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

NLM Citation: Wolfe L, Jethva R, Oglesbee D, et al. Short-Chain Acyl-CoA Dehydrogenase Deficiency. 2011 Sep 22 [Updated 2018 Aug 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Short-Chain Acyl-CoA Dehydrogenase Deficiency

Synonyms: SCADD, SCAD Deficiency

Lynne Wolfe, MS, CRNP, BC,[1] Reena Jethva, MD,[2] Devin Oglesbee, PhD,[3] and Jerry Vockley, MD, PhD[4]

Created: September 22, 2011; Updated: August 9, 2018.

Summary

Clinical characteristics

Most infants with short-chain acyl-CoA dehydrogenase deficiency (SCADD) identified through newborn screening programs have remained well, and asymptomatic relatives who meet diagnostic criteria are reported. Thus, SCADD is now viewed as a biochemical phenotype rather than a disease. A broad range of clinical findings was originally reported in those with confirmed SCADD, including severe dysmorphic facial features, feeding difficulties / failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizures, hypotonia, dystonia, and myopathy. However, individuals with no symptoms were also reported. In a large series of affected individuals detected on metabolic evaluation for developmental delay, 20% had failure to thrive, feeding difficulties, and hypotonia; 22% had seizures; and 30% had hypotonia without seizures. In contrast, the majority of infants with SCADD have been detected by expanded newborn screening, and the great majority of these infants remain asymptomatic. As with other fatty acid oxidation deficiencies, characteristic biochemical findings of SCADD may be absent except during times of physiologic stress such as fasting and illness. A diagnosis of SCADD based on clinical findings should not preclude additional testing to look for other causes.

Diagnosis/testing

SCADD has been defined as the presence of:

- Increased butyrylcarnitine (C4) concentrations in plasma and/or increased ethylmalonic acid (EMA) concentrations in urine under non-stressed conditions (on at least two occasions);

  AND

- Biallelic *ACADS* pathogenic variants.

Author Affiliations: 1 National Human Genome Research Institute National Institutes of Health Bethesda, Maryland; Email: lynne.wolfe@nih.gov. 2 St Christopher's Hospital for Children Philadelphia, Pennsylvania; Email: reena.jethva@drexelmed.edu. 3 Mayo Clinic Rochester, Minnesota; Email: oglesbee.devin@mayo.edu. 4 University of Pittsburgh Pittsburgh, Pennsylvania; Email: gerard.vockley@chp.edu.

Management

Treatment of manifestations: As most individuals with SCADD are asymptomatic, there is no need for treatment. There are no generally accepted recommendations for dietary manipulation or use of carnitine and/or riboflavin supplementation.

Prevention of primary manifestations: No preventive measures are necessary.

Surveillance: Longitudinal follow up of persons with SCADD on a research basis may be helpful in order to more clearly define the natural history over the life span, including annual visits to a metabolic clinic to assess growth and development as well as nutritional status (protein and iron stores, concentration of RBC or plasma essential fatty acids, and plasma carnitine concentration).

Genetic counseling

SCADD is inherited in an autosomal recessive manner. At conception, each sib of an individual with SCADD has a 25% chance of inheriting biallelic *ACADS* pathogenic or susceptibility variants and possibly developing clinical findings associated with SCADD, a 50% chance of being a carrier of an *ACADS* pathogenic variant, and a 25% chance of not being a carrier. If the pathogenic variants in the family have been identified, carrier testing for at-risk family members is possible, and prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible but not necessary and not recommended.

Diagnosis

Short-chain acyl-CoA dehydrogenase deficiency (SCADD) has been defined as the presence of:

- Increased butyrylcarnitine (C4) concentrations in plasma and/or increased ethylmalonic acid (EMA) concentrations in urine under non-stressed conditions (on at least two occasions)

  AND

- Biallelic *ACADS* pathogenic variants.

Most infants with SCADD identified through newborn screening programs have remained well, and asymptomatic relatives who meet diagnostic criteria are reported. Thus, SCADD is now viewed as a biochemical phenotype rather than a disease. Some affected individuals have been identified through metabolic evaluation for developmental delay. As with other fatty acid oxidation deficiencies, characteristic biochemical findings of SCADD may be absent except during times of physiologic stress such as fasting and illness.

Suggestive Findings

Short-chain acyl CoA dehydrogenase deficiency (SCADD) **should be suspected** in infants with a positive newborn screening result and in symptomatic individuals with supportive clinical and laboratory findings.

Positive Newborn Screening (NBS) Result

NBS for SCADD is primarily based on acylcarnitine analysis by tandem mass spectrometry to detect elevated blood C4 (butyrylcarnitine).

Note: (1) Normal ranges for isolated C4 vary from state to state, necessitating confirmatory testing consistent with the American College of Medical Genetics (ACMG) ACT Sheet. (2) Isobutyryl-CoA dehydrogenase deficiency (IBDD) that leads to elevation of isobutyrylcarnitine, a C4 species also detectable by NBS, must be distinguished from SCADD by additional laboratory testing.

C4 values above the cutoff reported by the screening laboratory are considered positive and require additional biochemical testing and in most cases molecular genetic testing to establish the diagnosis (see Establishing the Diagnosis).

Symptomatic Individuals

For symptomatic individuals who were not identified on NBS, the following nonspecific clinical features and preliminary laboratory findings support a diagnosis of SCADD:

- **Clinical findings.** Hypotonia, dystonia, seizures, metabolic acidosis associated with illness, and/or hypoglycemia [Corydon et al 2001]
- **Preliminary laboratory findings.** Increased C4 concentrations in plasma and/or increased ethylmalonic acid (EMA) concentrations in urine on biochemical evaluation

  Note: Because elevations of these metabolites individually are not entirely specific to SCADD, follow-up testing to establish or rule out the diagnosis of SCADD is required (see Establishing the Diagnosis).

Establishing the Diagnosis

The diagnosis of SCADD **is established** in a proband with typical findings on biochemical testing and confirmed by molecular genetic testing of *ACADS* with the identification of biallelic pathogenic variants (see Table 1).

Note: Two common variants may lead to the biochemical phenotype, but are not clinically relevant (see Table 1, footnote 4).

Biochemical testing

- **Acylcarnitine profile** testing is used to confirm C4 elevations.
- **Urine acylglycines.** A random urine sample can be used to differentiate butyrylglycine and isobutyrylglycine and to detect elevated ethylmalonic acid (EMA) as part of either confirmatory testing after a positive newborn screen or diagnostic testing in older children and adults being evaluated for SCADD.
- **Urine organic acids.** A random urine sample can be collected to detect EMA and dicarboxylic acids, which may be helpful in confirmation of an abnormal newborn screen or during acute illnesses. Urine organic acid screening in symptomatic older children and adults may reveal elevated EMA [Pedersen et al 2008].

Molecular genetic testing approaches, which depend on 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. Children with the distinctive laboratory findings of SCADD described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas symptomatic individuals with nonspecific supportive clinical and laboratory findings (i.e., who had not undergone NBS or had normal NBS results) in whom the diagnosis of SCADD 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 SCADD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Perform sequence analysis first. If clinically necessary and only one or no pathogenic variant is found, gene-targeted deletion/duplication analysis could be considered; however, to date no large deletions or complex rearrangements involving *ACADS* have been reported for SCADD.

  Note: Two common *ACADS* variants, c.511C>T and c.625G>A, result in the SCADD biochemical abnormality when *in trans* with a pathogenic variant. Newborns homozygous for the c.625G>A variant have laboratory test values that overlap with those of affected (i.e., with 2 pathogenic variants) newborns. These variants are not associated with clinical manifestations of SCADD.

- **A multigene panel** that includes *ACADS* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of SCADD 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. Exome array (when clinically available) may be considered if exome sequencing is not diagnostic; however, to date no large deletions or complex rearrangements involving *ACADS* have been reported for SCADD.

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 SCADD

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ACADS	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown[6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. In individuals with biochemical findings consistent with the diagnosis of SCADD [van Maldegem et al 2006, Pedersen et al 2008, Gallant et al 2012]. Most infants with newborn screen results consistent with SCADD are either homozygous for a pathogenic variant on both *ACADS* alleles or compound heterozygous for a pathogenic variant on one allele and a c.511C>T or c.625G>A variant on the other allele [Lindner et al 2010]; however, newborns homozygous for the c.625G>A variant have laboratory test values that overlap with those of affected (i.e., with 2 pathogenic variants) newborns.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Most studies have performed only sequence analysis; therefore, no data on detection rate of gene-targeted deletion/duplication analysis are available. Given the proposed mechanism of disease, such events are likely to be rare.

Clinical Characteristics

Clinical Description

A broad range of clinical findings was originally reported in those with confirmed short-chain acyl-coA dehydrogenase deficiency (SCADD), including severe dysmorphic facial features, feeding difficulties / failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizures, hypotonia, dystonia, and myopathy. However, individuals with no symptoms were also reported.

SCADD was first reported in two neonates who had increased urinary ethylmalonic acid (EMA) excretion; the diagnosis was confirmed enzymatically in skin fibroblasts [Amendt et al 1987]. One of these infants died of overwhelming neonatal acidosis as would be typical of an organic acidemia. However, over the last 20 years more experience with the natural history of SCADD in persons with the biochemical phenotype has identified a much broader phenotypic spectrum than originally anticipated.

Since most infants with SCADD identified through newborn screening programs have been well at the time of diagnosis, the reported relationship of clinical manifestations to the deficiency of SCAD has come into question [Waisbren et al 2008]. Most recent publications based on newborn screening identification have suggested that SCADD causes only a biochemical phenotype that is not clinically relevant, although occasional publications demonstrating some cellular phenotype related to SCADD still appear in the literature [van Maldegem et al 2006, Jethva et al 2008, van Maldegem et al 2010c, Gallant et al 2012, Tonin et al 2016, Nochi et al 2017].

The most convincing study on the clinical relevance of SCADD was reported in 76 babies out of 2,632,058 screened in California over a five-year period [Gallant et al 2012]. Clinical follow up was available on 31 infants, none of whom had any findings suggestive of a metabolic disorder. Seven of these babies with available molecular information were homozygous or compound heterozygous for two pathogenic variants, eight had one pathogenic variant and either the c.511C>T or c.625G>A variant (see Table 1), and seven had two alleles that were either c.511C>T or c.625G>A. In an additional study of 12 individuals with biochemical findings suggestive of SCADD, ten were identified before age three weeks; all were either asymptomatic or reported to have mild hypotonia [Tonin et al 2016]. Two older individuals with variable symptoms were shown only to have the common benign polymorphisms.

All older reports on SCADD identified symptomatic individuals retrospectively; many of such reports did not differentiate between true deficiency and the presence of the c.511C>T or c.625G>A variant. Pedersen et al [2008] summarized the findings in 114 individuals, mostly children undergoing metabolic evaluation for developmental delay. Among the 114 with developmental delay, three subgroups were identified:

- 23 (20%) with failure to thrive, feeding difficulties, and hypotonia
- 25 (22%) with seizures
- 34 (30%) with hypotonia without seizures

Four individuals were asymptomatic, identified either through family studies or newborn screening programs.

In a retrospective study from the Netherlands, van Maldegem et al [2006] identified 31 individuals who met the biochemical and molecular diagnostic criteria for SCADD and also had sufficient information on health and development. The most frequently reported clinical findings were developmental delay (16; designated as "non-severe" in 15), epilepsy (11; non-severe in all), behavioral disorder (8; non-severe in 5), and history of hypoglycemia (6; non-severe in 5). Follow up ranged from one to 18 years: two had progressive clinical deterioration, 12 had no change in clinical findings, eight improved, and nine had complete recovery. In addition, three parents and six sibs were found to have *ACADS* genotypes identical to the proband; eight of the nine had increased levels of C4 and/or EMA, and one of the six sibs had transient feeding difficulties in the first year.

In a study of ten affected individuals of Ashkenazi Jewish ancestry, eight had developmental delay and four had muscle biopsy-proven multiminicore myopathy [Tein et al 2008]. It has been noted that persons with SCADD with a myopathy reported as multiminicore disease had not undergone a full evaluation and may have had another unrelated cause for their muscle disease such as pathogenic variants in *RYR1* or *SELENON* (*SEPN1*) [van Maldegem et al 2010c].

As in other fatty acid oxidation disorders, characteristic biochemical findings of SCADD may be absent in affected individuals except during times of physiologic stress including fasting and illness [Bok et al 2003, Pedersen et al 2008]. In addition, manifestations early in life that could be attributed to SCADD appear to resolve completely during long-term follow up for most individuals diagnosed with SCAD.

Individuals with biallelic common variants (c.511C>T and c.625G>A) are so prevalent in the general population that this finding cannot represent a significant risk for clinical disease (see Molecular Genetics). Individuals with an inactivating pathogenic variant on one allele and one of these variants on the other have enzymatic dysfunction that falls between the those with biallelic common variants and those with biallelic inactivating variants. However, California newborn screening data showed that these babies remained asymptomatic [Gallant et al 2012].

Pregnancy-related issues. Acute fatty liver of pregnancy (AFLP), preeclampsia, and/or HELLP syndrome in mothers of affected fetuses have been described, but causation has not been established [Matern et al 2001, Bok et al 2003, van Maldegem et al 2010c].

Genotype-Phenotype Correlations

No consistent clinical phenotype-genotype correlations have been observed. However, data have suggested a correlation between urinary levels of biomarkers (ethylmalonic acid and methylsuccinic acid) and presence of biallelic pathogenic variants versus one pathogenic and either the c.511C>T or c.625G>A variant on each allele [Gallant et al 2012].

Prevalence

Using fairly strict biochemical and molecular criteria, a birth prevalence of at least 1:50,000 has been estimated in the Netherlands [van Maldegem et al 2006]. A prevalence of 1:34,632 or approximately 1:35,000 was calculated from California data for the incidence in the US [Gallant 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 *ACADS*.

Differential Diagnosis

Other disorders to consider in the differential diagnosis:

- **Isobutyryl-CoA dehydrogenase deficiency (IBDD)** (OMIM 611283). IBDD, also detectable by NBS, leads to elevation of isobutyrylcarnitine, a C4 species indistinguishable from butyrylcarntine without additional separation techniques. IBDD presents with relatively mild and nonspecific hypotonia and is most often asymptomatic at birth. Thus, it is clinically identical to short-chain acyl-CoA dehydrogenase deficiency (SCADD) in newborns. IBDD is caused by biallelic variants in *ACAD8*.
- **Glutaric acidemia type II (GAII)**, also known as multiple acyl-CoA dehydrogenase deficiency (MADD), can present with ethylmalonic acid in urine and C4 in blood but has distinguishing biochemical

characteristics related to secondary deficiencies of all of the fatty acyl-CoA dehydrogenases. This disorder is caused by biallelic variants in one of three genes: *ETFA*, *ETFB*, or *ETFDH*.

- **Ethylmalonic encephalopathy** (OMIM 602473) presents with ethylmalonic acid in urine at much higher levels than in SCADD. C4 may be higher, but as in GAII, other metabolites may be elevated. The clinical characteristics of orthostatic acrocyanosis, petechiae, and severe neurologic symptoms distinguish it from SCADD. This disorder is caused by biallelic variants in *ETHE1*.
- **Mitochondrial respiratory chain defects** are a group of pleotropic disorders that may show mild elevation of ethylmalonic acid in urine and C4 in blood. In practice, these disorders may be the most difficult to distinguish from SCADD, and in minimally symptomatic individuals without lactic acidemia, molecular testing may be necessary to establish a diagnosis.
- **Jamaican vomiting sickness.** This condition, characterized by acute hypoglycemia, is caused by eating the unripe ackee fruit, which contains an inhibitor of the acyl-CoA dehydrogenases. The effect is most pronounced for long-chain and medium-chain enzymes, and thus, while small amounts of short-chain organic acids may be seen in urine, the biochemical diagnosis is straightforward.

Management

To establish the extent of disease and needs in an individual diagnosed with short-chain acyl-coA dehydrogenase deficiency (SCADD), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Evaluations Following Initial Diagnosis

Once a molecular diagnosis of SCAD deficiency is made, there is no need for additional clinical evaluation or further follow up.

Treatment of Manifestations

Since SCADD is now viewed as a biochemical phenotype rather than a disease, there is no need for treatment.

Given the paucity of research, especially long-term follow-up studies, enrollment in a long-term follow-up study with a biochemical geneticist can be offered.

Prevention of Primary Manifestations

Preventive measures if necessary include avoidance of fasting longer than 12 hours (during childhood) and an age-appropriate heart-healthy diet. For infants and toddlers, age-appropriate shorter limits on fasting periods would be required. No dietary fat restriction or specific supplements are recommended in SCADD [Bennett 2010, van Maldegem et al 2010a].

Surveillance

Longitudinal follow up of persons with SCADD on a research basis, including annual visits to a metabolic clinic to assess growth and development as well as nutritional status (protein and iron stores, concentration of RBC or plasma essential fatty acids, and plasma carnitine concentration), may be helpful in order to more clearly define the natural history over the life span.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

Short-chain acyl-CoA dehydrogenase deficiency (SCADD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a child with SCADD are obligate heterozygotes (i.e., carriers of one *ACADS* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing clinical findings related to SCADD.

Sibs of a proband

- At conception, each sib of an individual with SCADD has a 25% chance of inheriting biallelic *ACADS* pathogenic variants and possibly developing biochemical findings associated with SCADD, a 50% chance of being a carrier of an *ACADS* pathogenic variant, and a 25% chance of not being a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing clinical findings related to SCADD.

Offspring of a proband. The offspring of an individual with SCADD are obligate heterozygotes (carriers) for an *ACADS* pathogenic variant.

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

Carrier Detection

Carrier testing for at-risk family members is possible if the *ACADS* pathogenic variants in the family have been identified.

Related Genetic Counseling Issues

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 have SCADD, 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).

Prenatal Testing and Preimplantation Genetic Testing

Once the *ACADS* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are both possible but are unnecessary and not recommended.

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.

- **MedlinePlus**
  Short-chain acyl-coenzyme A dehydrogenase deficiency
- **FOD Family Support Group (Fatty Oxidation Disorder)**
  Phone: 517-381-1940
  Email: deb@fodsupport.org; fodgroup@gmail.com
  fodsupport.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Short-Chain Acyl-CoA Dehydrogenase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ACADS	12q24.31	Short-chain specific acyl-CoA dehydrogenase, mitochondrial	ACADS database	ACADS	ACADS

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 Short-Chain Acyl-CoA Dehydrogenase Deficiency (View All in OMIM)

201470	ACYL-CoA DEHYDROGENASE, SHORT-CHAIN, DEFICIENCY OF; ACADSD
606885	ACYL-CoA DEHYDROGENASE, SHORT-CHAIN; ACADS

Molecular Pathogenesis

Possible pathogenic explanations for the observation that most individuals with short-chain acyl-CoA dehydrogenase (SCAD) deficiency do not present with the classic picture of metabolic acidosis and hypoketotic hypoglycemia characteristic of many fatty acid oxidation disorders include the following:

- SCAD is only needed at the end of the β-oxidation cycle; therefore, gluconeogenesis and ketogenic capacity from the preceding steps of fatty acid oxidation may be sufficient to meet cellular energy needs [van Maldegem et al 2010b].
- Overlapping substrate specificity by medium-chain acyl CoA dehydrogenase (MCAD) may partially compensate for deficient SCAD activity [Bennett 2010].
- While developmental delay and seizures (findings uncommon in other fatty acid oxidation defects) raise the possibility of a neurotoxic effect in SCADD directly related to metabolite accumulation [Gregersen et al 2001, Jethva et al 2008, van Maldegem et al 2010c], clinical follow up of individuals identified by newborn screening argues against any pathogenicity.
  - Ethylmalonic acid (EMA) inhibits creatine kinase activity, increases lipid peroxidation and protein oxidation, and reduces glutathione levels in the cerebral cortex of Wistar rats [Chen et al 2003, Schuck et al 2010].
  - EMA inhibits electron transport chain activity in vitro [Barschak et al 2006].
  - Dicarboxylic acids such as EMA do not cross the blood-brain barrier, and thus sequester in the CNS, another possible explanation of EMA toxicity resulting in neurologic findings [Schuck et al 2010].
- EMA toxicity may play a role in the neurologic dysfunction observed in ethylmalonic encephalopathy, characterized by psychomotor delays and progressive pyramidal findings resulting from basal ganglia and white matter damage caused by accumulation of large amounts of butyrylcarnitine and EMA [Barth et al 2010]. However, ethylmalonic encephalopathy is caused by pathogenic variants in *ETHE1*, the gene encoding a mitochondrial protein involved in scavenging reactive oxygen species (ROS); thus, a direct role for EMA in neurotoxicity is not clear.
- Butyric acid, which accumulates in SCADD, can modulate gene expression at high levels as a result of its action as a histone deacetylase [Chen et al 2003]. Its volatile nature may also add to its neurotoxic qualities [Chen et al 2003, Pedersen et al 2008, Bennett 2010].
- Most pathogenic variants identified in persons diagnosed with SCADD, including the Ashkenazi Jewish *ACADS* pathogenic variant c.319C>T, are missense variants that lead to intramitochondrial aggregation of misfolded protein, suggesting that this protein aggregation itself could be cytotoxic [Gregersen et al 2001, Pedersen et al 2008, Bennett 2010]. The majority of diseases associated with misfolded proteins exhibit mitochondrial dysmorphology and evidence of increased oxidative stress in cells. In one in vitro study, astrocytes transfected with *ACADS* c.319C>T variant accumulated reactive oxygen species (ROS) and demonstrated mitochondrial dysmorphology consistent with a fission defect that could contribute to cellular apoptosis [Schmidt et al 2010]. Thus, it is possible that the effect on SCAD protein misfolding could be modulated by genetic background, which in turn would lead to variable expressivity of disease [Tein et al 2008, Schmidt et al 2010].

Gene structure. *ACADS* is approximately 13 kb long; the transcript NM_000017.2 comprises ten exons and includes 1,238 nucleotides of coding sequence [Jethva et al 2008]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. At least 70 *ACADS* pathogenic variants, most of which are missense, have been reported.

Common (susceptibility) variants. Two missense variants have been reported (Table 2) [van Maldegem et al 2010c]. Most individuals who are homozygous for either variant are asymptomatic, although the presence of the variants has been proposed to represent a susceptibility state that requires one or more other genetic factors (e.g., a pathogenic *ACADS* variant *in trans*) or environmental factors to be present for disease to develop [Gregersen et al 2001, van Maldegem et al 2010c].

- c.511C>T in exon 5
- c.625G>A in exon 6

Both variants are relatively common in the general population.

- In a study of 694 newborns in the United States, approximately 6% were c.625G>A homozygous, 0.3% were c.511C>T homozygous, and 0.9% were compound heterozygous (one allele with each variation) [van Maldegem et al 2010c]. This provides an allele frequency of 0.22 for the c.625G>A variant and 0.03 for the c.511C>T variant.
- In the US, 7% of the population is estimated to be either homozygous or compound heterozygous for one of these common variants [Lindner et al 2010]. Individuals homozygous for one of the variants have a higher incidence of increased excretion of EMA [Bennett 2010].
- In one European study, 14% of controls were homozygous for one of the variants as compared to 69% of 133 subjects with increased urinary EMA excretion.

Table 2. *ACADS* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
Pathogenic	c.319C>T rs61732144	p.Arg107Cys [2] (Arg83Cys) [3]	NM_000017.2 NP_000008.1
Susceptibility variants	c.511C>T rs1800556	p.Arg171Trp [2] (Arg147Trp) [3]	
	c.625G>A rs1799958	p.Gly209Ser [2] (Gly185Ser) [3]	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Residue in the precursor peptide
3. Residue in the mature enzyme, after cleavage of the 24 N-terminal amino acids of the transit peptide that directs the protein to the mitochondria

Normal gene product. Short-chain-specific acyl-CoA dehydrogenase, mitochondrial (SCAD) like all of the acyl-CoA dehydrogenases (ACAD), is a flavoprotein synthesized in the cytosol as a precursor protein. The precursor protein is transported to the mitochondria and further processed into a mature form via proteolytic cleavage of a mitochondrial targeting (transit) peptide at the amino terminus [Battaile et al 2002].

Abnormal gene product. Nearly all individuals identified with SCAD deficiency described to date have pathogenic missense variants that lead to protein misfolding, which has been postulated to cause pathologic cellular effects of SCAD [Schmidt et al 2010]. Although the loss of SCAD enzymatic activity clearly leads to the accumulation of abnormal organic acids, no specific clinical syndrome has been substantiated when unbiased patient populations are assessed. Aggregation of abnormally folded SCAD protein in patient cells is distinct and may lead to otherwise unexpected cellular toxicity [Schuck et al 2010]. Moreover, SCAD misfolding is

aggravated by environmental factors that may vary depending on the individual and may interact with currently uncharacterized factors, constituting a possible risk factor for disease [Gregersen et al 2001, Pedersen et al 2008, Bennett 2010, Schuck et al 2010].

References

Literature Cited

Amendt BA, Greene C, Sweetman L, Cloherty J, Shih V, Moon A, Teel L, Rhead WJ. Short-chain acyl-coenzyme A dehydrogenase deficiency. Clinical and biochemical studies in two patients. J Clin Invest. 1987;79:1303–9. PubMed PMID: 3571488.

Barschak AG, Ferreira Gda C, André KR, Schuck PF, Viegas CM, Tonin A, Dutra Filho CS, Wyse AT, Wannmacher CM, Vargas CR, Wajner M. Inhibition of the electron transport chain and creatine kinase activity by ethylmalonic acid in human skeletal muscle. Metab Brain Dis. 2006;21:11–9. PubMed PMID: 16773466.

Barth M, Ottolenghi C, Hubert L, Chrétien D, Serre V, Gobin S, Romano S, Vassault A, Sefiani A, Ricquier D, Boddaert N, Brivet M, de Keyzer Y, Munnich A, Duran M, Rabier D, Valayannopoulos V, de Lonlay P. Multiple sources of metabolic disturbance in ETHE1-related ethylmalonic encephalopathy. J Inherit Metab Dis. 2010;33 Suppl 3:S443–53. PubMed PMID: 20978941.

Battaile KP, Molin-Case J, Paschke R, Wang M, Bennett D, Vockley J, Kim JJ. Crystal structure of rat short chain acyl-CoA dehydrogenase complexed with acetoacetyl-CoA: comparison with other acyl-CoA dehydrogenases. J Biol Chem. 2002;277:12200–7. PubMed PMID: 11812788.

Bennett MJ. Pathophysiology of fatty acid oxidation disorders. J Inherit Metab Dis. 2010;33:533–7. PubMed PMID: 20824345.

Bok LA, Vreken P, Wijburg FA, Wanders RJ, Gregersen N, Corydon MJ, Waterham HR, Duran M. Short-chain acyl-CoA dehydrogenase deficiency: studies in a large family adding to the complexity of the disorder. Pediatrics. 2003;112:1152–5. PubMed PMID: 14595061.

Chen JS, Faller DV, Spanjaard RA. Short-chain fatty acid inhibitors of histone deacetylases: promising anticancer therapeutics? Curr Cancer Drug Targets. 2003;3:219–36. PubMed PMID: 12769690.

Corydon MJ, Vockley J, Rinaldo P, Rhead WJ, Kjeldsen M, Winter V, Riggs C, Babovic-Vuksanovic D, Smeitink J, De Jong J, Levy H, Sewell AC, Roe C, Matern D, Dasouki M, Gregersen N. Role of common gene variations in the molecular pathogenesis of short-chain acyl-CoA dehydrogenase deficiency. Pediatr Res. 2001;49:18–23. PubMed PMID: 11134486.

Gallant NM, Leydiker K, Tang H, Feuchtbaum L, Lorey F, Puckett R, Deignan JL, Neidich J, Dorrani N, Chang E, Barshop BA, Cederbaum SD, Abdenur JE. Biochemical, molecular, and clinical characteristics of children with short-chain acyl-CoA dehydrogenase deficiency detected by newborn screening in California. Mol Genet Metab. 2012;106:55–61. PubMed PMID: 22424739.

Gregersen N, Andresen BS, Corydon MJ, Corydon TJ, Olsen RK, Bolund L, Bross P. Mutation analysis in mitochondrial fatty acid oxidation defects: exemplified by acyl-CoA dehydrogenase deficiencies, with special focus on genotype-phenotype relationship. Hum Mutat. 2001;18:169–89. PubMed PMID: 11524729.

Jethva R, Bennett MJ, Vockley J. Short-chain acyl-coenzyme A dehydrogenase deficiency. Mol Genet Metab. 2008;95:195–200. PubMed PMID: 18977676.

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

Matern D, Hart P, Murtha AP, Vockley J, Gregersen N, Millington DS, Treem WR. Acute fatty liver of pregnancy associated with short-chain acyl-coenzyme A dehydrogenase deficiency. J Pediatr. 2001;138:585–8. PubMed PMID: 11295727.

Nochi Z, Olsen RKJ, Gregersen N. Short-chain acyl-CoA dehydrogenase deficiency: from gene to cell pathology and possible disease mechanisms. J Inherit Metab Dis. 2017;40:641–55. PubMed PMID: 28516284.

Pedersen CB, Kølvraa S, Kølvraa A, Stenbroen V, Kjeldsen M, Ensenauer R, Tein I, Matern D, Rinaldo P, Vianey-Saban C, Ribes A, Lehnert W, Christensen E, Corydon TJ, Andresen BS, Vang S, Bolund L, Vockley J, Bross P, Gregersen N. The ACADS gene variation spectrum in 114 patients with short-chain acyl-CoA dehydrogenase (SCAD) deficiency is dominated by missense variations leading to protein misfolding at the cellular level. Hum Genet. 2008;124:43–56. PubMed PMID: 18523805.

Schmidt SP, Corydon TJ, Pedersen CB, Bross P, Gregersen N. Misfolding of short-chain acyl-CoA dehydrogenase leads to mitochondrial fission and oxidative stress. Mol Genet Metab. 2010;100:155–62. PubMed PMID: 20371198.

Schuck PF, Busanello EN, Moura AP, Tonin AM, Grings M, Ritter L, Vargas CR, da Costa Ferreira G, Wajner M. Promotion of lipid and protein oxidative damage in rat brain by ethylmalonic acid. Neurochem Res. 2010;35:298–305. PubMed PMID: 19757035.

Tein I, Elpeleg O, Ben-Zeev B, Korman SH, Lossos A, Lev D, Lerman-Sagie T, Leshinsky-Silver E, Vockley J, Berry GT, Lamhonwah AM, Matern D, Roe CR, Gregersen N. Short-chain acyl-CoA dehydrogenase gene mutation (c.319C>T) presents with clinical heterogeneity and is candidate founder mutation in individuals of Ashkenazi Jewish origin. Mol Genet Metab. 2008;93:179–89. PubMed PMID: 18054510.

Tonin R, Caciotti A, Funghini S, Pasquini E, Mooney SD, Cai B, Proncopio E, Donati MA, Baronio F, Bettocchi I, Cassio A, Biasucci G, Bordugo A, la Marca G, Guerrini R, Morrone A. Clinical relevance of short-chain acyl-CoA dehydrogenase (SCAD) deficiency: exploring the role of new variants including the first SCAD-disease-causing allele carrying a synonymous mutation. BBA Clin. 2016;5:114–9. PubMed PMID: 27051597.

van Maldegem BT, Duran M, Wanders RJA, Niezen-Koning KE, Hogeveen M, Ijlst L, Waterham HR, Wijburg FA. Clinical, biochemical, and genetic heterogeneity in short-chain acyl-coenzyme A dehydrogenase deficiency. JAMA. 2006;296:943–52. PubMed PMID: 16926354.

van Maldegem BT, Duran M, Wanders RJ, Waterham HR, de Koning TJ, Rubio E, Wijburg FA. Fasting and fat-loading tests provide pathophysiological insight into short-chain acyl-coenzyme a dehydrogenase deficiency. J Pediatr. 2010a;156:121–7. PubMed PMID: 19800078.

van Maldegem BT, Duran M, Wanders RJ, Waterham HR, Wijburg FA. Flavin adenine dinucleotide status and the effects of high-dose riboflavin treatment in short-chain acyl-CoA dehydrogenase deficiency. Pediatr Res. 2010b;67:304–8. PubMed PMID: 19952864.

van Maldegem BT, Wanders JA, Wijburg FA. Clinical aspects of short-chain acyl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2010c;33:507–11. PubMed PMID: 20429031.

Waisbren SE, Levy HL, Noble M, Matern D, Gregersen N, Pasley K, Marsden D. Short-chain acyl-CoA dehydrogenase (SCAD) deficiency: an examination of the medical and neurodevelopmental characteristics of 14 cases identified through newborn screening or clinical symptoms. Mol Genet Metab. 2008;95:39–45. PubMed PMID: 18676165.

Chapter Notes

Author Notes

The American College of Medical Genetics has published online an algorithm delineating the appropriate response to an elevated C4 on newborn screening (ACMG-ACT Sheet and ACMG Algorithm [www.acmg.net]).

Revision History

- 9 August 2018 (ha) Comprehensive update posted live
- 7 August 2014 (me) Comprehensive update posted live
- 22 September 2011 (me) Review posted live
- 21 March 2011 (lw) Original submission

License