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Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

[*MCAD Deficiency*]

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Summary

Disease characteristics. Medium-chain acyl-coenzyme A dehydrogenase (MCAD) is one of the enzymes involved in mitochondrial fatty acid ß-oxidation, which fuels hepatic ketogenesis, a major source of energy once hepatic glycogen stores become depleted during prolonged fasting and periods of higher energy demands. In a typical clinical scenario, a previously healthy child with MCAD deficiency presents with hypoketotic hypoglycemia, vomiting, and lethargy triggered by a common illness. Seizures may occur. Such an episode may quickly progress to coma and death. Hepatomegaly and acute liver disease are often present. Children are normal at birth and typically present between three and 24 months of age; later presentation, even into adulthood, is possible. The prognosis is excellent once the diagnosis is established and frequent feedings are instituted to avoid any prolonged period of fasting.

Diagnosis/testing. Diagnosis requires the integrated interpretation of multiple analyses, including consideration of the clinical status of the affected individual (i.e., acutely symptomatic vs. asymptomatic) at the time of sample collection. Initial testing should include the following analyses and their proper interpretation: plasma acylcarnitines, plasma fatty acid (free or total) profile, urine organic acids, and urine acylglycines. The biochemical diagnosis of MCAD deficiency can be confirmed by measurement of MCAD enzyme activity in fibroblasts or other tissues and/or by molecular genetic testing of the *ACADM* gene; both test methods can be used for prenatal diagnosis. Based on newborn screening results, approximately 50% of individuals are homozygous for the common mutation, K304E, and approximately 40% are heterozygous for K304E and one of more than 40 rarer alleles. Both mutation analysis for the common K304E allele and sequence analysis to detect rarer alleles are available on a clinical basis.

Genetic counseling. MCAD deficiency is inherited in an autosomal recessive manner. At conception, the sibs of an affected individual have a 25% risk of being affected, a 50% risk of being asymptomatic carriers, and a 25% risk of being unaffected and not carriers. The risk could be 50% if one of the parents is also affected. Because asymptomatic parents and sibs may have MCAD deficiency, biochemical evaluation and/or molecular genetic testing should be offered to both parents and all sibs. Because of the high carrier frequency for the K304E mutation in Caucasians of northern European origin, carrier testing should be offered to

reproductive partners of individuals with MCAD deficiency. Prenatal testing is possible for pregnancies at 25% or higher risk by biochemical methods or molecular genetic testing if both parental mutations are known.

Diagnosis

Clinical Diagnosis

Fatty acid oxidation fuels hepatic ketogenesis, a major source of energy for peripheral tissues once glycogen stores become depleted during prolonged fasting and periods of higher energy demands. In a typical clinical scenario, a previously healthy child presents with:

- Hypoketotic hypoglycemia, 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 unexplained death.

The first acute episode usually occurs before two years of age, but affected individuals may present at any age including adulthood [Raymond et al 1999]. Sudden and unexplained death is often the first manifestation of MCAD deficiency [Iafolla et al 1994, Rinaldo et al 1999, Chace et al 2001].

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 ß-oxidation disorders and should prompt administration of intravenous glucose and the collection of urine and blood samples for metabolic testing.

Testing

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) is one of the enzymes involved in the pathway of mitochondrial fatty acid ß-oxidation (FAO). This pathway consists of four sequential reactions catalyzed first by a set of membrane-bound enzymes and then by a different set of matrix-soluble enzymes, producing at the end of each cycle a molecule of acetyl-CoA and a molecule of acyl-CoA with two fewer carbons. MCAD is responsible for the initial dehydrogenation of acyl-CoAs with a chain length between four and 12 carbon atoms. A defect of the MCAD enzyme leads to accumulation of medium-chain fatty acids, which are further metabolized to glycine- and carnitine-esters and to dicarboxylic acids. These metabolites are detectable in body fluids (blood, urine, bile) by gas chromatography/mass spectrometry and tandem mass spectrometry.

Because of the nonspecific clinical presentation of MCAD deficiency, the differential diagnosis from other FAO disorders is an increasingly complex process that can hardly be achieved by a single test. The diagnosis of MCAD deficiency, therefore, requires the integrated interpretation of multiple analyses, including consideration of the clinical status of the affected individual (acutely symptomatic vs. asymptomatic) at the time of sample collection. Initial testing should include the following analyses and their proper interpretation.

Plasma acylcarnitine analysis. The acylcarnitine profile of individuals with MCAD deficiency is characterized by accumulation of C6 to C10 species, with prominent octanoylcarnitine [Millington et al 1990, Chace et al 1997].

A potential pitfall of acylcarnitine analysis in the diagnosis of MCAD deficiency is the possibility that individuals with secondary carnitine deficiency may not show a significant

elevation of C6-C10 acylcarnitines [Clayton et al 1998]. Although free carnitine and acetylcarnitine are abnormally low in the profile of such individuals, such findings are nonspecific and indicative of a possible underlying metabolic disorder. For this reason, reliance on plasma acylcarnitine analysis as the sole biochemical screening is not advisable, and either urine organic acids (in acute episodes) or acylglycines should be analyzed to reach a correct biochemical diagnosis.

Plasma fatty acid analysis. Analyzed as a profile of free fatty acids [Costa et al 1998] or total fatty acids [Lagerstedt et al 2001], the plasma concentrations of octanoic acid, cis-4 decenoic acid and decanoic acid are characteristically elevated in both symptomatic and asymptomatic individuals.

Note: Care should be taken not to interpret as possible MCAD deficiency the elevated concentrations of octanoic acid and decanoic acid with normal cis-4 decenoic acid seen in individuals receiving MCT-oil supplements.

Urine organic acid analysis. In symptomatic individuals, medium-chain dicarboxylic acids are elevated with a characteristic pattern (C6>C8>C10), while ketones are inappropriately low. During acute episodes, 5-hydroxy hexanoic acid, hexanoylglycine, phenylpropionylglycine, and particularly suberylglycine represent additional biochemical markers of MCAD deficiency [Gregersen et al 1983].

Note: 1) Although hypoketotic dicarboxylic aciduria is a common finding, ketone body production could be normal at times of acute decompensation [Patel & Leonard 1995, personal observations]; therefore, the detection of ketonuria by routine urine analysis should not be taken as evidence against a possible diagnosis of MCAD deficiency. 2) Standard urine organic acid profiles are often uninformative in individuals with MCAD deficiency who are stable and are not fasting [Rinaldo et al 2001] because under these conditions the urinary excretion of the three acylglycines is often less than 5 mmol/mol creatinine, levels not readily detectable by routine organic acid analysis.

Urine acylglycine analysis. The acylglycine method is based upon the quantitative determination by stable isotope dilution analysis of urinary n-hexanoylglycine, 3-phenylpropionylglycine, and suberylglycine [Rinaldo et al 1988]. The corresponding free acids are endogenous intermediates of fatty acid metabolism or, for phenylpropionic acid, an end product of the anaerobic metabolism of intestinal bacteria. During an acute episode, affected individuals excrete large amounts of hexanoylglycine and suberylglycine, which are readily detected by organic acid analysis. The test, requiring only a random urine sample from asymptomatic subjects and no provocative tests, is informative immediately after birth [Bennett et al 1991].

Most individuals with MCAD deficiency remain asymptomatic for long periods of time, some for their entire lives [Fromenty et al 1996]. Therefore, diagnostic methods for MCAD deficiency should be sensitive enough to identify asymptomatic affected individuals without provocative tests.

Analysis of fatty acid ß-oxidation in cultured fibroblasts. This assay 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 above for plasma analysis confirms the diagnosis [Roe & Roe 1999, Shen et al 2000, Giak Sim et al 2002]. An alternative cell-based method determines the release of tritiated water in the medium of fibroblasts following incubation with labeled medium-chain fatty acids [Olpin et al 1999].

Analysis of MCAD enzyme activity. Measurement of the activity of the MCAD enzyme in leukocytes, cultured fibroblasts, liver, heart, skeletal muscle, or amniocytes by the ETF reduction assay can be used to confirm the diagnosis of MCAD deficiency. Hale and colleagues (1990) showed that individuals with MCAD deficiency usually exhibit less than 10% of normal MCAD enzymatic activity. The same group found carriers to have on average 49% of normal MCAD enzymatic activity [Hale et al 1990]. This assay is currently available on a research basis only.

Newborn screening. MCAD deficiency meets existing newborn screening criteria [Chace et al 1997, Charrow et al 2000]; several studies have demonstrated that newborn screening for MCAD deficiency is cost-effective [Insinga et al 2002, Venditti et al 2003, Pandor et al 2004]. Since the early 1990s, tandem mass spectrometry (MS/MS) has been applied to the analysis of newborn screening blood spots. Today, several states [National Newborn Screening Status Report (pdf)] and countries have introduced this technology into their newborn screening programs [Matern 2002].

Of note, the specificity of MS/MS to identify MCAD deficiency appears to be 100% because no false negative results have been reported to date [Maier et al 2005, personal observations]. Interestingly, the number of newborns detected with MCAD deficiency exceeds that expected based on the population frequency of the common 985A↓G mutation [Andresen et al 2001, Maier et al 2005]. The positive predictive value (PPV) for identification of MCAD deficiency by acylcarnitine analysis was found to be 19% [Zytkovicz et al 2001] and 46% [Maier et al 2005] by different screening laboratories, significantly higher than that for the disorders screened by the traditional, non-MS/MS methods (0.5-6.0%) [Kwon & Farrell 2000].

The false positive rate for MCAD deficiency most likely varies between screening programs because of differences in acylcarnitine analysis and profiling. Programs that screen for MCAD deficiency but not other fatty acid oxidation disorders often limit their analysis to octanoylcarnitine, the predominant marker for MCAD deficiency. However, octanoylcarnitine is not specific for MCAD deficiency and is expected to be elevated in several other disorders (i.e., medium-/short-chain 3-hydroxy acyl-CoA dehydrogenase deficiency, medium-chain 3-keto acyl-CoA thiolase deficiency, glutaric acidemia type II) and in newborns treated with valproate or fed a diet rich in medium-chain triglycerides [Matern 2002]. Consideration disorders included in the differential diagnosis should minimize the false positive rate.

Postmortem testing. MCAD deficiency frequently manifests with sudden and unexpected death [Rinaldo et al 2002]. If an autopsy is performed, diffuse fatty infiltration of the liver and potentially other organs is often, but not always, present. Additionally, a family history of sudden death or Reye syndrome and evidence of lethargy, vomiting, and/or fasting in the 48 hours prior to death are frequent findings. Although collection and biochemical testing of tissues and cultured skin fibroblasts are possible, these approaches have been deemed impractical and thus have had limited application. On the other hand, postmortem blood [Chace et al 2001] and bile [Rashed et al 1995] could be routinely collected and spotted on a filter paper card of the same kind used for newborn screening. Collection of both specimens provides a better chance of detecting affected individuals and independently confirming the diagnosis. Because most FAO disorders can present with sudden unexpected death, the biochemical 'screening' approach allows identification of a diagnosis that can then often be confirmed by molecular genetic analysis using postmortem blood spots.

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *ACADM* is the only gene known to be associated with medium-chain acyl-coenzyme A dehydrogenase deficiency.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** K304E (985A↓G) is the only prevalent mutation in Caucasians. Newborn screening for MCAD deficiency in diverse populations revealed an allele frequency of 71% (192/272) and homozygosity for the K304E mutation in 52% (70/136) of identified newborns (Table 1) [Carpenter et al 2001,Zytkovicz et al 2001,Chace et al 2002,Maier et al 2005]. Testing for the K304E (985A↓G) mutation is widely available on a clinical basis.
- **Sequence analysis.** Sequence analysis identifies non-K304E mutations which are usually present only in heterozygous form [Andresen et al 1997]. Forty-five additional mutant alleles, 31 listed in the HGMD database, 13 new mutations reported by Maier et al (2005), and one described by Tajima et al (2004), have been identified; most are family-specific mutations.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Test Method	Mutations Detected	Mutation Detection Rate		Test Availability
		Homozygous	Heterozygous	
Targeted mutation analysis	K304E (985A↓G) *ACADM* mutation	~52%	~38%	Clinical Testing
Sequence analysis	*ACADM* mutations	95-100% [1]		

1. Andresen et al 2001, Maier et al 2005

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related Disorders

No other phenotype is associated with mutations in the *ACADM* gene.

Clinical Description

Natural History

Fatty acid oxidation fuels hepatic ketogenesis, a major source of energy for peripheral tissues once glycogen stores become depleted during prolonged fasting and periods of higher energy demands.

Classic MCAD deficiency. Individuals with MCAD deficiency appear normal at birth and usually present between three and 24 months of age; however, presentation in adulthood is also possible [Duran et al 1986, Raymond et al 1999, Feillet et al 2003]. 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. Such instances of metabolic stress lead to vomiting and lethargy, which may quickly progress to coma and death. The episodes may also begin with or be accompanied by seizures.

If the diagnosis of MCAD has not been previously established, at least 18% of affected individuals die during their first metabolic crisis [Iafolla et al 1994].

Hepatomegaly is usually present during acute decompensation, which is also characterized by hypoketotic (not necessarily nonketotic) hypoglycemia, increased anion gap, hyperuricemia, elevated liver transaminases, and mild hyperammonemia.

Individuals with classic MCAD deficiency are at risk of losing developmental milestones and acquiring aphasia and attention deficit disorder, which are thought to be secondary to brain injury occurring during the acute metabolic event. Chronic muscle weakness is observed in 18% of individuals who experience several episodes of metabolic decompensation [Iafolla et al 1994].

McCandless and colleagues (2002) reported that all of 41 newborns with MCAD deficiency identified by newborn screening in North Carolina since 1997 were developing normally. None experienced hypoglycemic episodes, but some required precautionary hospitalization during intercurrent illnesses. Although the prognosis is excellent once the diagnosis is established, unexpected death during the first metabolic decompensation is common [Iafolla et al 1994, Rinaldo et al 1999, Chace et al 2001] and may occur as late as adulthood (e.g., during metabolic stress precipitated by surgery) [Raymond et al 1999].

Findings at autopsy include cerebral edema and fatty infiltration of the liver, kidneys, and heart [Boles et al 1998].

Maternal pregnancy complications such as HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) and acute fatty liver of pregnancy (AFLP) may be more frequent, as for other fatty acid ß-oxidation disorders, when the fetus has MCAD deficiency [Nelson et al 2000, Rinaldo et al 2001, Yang et al 2002].

"Mild" MCAD deficiency. The expansion of newborn screening programs using MS/MS had led to the identification of individuals with milder abnormalities in their acylcarnitine profiles who either are compound heterozygotes for the common *ACADM* mutation (K304E) or have two non-K304E mutations [Andresen et al 2001, Zschocke et al 2001, Maier et al 2005]. The allele frequency of one of these mutations, Y42H, is approximately 7% in MCAD-deficient newborns [Andresen et al 2001, Maier et al 2005] and was shown not to completely abolish MCAD enzymatic activity [Andresen et al 2001]. Over a relatively short follow-up period, none of these individuals had metabolic crises while being treated; however, none was reported to have undergone metabolic challenges such as a fasting test. Despite having higher residual MCAD enzymatic activity [Zschocke et al 2001], such individuals should be considered at risk of developing clinical manifestations. Follow-up for treatment should be initiated [Rinaldo et al 2002]. To determine disease risk, detailed investigations, including carefully executed fasting challenges, should be considered.

Genotype-Phenotype Correlations

Classic MCAD deficiency. The frequent observation of intrafamilial differences of the phenotypic expression of MCAD deficiency is inconsistent with a possible genotype-phenotype correlation. Therefore, it is reasonable to assume that environmental factors (e.g., diet, stress, intercurrent illnesses) are critical in determining the natural history of this disorder [Andresen et al 1997].

"Mild" MCAD deficiency. Mild MCAD deficiency is observed in individuals who are either compound heterozygotes for the common K304E (985A↓G) mutation and another mutation in

ACADM, or homozygous for other mutations [Albers et al 2001, Andresen et al 2001, Zschocke et al 2001].

Prevalence

MCAD deficiency is prevalent in Caucasians, especially those of Northern European descent. The overall frequency of the disease has been estimated to range between 1:4,900 and 1:17,000, a variability related to the ethnic background of the population studied. Based on newborn screening programs worldwide, the incidence of MCAD deficiency has been defined in Northern Germany (one in 4,900 newborns) [Sander et al 2001], Southern Germany (one in 8,500 newborns) [Maier et al 2005], New South Australia (one in 25,000) [Carpenter et al 2001], and the USA (one in 15,700) [Chace et al 2002]. Maier et al (2005) found the disorder to be equally common among Germans and Turks. MCAD deficiency is considered less common in the Hispanic population, a view that may be called into question by the detection of several Hispanic cases in the pilot MS/MS phase of the California newborn screening program; only a few affected African-Americans and Native-Americans have been reported. Most recently, the first affected Asians have been identified through newborn screening [Tajima et al 2004; personal observations].

The carrier frequency for the K304E mutation of the *ACADM* gene is between 1:40 and 1:100, suggestive of a founder effect [Tanaka et al 1997].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

MCAD belongs to the acyl-CoA dehydrogenase (ACAD) gene family, which also includes three other dehydrogenases involved in the fatty acid oxidation pathway: short-chain (SCAD), long-chain (LCAD), and very long-chain acyl-CoA dehydrogenase (VLCAD) [Ikeda et al 1985, Izai et al 1992]. Recently, another gene, ACAD-9 encoding a protein with dehydrogenase activity on palmitoyl-CoA, has been reported [Zhang et al 2002]. Additional dehydrogenases with homology to MCAD are isovaleryl-CoA dehydrogenase (IVD), 2-methyl branched-chain acyl-CoA dehydrogenase (ACADSB) [Gibson et al 2000, Andresen et al 2000], and isobutyryl-CoA dehydrogenase (ACAD8) [Nguyen et al 2002].

- With the exceptions of the LCAD and ACAD-9 genes, defects have been reported for all members of the ACAD gene family.
- SCAD deficiency is a highly heterogeneous disorder [Bhala et al 1995], with phenotypic manifestations possibly modulated by two polymorphisms that are found in 7-14% of the general population [Gregersen et al 1998, Corydon et al 2001, Nagan et al 2003].
- Although the presentation of VLCAD deficiency may be similar to that of MCAD deficiency, the majority of individuals with VLCAD present with cardiomyopathy [Mathur et al 1999].
- The lack of a true case with LCAD deficiency is surprising, as an animal model obtained by genetic manipulation manifests with fasting intolerance and a biochemical phenotype very similar to those observed in human VLCAD deficiency [Kurtz et al 1998].

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, including other disorders of fatty acid ß-oxidation, defects in ketogenesis, urea cycle disorders

(see Urea Cycle Disorders Overview), organic acidurias, respiratory chain defects, and inborn errors of carbohydrate metabolism (e.g., hereditary fructose intolerance).

Although the same biochemical markers elevated in MCAD deficiency are also elevated in glutaric acidemia type 2, the presence of several additional organic acids (glutaric acid, 2-hydroxy glutaric acid, ethylmalonic acid), C4 and C5 carnitine, and glycine esters [Millington et al 1992], and the normal excretion of phenylpropionylglycine [Rinaldo et al 1988] are important discriminators.

In order to rapidly reach a conclusive diagnosis in young children who present with acute liver dysfunction and impaired vigilance, it is recommended that a number of diagnostic laboratory tests be performed on specimens collected early in the metabolic decompensation [Rinaldo et al 2002]. These tests should include at least two of the above-mentioned screening methods (e.g., urine organic acids, plasma acylcarnitines).

Management

Treatment of Manifestations

All affected individuals should have a frequently updated "emergency" letter to 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.

Prevention of Primary Manifestations

The mainstay in the treatment of MCAD deficiency is avoidance of fasting for more than 12 hours.

- Infants require frequent feedings.
- It is recommended that toddlers receive 2 g/kg of uncooked cornstarch as a source of complex carbohydrates at bedtime to ensure sufficient glucose supply overnight.
- A relatively low-fat diet (e.g., <30% of total energy from fat) could be beneficial.

Prevention of Secondary Complications

- Newborn screening results suggest an excellent prognosis when treatment is initiated prior to the onset of symptoms.
- Hypoglycemia must be avoided, if necessary by intravenous administration of glucose.

Agents/Circumstances to Avoid

Infant formulas containing medium-chain triglycerides as the primary source of fat are contraindicated in MCAD deficiency.

Testing of Relatives at Risk

Siblings and parents should be tested by plasma acylcarnitine and urine acylglycine analysis.

Therapies Under Investigation

Gene therapy has been suggested but not attempted in humans with MCAD deficiency.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Although a tangible clinical benefit of carnitine supplementation in individuals with MCAD deficiency has not been proven, 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]. This approach is popular despite the fact that carnitine-mediated detoxification of medium-chain fatty acids, assessed by urinary excretion of medium-chain acylcarnitines, is quantitatively negligible [Rinaldo et al 1993] and carnitine supplementation does not, under controlled circumstances, improve the response to a fasting challenge [Treem et al 1989]. The cost of long-term supplementation with carnitine could be significant. On the other hand, no untoward effects of L-carnitine have been reported in individuals with MCAD deficiency, in contrast to LCHAD deficiency, in which the formation of long-chain 3-hydroxy acylcarnitine species is believed by some authors to be detrimental [Ribes et al 1992, Rocchiccioli et al 1990].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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 and, accordingly, are both carriers of a mutation within the *ACADM* gene.
- Carriers are asymptomatic.
- Since "asymptomatic" parents of children with MCAD deficiency have been reported to be homozygous for *ACADM* gene mutation(s) [Duran et al 1986, Kelly et al 1990, Andresen et al 1997, Bodman et al 2001], biochemical testing and/or DNA-based mutation analysis should be offered to both parents.

Sibs of a proband

- At conception, the sibs of an affected individual have a 25% chance of being affected, a 50% chance of asymptomatic carriers, and a 25% chance of being unaffected and not carriers.
- Given that a clear genotype/phenotype correlation does not exist for MCAD deficiency and individuals may remain asymptomatic until late adulthood, apparently unaffected sibs should be tested for MCAD deficiency [Roe et al 1986, Rinaldo et al 1999].
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.

Offspring of a proband

- The offspring of an individual with MCAD deficiency inherit a disease-causing mutation in the *ACADM* gene from their affected parent.
- The risk that the reproductive partner of an individual with MCAD deficiency is heterozygous for an *ACADM* disease-causing allele may be as high as one in 40. Thus, the risk to the offspring of an affected individual and reproductive partner of northern European origin of having MCAD deficiency is about 1 in 80.
- It is appropriate to test the offspring of an individual with MCAD deficiency for MCAD deficiency.

Other family members. Sibs of the proband's parents are at 50% risk of also being carriers.

Carrier Detection

- Carrier testing using molecular genetic techniques is available on a clinical basis once the mutations have been identified in a proband.
- Carriers for MCAD deficiency can be detected by measurement of MCAD enzymatic activity in various tissues.
- Biochemical screening tests such as acylcarnitine, organic acid, or acylglycine analyses are not useful in determining carrier status.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA, particularly in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

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. See genes-r-us.uthscsa.edu/resources/newborn/newborn_menu.htm for each state's newborn screening laboratory contact information.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at

about 15-18 weeks' gestation* or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed [Rinaldo et al 2001].

Biochemical testing. Prenatal diagnosis for pregnancies at increased risk is also possible by assay of MCAD enzymatic activity in CVS or amniocyte cultures. Amniocyte cultures can also be used for analysis of fatty acid oxidation as it is done in fibroblast cultures (see above).

Prenatal diagnosis, with its inherent risks, offers no advantage to timely postnatal measurement of plasma acylcarnitines and urine acylglycines. Prompt postnatal testing and consultation with a biochemical geneticist are indicated.

Requests for prenatal testing for conditions such as MCAD deficiency that do not affect intellect and have effective treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

* Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Gene Symbol	Chromosomal Locus	Protein Name
ACADM	1p31	Medium-chain acyl-CoA dehydrogenase (MCAD)

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

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

Table C. Genomic Databases for Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Gene Symbol	Entrez Gene	HGMD
ACADM	34 (MIM No. 607008)	ACADM

For a description of the genomic databases listed, click here.

Normal allelic variants: *ACADM* is a nuclear gene. It consists of 12 exons that span more than 44 kb and encode a precursor monomer of 421 amino acids.

Pathologic allelic variants: Forty-five mutations have been described to date (see HGMD, Tajima et al 2004, Maier et al 2005). One mutation located in exon 11, 985A→G, which causes an amino acid change from lysine to glutamate at residue 304 (K304E) of the mature MCAD protein, is present in 76% of alleles in individuals with MCAD deficiency based on newborn screening results in diverse populations [Carpenter et al 2001, Zytkovic et al 2001, Chace et al 2002, Maier et al 2005]. The K304E mutation was independently described by four groups [Matsubara et al 1990, Yokota el al 1990, Kelly et al 1990, Gregersen et al 1991] and early

estimates of the frequency of K304E, based on retrospective clinical studies, were close to 90% of all alleles investigated [Tanaka et al 1992]. With the advent of newborn screening for MCAD deficiency, however, this frequency is continuously declining as additional mutations are identified [Ziadeh et al 1995, Tortorelli et al 2004].

Normal gene product: The mature MCAD protein is a homotetramer encoded by a nuclear gene and 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: The known pathologic mutations within the *ACADM* gene represent primarily missense mutations, followed by deletions, nonsense mutations, and splicing mutations. The common mutation, K304E, is a missense mutation and leads to reduced production of an unstable protein, but does not impair the enzyme's active site.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Medium-chain acyl-coenzyme A dehydrogenase deficiency

FOD (Fatty Oxidation Disorder) Family Support Group
1559 New Garden Rd, 2E
Greensboro, NC 27410
Phone: 336-547-8682
Fax: 336-292-0536
Email: deb@fodsupport.org
www.fodsupport.org

Organic Acidemia Association
13210 - 35th Avenue North
Plymouth, MN 55441
Phone: 763-559-1797
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References

Medical Genetics Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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