

Testimony in support of HB6580 An Act Creating an Advisory Council on Rare Diseases

February 20, 2015

Testimony for public hearing Public Health Committee

Michelle Cotton, BS RT (R, M, CT, MRI), ILST

60 Corona Drive

Milford, CT 06460

203.521.7824

ctmikki@hotmail.com

To Chairman Ritter, Chairman Gerratana, and Members of the Public Health Committee:

I am writing this testimony in support of HB6580, an act creating an Advisory Council on Rare Diseases. When we were trying to get pregnant, the one thing that we never questioned was 'what if something was wrong with our baby', especially after going through three years of endless infertility testing and heartbreak!

Then the call came from Yale, a week after my little baby bug Michael was born. It's the call you never ever want to get. They said some of his testing from his newborn screening had come back irregular, it was probably nothing, but said to call our pediatrician ASAP. They also implored me many times to make SURE we were feeding him every 2 hours. We were not told anything else. They did another heel stick the next day at the pediatricians. Of course, the labs at Yale were 'down', so this would take longer to send them to another hospital out of state. They called again, saying they wanted Mikey back for more tests. They were still inconclusive and evasive as to why. The third and subsequent fourth tests they wanted done at Yale. After demanding someone tell us what they were testing for, the genetics department FINALLY made an appointment to sit down and tell us he probably had what is called an FOD, 'Fatty Oxidation Disorder'the final testing had confirmed this.

He was diagnosed with an FOD called SCADD.

SCADD is an extremely rare genetic disorder. There are around 500 families on our online support group currently. SCADD occurs when an enzyme, called "short chain acyl-CoA dehydrogenase" (SCAD) is either missing or not working properly. This enzyme's job is to break down fats from the food we eat into energy, as well as fat already stored in the body. Our bodies rely on fat when we don't eat for a stretch

of time – like when we miss a meal, sleep or are ill. People with SCADD therefore cannot break down their stored fats, and have to rely on only the food they eat for energy. All FOD's are different, and every person presents differently clinically. Many SCADDers do not present with ANY symptoms or many issues at all.

Mikey is different unfortunately. He is one of the few symptomatic SCADDers. The first year and a half I had to wake him every two hours to feed him, then at three months to three hours, and so forth. Try essentially going without sleep and in fear for your child's life for almost two years while working and going about your daily life! So, you ask, how did we figure out we could go longer between feedings? By trial and error. If he started becoming lethargic and into a crisis, we knew we couldn't go as long. Essentially every single case is different, therefore, it's like a science experiment. But, with your child's life. Currently he can go up to three hours when awake, and up to twelve hours asleep without being woken up. In essence, when Mikey doesn't eat on time, or something 'throws him off', such as any type of sickness, change of schedule, or especially a stomach bug where he's not replacing his calories, he can go into crisis. When he's starting to go into a crisis, he quickly gets cranky, lethargic, spacey, complains of intense leg pain, gets quiet, and becomes unresponsive. He then can have breathing problems, seizures, coma and death. Since the first signs are behavioral only, the only way to notice this is to watch his everyday personality. The signs are similar to a diabetic, but follow through much more quickly.

My Mikey has been hospitalized five times....and he turned five yesterday. When he's admitted he needs an immediate IV of dextrose and saline. We carry an emergency letter that outlines his protocol and how to contact the geneticist and pediatrician for instructions, because the majority of doctors we have encountered have no idea what this disorder is and how to treat it. Every time he's been admitted, the cost has ranged from \$9,000 to \$18,000...for each incident. Mikey's first hospitalization was at 3 months at Yale, due to a flu he got his first weeks at daycare. We brought him in like a limp rag. Twenty four hours in a regular room and an IV with saline and dextrose that cost \$9,000.

When Yale still wouldn't answer questions and educate us, and instead wanted to charge my husband and I a \$1,000 each to do genetic testing for research on ourselves, we found another geneticist that was fantastic, Dr Rosengren. She put us in touch with Dr Natt, head of pediatrics at Bridgeport Hospital. Dr Natt has been our savior. She called us and met with us, preregistered Mikey for emergencies so he wouldn't be stuck in the ER for long in a crisis, and gave him a tour so he'd be familiar with the hospital. Those two doctors have gone out of their way to help us in all of his crisis's since. We have spoken to countless doctors for diagnoses and help. Even when shown the emergency letter, they still don't follow it and treat him accordingly.

We cannot go on a cruise or a long plane flight in case he needs an immediate IV, as we found out on his first flight. He went into a crisis as the plane took off. He was immediately admitted to Miami Children's Hospital. Thank goodness they have an excellent genetics department....but, they hardly spoke English.

I had to fight to remember all of my Spanish to make sure he was seen immediately. And that's with us calling ahead to be admitted. Two days and an IV with saline and dextrose again.....this time \$18,000. Then, he then went into another crisis on the flight home. We made it home fine and he was not hospitalized this time. Every time we go farther than an hour away from home, we have to call our geneticist, find the nearest hospital that knows about his disorder, and she alerts them that we will be in the area should the need arise.

I am therefore here in support of HB6580, An Act Creating an Advisory Council on Rare Diseases, because I am the mom of a little now five year old boy who has fought to survive every day of his life.

First and foremost, we need to find cures for these rare diseases obviously. We are in desperate need of research. Anything we do know, we or another FOD family have figured out on their own.

We need more of these rare diseases to be caught early on. Not every disorder is on every states newborn screening tests. SCADD is on the NBS for Connecticut, but not every state.....so, if Mikey had been born in certain others, he would have not been diagnosed, and we would have lost him the first time he slept through the night as a newborn. Many of these kids are never diagnosed. The parents never find out why, and the cause of death is mistakenly labeled 'SIDS'.

We also need faster results on the newborn screening test. It took about a week for us to get the phone call that there was an abnormality with the labwork. If a lab is closed, we need more backup facilities to rush the results faster!

We also need more education for physicians. Most doctors are not trained to care for such disorders. And, the ones that are, are few and far between.

But more importantly, we need to find a universal system to have people whom do suffer with these disorders to be able to obtain immediate and adequate medical help when in crisis. Something where there can be a 'flag' on the patients chart that there are special considerations in their care. The last time Mikey was admitted last February, the ER doctor chose not to call the pediatrician or geneticist, and chose not to follow the emergency letter either. She let him sit without an IV in the ER for over an hour, to the point where his eyes rolled back in his head, and was unresponsive. Let me tell you something, you have never gone through anything as horrible until you've watched your own child fade from you. If she had just read his protocol and followed it, none of it would have happened.

The only benefit is meeting tons of wonderful supportive people on our online support group, www.fodsupportgroup.org . We have become friends with a family from Boston, and had a video we

made at our first meeting at Mystic with both our kids go viral last year. Hundreds of news outlets across the world carried it and the details of their disorder.

I'm enclosing the link to the interview if you'd like to watch it:

<http://www.nbcnews.com/nightly-news/kids-who-encountered-peek-boo-beluga-whale-share-their-story-n189621>

In closing, we never have an 'easy' day. We are ALWAYS watching for a crisis, and worried about a hospitalization. We never ever can just let our guard down and just enjoy the day. If we do, he can die. We are ALWAYS, every single moment, calculating how many calories he's eaten, and counting how many hours it's been since he last ate..... So put yourself in my shoes and understand what it is to appreciate the sound of hearing my child laugh just like any other child in a moment of wellness. It really is a moment of pure joy.

Michelle L Cotton

I have also included more information on his disorder below:

Everyone has a pair of genes that make the SCAD enzyme. In children with SCADD, neither of these genes works correctly. These children inherit one non-working gene for the condition from each parent. Therefore the parents are usually asymptomatic carriers of the gene, and with two parents as such, there is a 25% chance with each pregnancy of having a child with SCADD.

IN A SCADD CRISIS:

Some of the first symptoms of a metabolic crisis are:

- extreme sleepiness
- behavior changes
- irritable mood
- poor appetite

Other symptoms then follow:

- fever
- diarrhea
- vomiting
- increased levels of acidic substances in the blood, called metabolic acidosis

If a metabolic crisis is not treated, a child with SCADD can develop:

- breathing problems
- seizures
- coma, sometimes leading to death

Other effects of SCADD seen in some infants and children:

- poor weight gain
- delays in learning

- delays in walking and other motor skills
- hyperactivity
- decreased or increased muscle tone
- muscle weakness
- enlarged liver
- enlarged spleen

Symptoms of a metabolic crisis often happen after having nothing to eat for more than a few hours. Symptoms are also more likely when a child with SCADD gets sick or has an infection.

SCADD INFORMATION FROM THE GENETICS WEBSITE.

Short-Chain Acyl-CoA Dehydrogenase Deficiency

Synonym: SCAD Deficiency

Lynne Wolfe, MS, CRNP, BC

NIH/NHGRI

Bethesda, Maryland

vog.hin@efloW.ennyl

Reena Jethva, MD

St Christopher's Hospital for Children

Philadelphia, Pennsylvania

ude.demlexerd@avhtej.aneer

Devin Oglesbee, PhD

Mayo Clinic

Rochester, Minnesota

ude.oyam@niveD.eebseigO

Jerry Vockley, MD, PhD

University of Pittsburgh

Pittsburgh, Pennsylvania

ude.phc@yelkcoV.drareG

Initial Posting: September 22, 2011; Last Update: August 7, 2014.

Summary

Disease characteristics.

The clinical findings in those with confirmed short-chain acyl-coA dehydrogenase (SCAD) deficiency range from severe (dysmorphic facial features, feeding difficulties/failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizures, hypotonia, dystonia, and myopathy) to normal. As in other fatty acid oxidation disorders, characteristic biochemical findings of SCAD deficiency may be absent except during times of physiologic stress such as fasting and illness. In the largest series of affected individuals published to date, 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 SCAD deficiency have been detected by expanded newborn screening, and the great majority of these infants remain asymptomatic. Because most infants with SCAD deficiency identified through newborn screening programs have been well at the time of diagnosis and asymptomatic relatives who meet diagnostic criteria are reported, the relationship of clinical manifestations to SCAD deficiency has come into question.

Diagnosis/testing.

SCAD deficiency 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 or one pathogenic variant in trans with an ACADS susceptibility variant.

Of note, it is recommended that other diagnoses be pursued as appropriate in symptomatic individuals (especially infants and young children) with a presumptive diagnosis of SCAD deficiency.

Management.

Treatment of manifestations: As most individuals with SCAD deficiency are asymptomatic, the need for treatment when well is unclear. There are no generally accepted recommendations for dietary manipulation or use of carnitine and/or riboflavin supplementation.

Prevention of primary manifestations: An age-appropriate heart-healthy diet; avoidance of fasting longer than age-appropriate fasting periods for infants and toddlers and longer than 12 hours for older children.

Surveillance: Annual visits to a metabolic clinic to assess growth and development and nutritional status (including protein and iron stores, levels of RBC or plasma essential fatty acids and plasma carnitine). Closer follow up and surveillance as needed for those with a history of metabolic acidosis, hypoglycemia, and/or other acutely presenting symptoms.

Genetic counseling.

SCAD deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if the pathogenic and/or susceptibility variants in the family have been identified. Of note, requests for prenatal testing for conditions which (like SCAD deficiency) may not affect intellect and have a high likelihood of normal clinical outcome are not common.

Diagnosis

Clinical Diagnosis

In the US, most infants with short-chain acyl CoA dehydrogenase (SCAD) deficiency are identified through newborn screening (NBS) programs.

Older children and adults may be identified with SCAD deficiency after undergoing a biochemical evaluation, typically for hypotonia, dystonia, seizures, metabolic acidosis associated with illness, and/or hypoglycemia [Corydon et al 2001].

Testing

SCAD deficiency has been defined by van Maldegem et al [2006] as the presence of:

- On at least two occasions, increased butyrylcarnitine (C4) concentrations in plasma or bloodspot, and/or increased ethylmalonic acid (EMA) concentrations in urine under non-stressed conditions;
- Biallelic ACADS pathogenic variants or compound heterozygosity for pathogenic variants and a susceptibility variant (see Molecular Genetics). Pathogenic variants are typically missense changes that inactivate or impair SCAD enzymatic activity; the known susceptibility variants are c.511C>T and c.625G>A (see Molecular Genetics). The susceptibility variants are thought to represent a susceptibility state that requires one or more other genetic (e.g., a pathogenic ACADS variant in trans) or environmental factors to be present for disease to development [Gregersen et al 2001, van Maldegem et al 2010c].

In the literature, the genotypes of individuals with SCAD deficiency may be generally described as mutation/mutation, mutation/variant, or variant/variant.

Relatives are considered affected if they have the same ACADS genotype as the proband and increased C4-C concentrations in plasma and/or increased EMA concentrations in urine [van Maldegem et al 2006].

Acylcarnitine profile

- Acylcarnitine analysis by tandem mass spectrometry is used to detect elevated blood C4 (butyrylcarnitine) on newborn screening.

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 Sheets (see Image ACMGACT.jpg). Depending on the screening cutoff values used for butyrylcarnitine concentration, most infants with abnormal results are either homozygous for a pathogenic variant on both ACADS alleles or compound heterozygous for a pathogenic variant on one allele and a common susceptibility variant (c.511C>T or c.625G>A) on the other allele [Lindner et al 2010]; however, butyrylcarnitine concentrations from newborns homozygous for the c.625G>A variant overlap with butyrylcarnitine concentrations in newborns homozygous for a pathogenic variant or compound heterozygous for a pathogenic variant and a susceptibility variant. Thus, molecular confirmation of the diagnosis of SCAD deficiency is still often necessary. (2) Isobutyryl-CoA dehydrogenase deficiency (IBDD) that leads to elevation of isobutyrylcarnitine, a C4 species also detectable by NBS, must be distinguished from SCAD deficiency by additional laboratory testing.

- Plasma acylcarnitines can also be used when age-referenced norms are available to detect C4 elevations in older children and adults suspected of having SCAD deficiency.

Urine acylglycines. A random urine sample can be used to differentiate butyrylglycine and isobutyrylglycine and to detect elevated EMA as part of either confirmatory testing after a positive newborn screen or diagnostic testing in older children and adults being evaluated for SCAD deficiency.

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]. While butyrylcarnitine concentrations from newborns homozygous for the c.625G>A variant overlap with butyrylcarnitine concentrations in newborns with biallelic pathogenic variants or with compound heterozygosity for a pathogenic variant and a susceptibility variant, other biochemical data from urine organic acids (e.g., ethylmalonic acid and methylsuccinic acid levels) tend to be significantly higher in patients with two deleterious pathogenic variants [Gallant et al 2012].

Carnitine levels. Total and free carnitine levels can be used to detect free carnitine deficiency; however, carnitine levels are usually normal in individuals with SCAD deficiency.

SCAD enzyme activity is difficult to obtain clinically and probably not helpful.

Skin fibroblast, fatty acid oxidation studies. In vitro fatty acid probe analysis, a functional assay that assesses function of the entire beta-oxidation pathway, can reflect residual enzyme levels, which may be useful clinically to confirm SCAD deficiency [Young et al 2003].

Molecular Genetic Testing

Gene. ACADS is the only gene in which pathogenic variants are known to cause short-chain acyl-coA dehydrogenase (SCAD) deficiency.

Clinical testing

Table 1.

Summary of Molecular Genetic Testing Used in SCAD Deficiency

Gene 1

Test Method

Proportion of Probands with a Pathogenic Variant Detectable by This Method

ACADS Sequence analysis 2 ~100% 3

Targeted mutation analysis 4, 5 61% for these 3 nucleotide changes 5, but may be higher in certain populations

Sequence analysis of select exons 6 See footnote 7

Deletion/duplication analysis 8 Unknown, None reported

1. See Table A. Genes and Databases for chromosome locus and protein name. See Molecular Genetics for information on allelic variants detected in this gene.

2. Sequence analysis detects variants that are benign, likely benign, of unknown significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exonic or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

3. In individuals with biochemical findings consistent with the diagnosis of SCAD deficiency

4. Testing for a specific pathogenic variant(s) or susceptibility variants. Note: Variants included in a panel may vary by laboratory.
5. Pathogenic variants tested for may include c.319C>T and the susceptibility variants c.511C>T, c.625G>A.
6. Susceptibility variants c.511C>T and c.625G>A in exons 5 and 6 are typically included in targeted analysis.
7. May be useful for follow up of abnormal newborn screening and/or elevated ethylmalonic acid results.
8. Testing that identifies exonic or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

Testing Strategy

To confirm the diagnosis in a proband. See Image ACMGACT.jpg.

1. Obtain acylcarnitine profile from a dried blood spot (newborn screening) or plasma. If C4-C (butyrylcarnitine) is elevated:
2. Analyze urine acylglycines or urine organic acids to confirm that C4 (butyrylcarnitine) is elevated and/or ethylmalonic acid (EMA) concentrations are increased; then:
3. Perform molecular genetic testing to confirm the diagnosis of SCAD deficiency using ONE of the following:
 - Sequence analysis of ACADS
 - For some individuals:
 - A targeted mutation panel comprising the ACADS pathogenic variant c.319C>T and the susceptibility variants c.511C>T and c.625G>A. If neither or only one variant is identified:
 - Sequence analysis of ACADS
4. If no ACADS pathogenic variant is identified consider ETHE1 sequence analysis to detect EMA encephalopathy [Tiranti et al 2004]. See Differential Diagnosis.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this GeneReview are known to be associated with mutation of ACADS.

Clinical Description

Natural History

The phenotypic spectrum described in short-chain acyl-coA dehydrogenase (SCAD) deficiency ranges from severe (dysmorphic facial features, feeding difficulties/failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizures, hypotonia, dystonia, and myopathy) to normal, raising questions about the relationship between the biochemical phenotype and clinical manifestations [Gregersen et al 2001, van Maldegem et al 2006, Jethva et al 2008, Pedersen et al 2008, van Maldegem et al 2010c].

SCAD deficiency 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 SCAD deficiency in persons with the biochemical phenotype has identified a much broader phenotypic spectrum than originally anticipated.

In the largest series published to date, Pedersen et al [2008] summarized the findings in 114 affected individuals who were mostly children undergoing metabolic evaluation for developmental delay. Among the 114 with developmental delay, three sub-groups 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 SCAD deficiency who 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, 8 improved, and 9 had complete recovery. In addition, three parents and six sibs were found to have

ACADS genotypes that were identical to the proband; eight of the nine had increased levels of C4-C 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 mini-multicore myopathy [Tein et al 2008]. It has been noted that persons with SCAD deficiency with a myopathy reported as multimicore disease had not undergone a full evaluation and may have had another unrelated cause for their muscle disease such as mutation of RYR1 or SEPN1 [van Maldegem et al 2010c]. (See Multimicore Disease.)

As in other fatty acid oxidation disorders, characteristic biochemical findings of SCAD deficiency 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 SCAD deficiency appear to resolve completely during long-term follow up for most individuals diagnosed with SCAD.

Since most infants with SCAD deficiency 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]. If there is an increased risk for clinical manifestations, it is most likely in those individuals with biallelic pathogenic variants that inactivate or impair enzymatic activity. Individuals with biallelic susceptibility variants (c.511C>T and c.625G>A) are so frequent 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 a susceptibility variant on the other have enzymatic dysfunction that falls between the other two groups, as may their clinical risk. The largest series to date of diagnosed cases was from California newborn screening data and indicated that even when associated with two pathogenic variants, babies with SCAD deficiency remained asymptomatic [Gallant et al 2012].

Since the long-term risk for development of symptoms is not known, it seems prudent to:

- Offer individuals diagnosed with SCAD deficiency ongoing follow up in order to monitor them and expand clinical knowledge of the disorder;
- Consider post-mortem evaluation and testing to determine cause of death in any individual with a diagnosis of SCAD deficiency since the disorder is not usually life threatening;
- Proceed with further diagnostic evaluation in symptomatic individuals (especially infants and young children) with a presumptive diagnosis of SCAD deficiency [Pedersen et al 2008, Bennett 2010, van Maldegem et al 2010c].

Pregnancy-related issues. Acute fatty liver of pregnancy (AFLP), preeclampsia, and/or HELLP syndrome in mothers of affected fetuses have been described [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, recent data have suggested a correlation between urinary levels of biomarkers (ethylmalonic acid and methylsuccinic acid) and presence of biallelic pathogenic variants or one pathogenic and one susceptibility 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 USA [Gallant et al 2012].

SCAD deficiency appears to be pan ethnic.

Differential Diagnosis

Isobutryl acyl-CoA dehydrogenase deficiency and SCAD deficiency must be differentiated by confirmatory testing of C4-C elevations identified on newborn screen.

Other disorders to consider in the differential diagnosis:

- Glutaric acidemia type II (GAII), also known as multiple acyl-CoA dehydrogenase deficiency (MADD)
- Ethylmalonic encephalopathy (OMIM 602473)
- Mitochondrial respiratory chain defects
- Jamaican vomiting sickness

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to SimulConsult®, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with short-chain acyl-coA dehydrogenase (SCAD) deficiency, the following evaluations are recommended:

- Carnitine levels. Total and free carnitine levels can be used to detect free carnitine deficiency; however, carnitine levels are usually normal in individuals with SCAD deficiency.
- Urine organic acids; used to detect ethylmalonic acid (EMA) during acute illnesses
- Medical genetics consultation

Treatment of Manifestations

Since most individuals with SCAD deficiency are asymptomatic, the need for treatment when well is unclear.

Given the paucity of research, especially long-term follow up studies, there are no generally accepted recommendations for dietary manipulation or the use of carnitine and/or riboflavin supplementation in SCAD deficiency.

However, since the risk for episodes of metabolic decompensation is increased above background risk, increased alertness for dehydration, metabolic acidosis, and/or hypoglycemia during times of otherwise minor illness is prudent.

Basic management of acute metabolic acidosis should be similar to that for other fatty acid oxidation disorders: promoting anabolism and providing alternative sources of energy, both of which can be accomplished by administration of intravenous fluids with high dextrose concentrations with or without insulin. Usually 10% dextrose is given at a rate to provide 8-10 mg/kg/min of glucose. This approach is especially important if nausea and vomiting prevent the oral intake of fluids.

Hypoglycemia is uncommon but can be treated in the same fashion as acute metabolic acidosis.

Flavin adenine dinucleotide (FAD) is an essential cofactor for SCAD function. Thus, riboflavin (vitamin B2) supplementation has been suggested as a possible therapy for SCAD deficiency. In one study, a Dutch cohort of 16 individuals with confirmed SCAD deficiency and at-risk genotypes (biallelic for pathogenic variants; compound heterozygous for pathogenic variant and a susceptibility variant; biallelic for susceptibility variants) were treated with riboflavin 10 mg/kg/day for a maximum dose of 150 mg divided three times daily [van Maldegem et al 2010b].

- FAD levels were within normal range in all individuals throughout the study, though they were the lowest in the subgroups with genotypes that were either compound heterozygous for pathogenic variant and susceptibility variant or biallelic for a susceptibility variant.
- Plasma levels of C4-C (butyrylcarnitine) remained essentially unchanged throughout the study period across all subgroups.
- Urine EMA levels decreased only in the subgroup of compound heterozygotes for pathogenic variant and susceptibility variant.
- Four of 16 demonstrated biochemical changes and exhibited clinical improvement per parent report. Of note, these four individuals had the lowest baseline FAD levels and maintained biochemical and clinical improvements even after riboflavin supplements were discontinued. No genotype-phenotype correlations for riboflavin responsiveness could be identified.

In another retrospective study, 15 individuals with SCAD deficiency ascertained over a period of seven years were challenged with fasting and fat-loading tests [van Maldegem et al 2010a]. Three genotypic

subgroups were defined: biallelic for pathogenic variants, heterozygous for a pathogenic variant and a susceptibility variant, and biallelic for susceptibility variants.

- Free carnitine levels were normal in all individuals.
- When fasted, three individuals developed ketotic hypoglycemia associated with decreased insulin levels and increased levels of growth hormone and cortisol. Lactate, pyruvate, and plasma ammonia concentrations were normal and plasma amino acid concentrations were consistent with normal gluconeogenesis and normal proximal urea cycle function [van Maldegem et al 2010a].

Note: In contrast, in disorders of medium- and long-chain fatty acid oxidation, fasting has been associated with a Reye-like illness with elevated plasma ammonia concentrations and severe hypoketotic hypoglycemia, suggesting impairment of gluconeogenesis and the proximal urea cycle.

- Fat loading elicited a normal ketogenic response without a rise in urine EMA, confirming previous speculation that ketogenesis is likely normal in SCAD deficiency [Bennett 2010, van Maldegem et al 2010a].

In the two studies described above as well as previous case reports, hypoglycemia occurred in fewer than 20% of individuals with SCAD deficiency and normal ketogenesis was observed, ensuring cellular energy during some physiologic stressors.

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. Age-appropriate shorter fasting periods would be required in infants and toddlers. No dietary fat restriction or specific supplements are recommended in SCAD deficiency [Bennett 2010, van Maldegem et al 2010a].

Surveillance

Longitudinal follow up of persons with SCAD deficiency 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).

For individuals with a history of metabolic acidosis, hypoglycemia, and/or other acutely presenting symptoms, the need for closer follow up and surveillance should be determined by the physician.

Agents/Circumstances to Avoid

Fasting longer than 12 hours especially during a febrile or gastrointestinal illness may predispose an affected individual to dehydration, metabolic acidosis, and/or hypoglycemia. Shorter fasting periods (at least the normal age-appropriate recommendations) should be followed in infants and toddlers.

Evaluation of Relatives at Risk

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

- If the pathogenic and/or susceptibility variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic and/or susceptibility variants in the family are not known, biochemical genetic testing, such as plasma acylcarnitines and urinary organic acids, can be used to clarify the genetic status of at-risk sibs.

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

Pregnancy Management

Mothers of children diagnosed with fatty acid oxidation disorders, including SCAD deficiency, should inform their obstetrician so that routine monitoring for pregnancy complications can be observed.

Therapies Under Investigation

Search ClinicalTrials.gov 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, 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. —ED.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one pathogenic allele).
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with SCAD deficiency are obligate heterozygotes (carriers) for an ACADS pathogenic or susceptibility variant.

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

Carrier Detection

Carrier testing for at-risk family members is possible if the pathogenic and/or susceptibility variants in the family have been identified.

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 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 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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

Molecular genetic testing. If the ACADS pathogenic and/or susceptibility variants have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing.

Biochemical genetic testing. If both variants have not been identified, results of quantification of butyrylcarnitine or butyrylglycine in amniotic fluid may identify affected fetuses; however, the sensitivity and specificity are unknown.

Requests for prenatal testing for conditions which (like SCAD deficiency) do not affect intellect and have a high likelihood of normal clinical outcome are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although decisions about prenatal testing are the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the ACADS pathogenic and/or susceptibility variants have been identified.

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.

- National Library of Medicine Genetics Home Reference

Short-chain acyl-coenzyme A dehydrogenase deficiency

- Save Babies Through Screening Foundation, Inc.

P. O. Box 42197

Cincinnati OH 45242

Phone: 888-454-3383

Email: email@savebabies.org

<http://www.savebabies.org/>

•Children Living with Inherited Metabolic Diseases (CLIMB)

Climb Building

176 Nantwich Road

Crewe CW2 6BG

United Kingdom

Phone: 0800-652-3181 (toll free); 0845-241-2172

Fax: 0845-241-2174

Email: info.svcs@climb.org.uk

www.climb.org.uk

•FOD Family Support Group (Fatty Oxidation Disorder)

PO Box 54

Okemos MI 48805-0054

Phone: 517-381-1940

Fax: 866-290-5206 (toll-free)

Email: deb@fodsupport.org; fodgroup@gmail.com

www.fodsupport.org

•United Mitochondrial Disease Foundation (UMDF)

8085 Saltsburg Road

Suite 201

Pittsburg PA 15239

Phone: 888-317-8633 (toll-free); 412-793-8077

Fax: 412-793-6477

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 Symbol

Chromosomal Locus

Protein Name

Locus Specific

HGMD

ACADS 12q24.31 Short-chain specific acyl-CoA dehydrogenase, mitochondrial ACADS database ACADS

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) 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 Genetic 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].

- Developmental delay and seizures, findings uncommon in other fatty acid oxidation defects, raise the possibility of a neurotoxic effect in SCAD deficiency directly related to metabolite accumulation [Gregersen et al 2001, Jethva et al 2008, van Maldegem et al 2010c].

- 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 SCAD deficiency, 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 mutations identified in persons diagnosed with SCAD deficiency, including the Ashkenazi Jewish ACADS pathogenic variant c.319C>T, are missense mutations 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 Symbol.

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

Susceptibility allelic variants. Two missense susceptibility variants have been reported (Table 2) [van Maldegem et al 2010c]. Most individuals who are homozygous for the either variant are asymptomatic, although the presence of the variants is thought to represent a susceptibility state that requires one or more other genetic (e.g., a pathogenic ACADS variant in trans) or environmental factors to be present for disease to development [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 for one of the susceptibility variants or compound heterozygous [Lindner et al 2010]. Individuals homozygous for one of the variants have an increased incidence of 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.

Selected ACADS Allelic Variants

Variant Classification

DNA Nucleotide Change

Protein Amino Acid Change

(Alias 1)

Reference Sequences

Pathogenic c.319C>T

rs61732144 p.Arg107Cys 2

(Arg83Cys) 3 NM_000017.2

NP_000008.1

Susceptibility variants

(i.e., common variants with uncertain pathogenicity) c.511C>T

rs1800556 p.Arg171Trp 2

(Arg147Trp) 3

c.625G>A

rs1799958 p.Gly209Ser 2

(Gly185Ser) 3

Note on variant classification: Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.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 that is transported to and further processed to a mature form in mitochondria including proteolytic cleavage of a mitochondrial targeting (transit) peptide at the amino terminus [Battaile et al 2002].

Study of the crystal structure of recombinant rat SCAD has revealed a homotetramer arranged as a dimer of dimers that is highly conserved with the other ACAD structures: a glutamic acid residue located at amino acid position 368 of the mature rat SCAD protein (homologous to position 376 in MCAD) acts as the catalytic base to initiate the catalytic reaction [Battaile et al 2002]. In vitro studies show that mutation of this residue in the rat SCAD enzyme to a Gln or Ala inactivates the enzyme. Each enzyme also has amino acid residues specific to its particular function. In vitro studies in rat SCAD also show that amino acid residues Gln254 and Thr364 appear to shorten the substrate binding pocket and contribute to its substrate specificity [Kim et al 1993].

Abnormal gene product. Nearly all individuals identified with short-chain acyl-coA dehydrogenase (SCAD) deficiency described to date have missense mutations that lead to protein misfolding, which may provide insight into possible pathologic effects of SCAD [Schmidt et al 2010]. The loss of SCAD enzymatic activity clearly leads to the accumulation of abnormal organic acids; the true risk of this loss of function may be acute metabolic acidosis with physiologic stress [Schuck et al 2010]. 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 person to person, and interact with currently uncharacterized factors to cause disease in some individuals [Gregersen et al 2001, Pedersen et al 2008, Bennett 2010].

References

Literature Cited

1. 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. [PMC free article: PMC424368] [PubMed: 3571488]

2. 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: 16773466]
3. 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: 20978941]
4. 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: 11812788]
5. Bennett MJ. Pathophysiology of fatty acid oxidation disorders. *J Inherit Metab Dis.* 2010;33:533–7. [PubMed: 20824345]
6. 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: 14595061]
7. 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: 12769690]
8. 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: 11134486]
9. 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: 22424739]

10. 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: 11524729]

11. Jethva R, Bennett MJ, Vockley J. Short-chain acyl-coenzyme A dehydrogenase deficiency. *Mol Genet Metab.* 2008;95:195–200. [PMC free article: PMC2720545] [PubMed: 18977676]

12. Kim JJP, Wang M, Djordjevic S, Paschke R, Bennett DW. Three-dimensional structures of acyl-CoA dehydrogenases: structural basis of substrate specificity. In: Yagi K, ed. *Flavins and Flavoproteins*. New York, NY: Walter de Gruyter; 1993:273–82.

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

14. 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: 11295727]

15. Pedersen CB, Kølvrå S, Kølvrå A, Stenbroen V, Kjeldsen M, Ensenaer 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: 18523805]

16. 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: 20371198]

17. 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: 19757035]

18. 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: 18054510]

19. Tiranti V, D'Adamo P, Briem E, Ferrari G, Mineri R, Lamantea E, Mandel H, Balestri P, Garcia-Silva MT, Vollmer B, Rinaldo P, Hahn SH, Leonard J, Rahman S, Dionisi-Vici C, Garavaglia B, Gasparini P, Zeviani M. Ethylmalonic encephalopathy is caused by mutations in *ETHE1*, a gene encoding a mitochondrial matrix protein. *Am J Hum Genet.* 2004;74:239–52. [PMC free article: PMC1181922] [PubMed: 14732903]

20. 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: 16926354]

21. 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: 19800078]

22. 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: 19952864]

23. van Maldegem BT, Wanders JA, Wijburg FA. Clinical aspects of short-chain acyl-CoA dehydrogenase deficiency. *J Inherit Metab Dis.* 2010c;33:507–11. [PMC free article: PMC2946545] [PubMed: 20429031]

24. 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. [PMC free article: PMC4204643] [PubMed: 18676165]

25. Young SP, Matern D, Gregersen N, Stevens RD, Bali D, Liu HM, Koeberl DD, Millington DS. A comparison of in vitro acylcarnitine profiling methods for the diagnosis of classical and variant short chain acyl-CoA dehydrogenase deficiency. *Clin Chim Acta.* 2003;337:103–13. [PubMed: 14568186]

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 (Image ACMGACT.jpg and Image ACMGalg.jpg [www.acmg.net]).

Revision History

- 7 August 2014 (me) Comprehensive update posted live

22 September 2011 (me) Review posted live

21 March 2011 (lw) Original submission

Copyright © 1993-2015, University of Washington, Seattle. All rights reserved.

For more information, see the GeneReviews Copyright Notice and Usage Disclaimer.

For questions regarding permissions: ude.wu@tssamda.

Bookshelf ID: NBK63582 PMID: 21938826