

#201470 ACYL-CoA DEHYDROGENASE, SHORT-CHAIN, DEFICIENCY OF

Alternative titles; symbols

ACADS DEFICIENCY
LIPID-STORAGE MYOPATHY SECONDARY TO SHORT-CHAIN ACYL-CoA
DEHYDROGENASE DEFICIENCY
SCADH DEFICIENCY
SCAD DEFICIENCY

Gene map locus [12q22-qter](#)

TEXT

A number sign (#) is used with this entry because the disorder is caused by mutation in the gene encoding short-chain acyl-CoA dehydrogenase (ACADS; [606885](#)).

CLINICAL FEATURES

Two distinct clinical phenotypes of hereditary short-chain acyl-CoA dehydrogenase deficiency have been identified. One type has been observed in infants with acute acidosis and muscle weakness; the other has been observed in middle-aged patients with chronic myopathy. SCAD deficiency is generalized in the former type and localized to skeletal muscles in the latter. Cases with neonatal onset have a variable phenotype that includes metabolic acidosis, failure to thrive, developmental delay, and seizures, as well as myopathy ([Roe and Ding, 2001](#)). There are no episodes of nonketotic hypoglycemia, which are characteristic of medium-chain (MCAD; [607008](#)) and long-chain (LCAD; [201460](#)) acyl dehydrogenase deficiencies. [30 PubMed Neighbors](#)

[Amendt et al. \(1987\)](#) described 2 unrelated patients, both of whom presented with neonatal metabolic acidosis and ethylmalonate excretion. Deficiency of short-chain acyl-CoA dehydrogenase was demonstrated in fibroblasts by both an electron-transfer flavoprotein (ETF)-linked dye-reduction assay and a tritium release ADH assay. [30 PubMed Neighbors](#)

[Coates et al. \(1988\)](#) demonstrated deficiency of SCAD in a 2-year-old female whose early postnatal life was complicated by poor feeding, emesis, and failure to thrive. She demonstrated progressive skeletal muscle weakness and developmental delay. Her plasma total carnitine level was low-normal, but was esterified to an abnormal degree. The same was true for skeletal muscle carnitine. Fibroblasts from this patient had 50% of control levels of acyl-CoA dehydrogenase activity towards butyryl-CoA as substrate. All of this residual activity was inhibited by an antibody against medium-chain acyl-CoA dehydrogenase. These data demonstrated that medium-chain acyl-CoA dehydrogenase accounted for 50% of the activity towards the short-chain substrate, butyryl-CoA, under these conditions, but that antibody against that enzyme could be used to unmask the specific and virtually complete deficiency of short-chain acyl-CoA dehydrogenase in this patient. [30 PubMed Neighbors](#)

[Bhala et al. \(1995\)](#) summarized the clinical and biochemical features of 6 cases of SCAD deficiency, including the only 4 authentic cases that they were able to identify in the literature. In contrast to MCAD and LCAD deficiency, they found no evidence of secondary carnitine deficiency, and further found that hypoglycemia may not be a prominent clinical feature. All patients with SCAD had neurologic deficits: hypotonia/hypertonia, hyperactivity, and/or developmental delay. [30 PubMed Neighbors](#)

[Ribes et al. \(1998\)](#) reported mild or absent clinical manifestations in monozygous twin sisters with SCAD deficiency. One twin developed hypotonia and decreased level of consciousness following an upper respiratory infection at 5 months. The other was essentially asymptomatic. Ethylmalonic acid was persistently, although sometimes only slightly, increased in both. SCAD activity was 25% and 16% of control levels. Immunoblot analysis in cultured skin fibroblasts indicated that SCAD protein was of normal size, but was less than 10% of control cell intensity. [30 PubMed Neighbors](#)

[Tein et al. \(1999\)](#) described a novel phenotype of multicore myopathy and ophthalmoplegia ([255320](#)) in a 13.5-year-old Israeli girl in whom there was no detectable SCAD protein on Western blot analysis. Decreased fetal movements as well as facial weakness and a fish mouth were noted at birth. Hypotonia was observed at 3 months of age. She became wheelchair dependent at age 5 years, with proximal weakness with wasting and contractures, areflexia, ptosis, progressive external ophthalmoplegia, and cataracts. At age 10 she developed transient heart failure. Intelligence, sensation, cerebellar function, and plantar responses were normal. [30 PubMed Neighbors](#)

[Gregersen et al. \(1998\)](#) investigated ethylmalonic aciduria in a Spanish girl and an African-American male, as well as in 133 patients with elevated ethylmalonic acid excretion. They concluded that ethylmalonic aciduria, a commonly detected biochemical phenotype, is a complex multifactorial/polygenic condition where, in addition to the emerging role of SCAD susceptibility alleles, other genetic and environmental factors are involved. [Corydon et al. \(2001\)](#) came to the same conclusion based on their study of 10 patients with ethylmalonic aciduria. [30 PubMed Neighbors](#)

HETEROGENEITY

Clinical Heterogeneity

[Baerlocher et al. \(1997\)](#) stated that up until 1996 about 10 patients in whom SCAD enzyme deficiency could be confirmed in fibroblasts had been described. Both the clinical and the biochemical pattern of the disease was heterogeneous, with all patients showing at least neuromuscular signs. [Baerlocher et al. \(1997\)](#) presented the case of a 16-year-old patient with growth failure, muscular wasting, and hypotonia since birth. [30 PubMed Neighbors](#)

[Turnbull et al. \(1984\)](#) reported the case of a 53-year-old woman who presented with a lipid-storage myopathy and low concentrations of carnitine in skeletal muscle. Impaired fatty acid oxidation in muscle was found to be caused by deficiency of short-chain acyl-CoA (butyryl-CoA) dehydrogenase activity in mitochondria. The authors suggested that the muscle carnitine deficiency was secondary to this enzyme deficiency and urged that it be considered in other cases of lipid-storage myopathy with carnitine deficiency ([212160](#)). Onset of myopathy was at age 46 years. The patient described by

[Turnbull et al. \(1984\)](#) had normal SCADH activity in fibroblasts, which raises the possibility that a distinct SCADH isoenzyme exists in mammalian muscle. However, [Amendt et al. \(1992\)](#) found that in mice SCAD is the same in both muscle and fibroblasts. For that reason, [Bhala et al. \(1995\)](#) proposed that the case of [Turnbull et al. \(1984\)](#) was not a primary case of SCAD deficiency but rather a case of riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency, as reported by [DiDonato et al. \(1989\)](#). [30 PubMed Neighbors](#)

INHERITANCE

SCAD deficiency is an autosomal recessive disorder. Fibroblasts from the parents of the patient reported by [Coates et al. \(1988\)](#) had intermediate levels of activity towards butyryl-CoA, consistent with autosomal recessive inheritance.

DIAGNOSIS

The definitive diagnostic test for SCAD deficiency is an ETF-linked enzyme assay with butyryl-CoA as a substrate, performed after immunoactivation of MCAD, which has similar activity ([Bhala et al., 1995](#); [Tein et al., 1999](#)).

PATHOGENESIS

[Farnsworth et al. \(1990\)](#) showed an absence of enzyme protein in skeletal muscle in the patient described by [Coates et al. \(1988\)](#). At least in some children with the severe systemic form of the disorder associated with metabolic acidosis, there is low activity of the enzyme but synthesis of normal-sized enzyme protein and mRNA. [30 PubMed Neighbors](#)

MOLECULAR GENETICS

[Naito et al. \(1989\)](#) studied the mutant SCAD enzyme and cultured fibroblasts from 3 patients with the deficiency. No difference was observed on Southern or Northern blot analysis, suggesting that the defects in these cell lines were caused by point mutation. In a patient with SCAD deficiency, [Naito et al. \(1989\)](#) found evidence of compound heterozygosity; see [606885.0001](#) and [606885.0002](#). [30 PubMed Neighbors](#)

GENOTYPE/PHENOTYPE CORRELATIONS

[Gregersen et al. \(2001\)](#) reviewed current understanding of genotype-phenotype relationships in VLCAD ([201475](#)), MCAD, and SCAD. They discussed both the structural implications of mutation type and the modulating effect of the mitochondrial protein quality control systems, composed of molecular chaperones and intracellular proteases. The realization that the effect of the monogene, such as disease-causing mutations in these 3 genes, may be modified by variations in other genes presages the need for profile analyses of additional genetic variations. They stated that the rapid development of mutation detection systems, such as chip technologies, made such profile analyses feasible. [30 PubMed Neighbors](#)

ANIMAL MODEL

In the course of screening mutant mice for organic acidurias using gas chromatography-mass spectrometry, [Wood et al. \(1989\)](#) discovered mice with SCAD deficiency. They had severe organic aciduria, excreting ethylmalonic and methylsuccinic acids and N-butyrylglycine, and developed a fatty liver on fasting or dietary fat challenge. After a fast they developed hypoglycemia and elevated urinary and muscle butyrylcarnitine concentrations. The mutation is at the butyryl-CoA dehydrogenase locus (Bcd1, or Acads), located on mouse chromosome 5 ([Prochazka and Leiter, 1986](#)). [Yamanaka et al. \(1992\)](#) studied the metabolic characteristics in these mice in a series of experiments using liver perfusion techniques and high pressure liquid chromatography. Studying 3 different cell lines from patients with SCAD deficiency, [Amendt et al. \(1992\)](#) authenticated the SCAD deficiency of the BALB/cByJ (J) mouse as a model of human SCAD deficiency. Both SCAD antigen and SCAD activity are totally lacking. The null allele was mapped to the structural locus for butyryl-CoA dehydrogenase on mouse chromosome 5 ([Schiffer et al., 1989](#)). [Hinsdale et al. \(1993\)](#) demonstrated that the null mutation is the result of a 278-bp deletion in the 3-prime end of the structural gene. Two major transcripts are produced in the mutant. One contains intronic sequence due to the absence of splicing, and the other results from missplicing of a normal splice donor site to a cryptic splice acceptor site in the 3-prime terminal exon. Both abnormal transcripts were found to have aberrant stop codons. [Armstrong et al. \(1993\)](#) described the histopathologic changes in the mouse model. [30 PubMed Neighbors](#)

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