letter for MCAD (pdf); see Acute Illness Protocol (page 4).

Prevention of Primary Manifestations

Avoidance of Fasting

Avoidance of fasting is the mainstay in treatment of MCAD deficiency. Derks et al [2007] studied the length of time that MCAD-deficient but asymptomatic individuals should be able to fast. In the absence of an intercurrent infection with fever or other stressing conditions, they recommend the following maximum fasting times:

- Up to eight hours in infants between ages six and 12 months
- Up to ten hours during the second year of life
- Up to 12 hours after age two years

Others have recommended a general rule of thumb: to avoid fasting for longer than four hours between birth and age four months, then add an additional hour of fasting for each month of age up to 12 months (see Genetic Metabolic Dietitians International).

To avoid excessive fasting:

- Infants require frequent feedings (every 2-3 hours), as is the practice with unaffected newborn infants.
- Overnight feedings, a bedtime snack, or 2 g/kg of uncooked cornstarch as a source of complex carbohydrates at bedtime to ensure sufficient glucose supply overnight have also been used. If an individual does not have an illness, this supplemental feeding may not be necessary.

- A normal, healthy diet containing no more than 30% of total energy from fat may be followed. Breastmilk or standard infant formulas are appropriate to meet nutritional needs during infancy, with introduction of solids per standard infant feeding guidelines [Frazier 2008].
- Individuals with MCAD deficiency do not need extra calories; overfeeding should be avoided because of the risk for obesity.

Prolonged fasting is not recommended, especially during times of illness when individuals with MCAD deficiency are at risk for metabolic crisis.

L-Carnitine Supplementation

L-carnitine supplementation is controversial. Individuals with MCAD deficiency may develop a secondary carnitine deficiency as excess acylcarnitines bind to free carnitine and are renally excreted.

- Several authors recommend oral supplementation with 100 mg/kg/day of carnitine to correct the frequently observed secondary carnitine deficiency and to enhance the elimination of toxic metabolites [Roe & Ding 2001].
- A NBS follow-up study from Spain and Portugal also reported the need for higher-dose carnitine supplementation due to the findings of low C0 levels associated with homozygosity for c.985A>G at diagnosis [Couce et al 2013].
- 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]. Low-intensity exercise for one hour on a cycle ergometer showed reduced fatty acid oxidation rates in affected individuals vs controls that were not improved by carnitine administration (100 mg/kg/day), while carnitine concentrations in muscle and plasma increased among those receiving carnitine supplementation [Madsen et al 2013].
- Carnitine-mediated detoxification of medium-chain fatty acids, assessed by urinary excretion of medium-chain acylcarnitines, is quantitatively negligible in individuals who have MCAD deficiency [Rinaldo et al 1993]. Under controlled circumstances, carnitine supplementation also did not improve the response to a fasting challenge [Treem et al 1989].
- The cost of long-term supplementation with carnitine could be significant. Furthermore, while no severe untoward effects of L-carnitine have been reported in individuals with MCAD deficiency [Potter et al 2012], some individuals have complained about nausea, diarrhea, abdominal pain, and a fishy odor when treated with 100 mg/kg/day of L-carnitine [Madsen et al 2013].

Given this information, the authors recommend the use of low-dose L-carnitine supplementation when free carnitine levels are below the normal range. Consensus as to whether additional carnitine is detrimental or efficacious has not been established.

Surveillance

A medical 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.

During the first months of life, monthly visits should be considered to ensure that families understand and are comfortable with treatment while the infant is otherwise well. A metabolic dietician (see gmdi.org) should be involved to ensure proper nutrition in terms of quality and quantity.

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

Long-term outcome studies revealed that persons treated for MCAD deficiency are prone to excessive weight gain [Derks et al 2006]. 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. Growth parameters should be monitored carefully at each clinic visit. Accordingly, follow up should include weight control measures such as regular education about proper nutrition and recommended physical exercise.

Although development is typically normal for individuals treated prospectively, those who experience metabolic decompensations requiring hospitalization often demonstrate developmental and neurologic disabilities. Neurodevelopmental assessments and intervention should be considered for such individuals [Derks et al 2006].

Agents/Circumstances to Avoid

Hypoglycemia must be avoided by frequent feedings 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 contraindicated in MCAD deficiency.

Popular high-fat/low-carbohydrate diets are not appropriate in 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 I clinical trial examining the use of glycerol phenylbutyrate (Ravicti®) at 2, 4, and 6 g/m^2/day in four adults with MCAD deficiency who had at least one copy of the c.985A>G pathogenic variant was completed in 2017. The primary outcome was changes in the assessment of metabolic stress pre- and post-dosing with Ravicti®. There were no serious adverse events. Previous molecular modeling has suggested that the MCAD enzyme may be able to utilize phenylbutyryl-CoA as a substrate [Kormanik et al 2012].

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 a child affected with MCAD deficiency are obligate heterozygotes (i.e., presumed to be carriers of at least one *ACADM* pathogenic variant based on the presence of biallelic *ACADM* pathogenic variants in their affected child).
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- If both parents are carriers of 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 may remain asymptomatic until late adulthood, apparently unaffected sibs should be tested for MCAD deficiency. See Management, Evaluation of Relatives at Risk.

Offspring of a proband

- The offspring of an individual with MCAD deficiency inherit an *ACADM* pathogenic variant from their affected parent.
- The carrier (heterozygote) frequency in the North American/European population for a pathogenic variant in *ACADM* may be as high as 1/40 individuals. Therefore, the risk to the offspring of an affected individual and a reproductive partner of northern European origin of having MCAD deficiency is ~1/80.
- 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, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

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

Note: States store leftover dried blood spot samples for variable lengths of time following newborn screening 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 molecular genetic testing for a pregnancy at increased risk 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 testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

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

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  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
  www.fodsupport.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.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

Gene structure. *ACADM*, a nuclear gene, comprises 12 exons that span more than 44 kb and encode a precursor monomer of 421 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Nearly 175 disease-associated variants have been described. (HGMD, accessed 7-26-23). These variants include missense, nonsense, and splicing variants, small deletions, small insertions, a small indel, and four large deletions.

The p.Tyr67His variant (previously referred to as p.Tyr42His) has been identified in 0.10% of European chromosomes and approximately 7% of alleles in individuals with a positive newborn screen result for MCAD deficiency [Maier et al 2005, Andresen et al 2001]. Studies of affected newborns and in vitro experiments demonstrate that p.Tyr67His is a mild folding variant that is associated with a milder biochemical and clinical phenotype. Affected individuals who are compound heterozygous for 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].

Table 2. Notable *ACADM* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	**Comments [Reference]**
NM_000016.5 NP_000007.1	c.985A>G	p.Lys329Glu	Commonly identified in persons of European descent [Rhead 2006, Gramer et al 2015]
	c.199T>C	p.Tyr67His	Mild folding variant assoc w/milder biochemical & clinical phenotype; commonly identified in persons of European descent [Maier et al 2009, Koster et al 2014, Hara et al 2016]
	c.449_452delCTGA	p.Thr150ArgfsTer4	Most commonly identified in Japanese population [Tajima et al 2016]
	c.1085G>A	p.Gly362Glu	
	c.50G>A	p.Arg17His	
	c.157C>T	p.Arg53Cys	
	c.843A>T	p.Arg281Ser	

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.

Normal gene product. 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.

Abnormal gene product. MCAD deficiency occurs through a loss-of-function mechanism. The common pathogenic variant, p.Lys329Glu, leads to reduced production of an unstable protein but does not impair the enzyme's active site, therefore resulting in normal protein expression [Hara et al 2016].

Chapter Notes

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