

<b>Disease Name</b>	<b>Ethylmalonic encephalopathy</b>
<b>Acronym</b>	EE
<b>Disease Classification</b>	Fatty Acid Oxidation Disorder
<b>Variants</b>	Yes
<b>Variant name</b>	Late-onset with chronic myopathy
<b>Symptom onset</b>	Neonatal - but very variable; may be asymptomatic.
<b>Symptoms</b>	Neonatal - failure to thrive, hypotonia, metabolic acidosis, seizures and developmental delay.
<b>Natural history</b>	Developmental delay, hypotonia and muscle weakness have been observed, but the vast majority of patients detected via MS/MS newborn screening have been entirely asymptomatic.
<b>Natural history with treatment</b>	The efficacy of treatment is unknown.
<b>Treatment</b>	Carnitine supplementation, restriction of dietary fat. A few patients have shown improvements on riboflavin supplements.
<b>Other</b>	Acute fatty liver of pregnancy and HELLP syndrome have been reported as maternal complications in pregnancy, but may be coincidental.
<b>Physical phenotype</b>	None reported
<b>Inheritance</b>	Autosomal recessive
<b>General population incidence</b>	1:40,000 – 1:100,000
<b>Ethnic differences</b>	None
<b>Population</b>	N/A
<b>Ethnic incidence</b>	N/A
<b>Enzyme location</b>	Mitochondrial matrix in liver, muscle, fibroblasts
<b>Enzyme Function</b>	
<b>Missing Enzyme</b>	Short-chain acyl-CoA dehydrogenase
<b>Metabolite changes</b>	Ethylmalonic acid in urine, methylsuccinate and butyrylglycines in urine.
<b>Gene</b>	ACADS
<b>Gene location</b>	12q22-qter
<b>DNA testing available</b>	Yes - but interpretation of results is difficult.
<b>DNA testing detail</b>	Limited mutational hotspots and common susceptibility alleles
<b>Prenatal testing</b>	Enzymatic
<b>MS/MS Profile</b>	Elevated C4 Cbutyrylcarnitine
<b>OMIM Link</b>	<a href="http://www.ncbi.nlm.nih.gov/omim/606885">http://www.ncbi.nlm.nih.gov/omim/606885</a>
<b>Genetests Link</b>	<a href="http://www.genetests.org">www.genetests.org</a>
<b>Support Group</b>	FOD Family Support Group <a href="http://www.fodsupport.org">http://www.fodsupport.org</a>
	Save Babies through Screening Foundation <a href="http://savebabies.org">http://savebabies.org</a>

## Newborn Screening ACT Sheet

### [Elevated C4 Acylcarnitine]

### Short-Chain Acyl-CoA Dehydrogenase (SCAD) Deficiency

**Differential Diagnosis:** Short-chain acyl CoA dehydrogenase (SCAD) deficiency; Isobutyryl-CoA dehydrogenase (IBDH) deficiency (also referred to as isobutyrylglycinuria (IBG)); Ethylmalonic encephalopathy (EE).

**Condition Description:** SCAD deficiency is a fatty acid oxidation (FAO) disorder. FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. IBG results from IBDH deficiency. IBDH is an enzyme involved in the degradation of the branched chain amino acid valine. EE is a related disorder that seems to be due to a defective mitochondrial matrix protein, the precise function of which is yet unknown. In all three conditions, potentially toxic metabolites accumulate.

#### **YOU SHOULD TAKE THE FOLLOWING ACTIONS:**

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- Consultation with pediatric metabolic specialist.
- Evaluate infant (hypoglycemia, lethargy, metabolic acidosis).
- Emergency treatment if symptomatic.
- Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- Educate family about need for infant to avoid fasting and explain signs, symptoms and need for urgent treatment if infant becomes ill.
- Report finding to newborn screening program.

**Diagnostic Evaluation:** In SCAD deficiency urine organic acids show increased ethylmalonic acid. In IBG, plasma and urine acylcarnitines will show increased isobutyrylcarnitine (C4-acylcarnitine) and urine organic acids/acylglycine may show isobutyrylglycine. In EE, plasma acylcarnitine analysis will typically show C-f- and C5-acylcarnitine and urine organic acids/acylglycine analysis will show increased EE and isovalerylglycine. Molecular genetic analysis to confirm the suspected diagnosis is possible for these conditions.

**Clinical Considerations:** SCAD deficiency can have a variable presentation. Most affected neonates are asymptomatic. An affected neonate however, can be extremely ill with vomiting, lethargy, seizures, and hypoketotic hypoglycemia. Treatment consists primarily of avoidance of fasting and vitamin/cofactor supplementation. Isobutyryl-CoA dehydrogenase deficiency may be benign (anemia and cardiomyopathy has been reported in one case). EE encephalopathy presents in infancy with developmental delay, diarrhea, and petechiae.

#### **Additional Information:**

[New England Consortium of Metabolic Programs](#)  
[OMIM EE](#)

#### **Referral (local, state, regional and national):**

[Testing](#)  
[Clinical Services](#)

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.

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