Test Definition: SCADZ

SCAD Deficiency, Full Gene Analysis

Overview

Useful For

Preferred molecular analysis to confirm a diagnosis of short-chain acyl-CoA dehydrogenase deficiency (as a follow-up to the biochemical analyses only)

Testing Algorithm

See Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma or serum C4 acylcarnitine elevation) in Special Instructions.

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma or serum C4 acylcarnitine elevations)
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions

Method Name

Polymerase Chain Reaction (PCR)/DNA Sequence Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

Preferred:

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Specimen Type: Cultured fibroblasts

Container/Tube: T-25 flask

Specimen Volume: 2 Full flasks

Specimen Stability Information: Ambient (preferred)/Refrigerated

Specimen Type: Blood spot

Supplies: Card - Blood Spot Collection (Filter Paper) (T493)

Container/Tube:

Preferred: Collection card (Whatman Protein Saver 903 Paper)

Acceptable: Ahlstrom 226 filter paper, or Blood Spot Collection Card (T493)

Specimen Volume:2 to 5 Blood Spots on collection card (Whatman Protein Saver 903 Paper; Ahlstrom 226 filter paper; or Blood Spot Collection Card, T493)

Collection Instructions:

1. An alternative blood collection option for a patient >1 year of age is finger stick.

2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 3 hours.

3. Do not expose specimen to heat or direct sunlight.

4. Do not stack wet specimens.

5. Keep specimen dry.

Additional Information:

1. For collection instructions, see Blood Spot Collection Instructions in Special Instructions.

2. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777) in Special Instructions.

3. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800) in Special Instructions.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Biochemical Disorders Patient Information(T527) in Special Instructions

3. If not ordering electronically, complete, print, and send an Inborn Errors of Metabolism Test Request (T798) with the specimen.

Specimen Minimum Volume

Blood: 1 mL
Blood Spots: 5 punches-3 mm diameter

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical and Interpretive

Clinical Information

Short-chain acyl-CoA dehydrogenase (SCAD) catalyzes the first step in the mitochondrial beta-oxidation of fatty acids with a chain length of 6 to 4 carbons. SCAD deficiency is a rare autosomal recessive condition. The clinical phenotype of SCAD shows considerable variability and is incompletely defined. Of those reported cases, hypoglycemia, developmental delay, and muscle hypotonia are the most common indicated features. The diagnosis of SCAD deficiency is challenging and should be based on the clinical presentation, 2 or more findings of ethylmalonic aciduria, and determination of fatty acid flux in fibroblasts indicating deficient SCAD activity. Molecular genetic analysis of the gene associated with SCAD (*ACADS*) may confirm the biochemical phenotype of SCAD deficiency.

The first step in evaluation for SCAD deficiency is identification of 2 or more findings of ethylmalonic aciduria, as determined by either OAU / Organic Acids Screen, Urine or ACYLG / Acylglycines, Quantitative, Urine. Ethylmalonic aciduria is a common, although not specific, laboratory finding in patients with SCAD deficiency. Determination of fatty acid flux in fibroblasts (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture) is warranted for an individual with 2 or more findings of ethylmalonic aciduria.

DNA sequencing of the *ACADS* gene is typically utilized only when SCAD deficiency is identified through biochemical analysis. The *ACADS* gene, associated with SCAD deficiency, is located on chromosome 12q22 and consists of 10 exons. Molecular genetic studies revealed that some patients carry *ACADS* gene mutations that cause complete absence of SCAD activity, while others carry *ACADS* gene variants (511C->T;625G->A) that may confer disease susceptibility only in association with other factors. The allele frequencies in the general population of the

511C->T and 625G->A gene variants are 3% and 22%, respectively. The presence of 2 of these gene variants is not considered an independent diagnostic marker for SCAD deficiency. Although further investigation is needed, it is most likely that these variants are not clinically significant.

Identification of 2 *ACADS* gene mutations that cause complete absence of SCAD activity alone is not sufficient to explain or determine possible clinical phenotype or prognosis. The clinical significance of carrying 2 mutations is often uncertain. Therefore, the results of *ACADS* gene sequencing for SCAD deficiency should be interpreted in light of the clinical presentation and biochemical findings in each case.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

A small percentage of individuals who are carriers or have a diagnosis of short-chain acyl-CoA dehydrogenase (SCAD) deficiency may have a mutation that is not identified by this method (eg, large genomic deletions, promoter mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of SCAD deficiency. For carrier testing, it is important to first document the presence of an *ACADS* gene mutation in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical and biochemical findings, additional testing should be considered.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424

2. Nagan N, Kruckeberg KE, Tauscher AL, et al: The frequency of short-chain acyl-CoA dehydrogenase gene variants in the US population and correlation with the C4-acylcarnitine concentration in newborn blood spots. Mol Genet Metab 2003 April;78:239-246

3. Corydon MJ, Vockley J, Rinaldo P, et al: Role of common gene variations in the molecular pathogenesis of short-chain acyl-CoA dehydrogenase deficiency. Pediatr Res 2001 January;49(1):18-23

4. van Maldegem BT, Duran M, Wanders RJ, et al: Clinical, biochemical, and genetic heterogeneity in short-chain acyl-coenzyme A dehydrogenase deficiency. JAMA 2006 August;296(8):943-952

Performance

Method Description

Bi-directional sequence analysis is performed to test for the presence of a mutation in all coding regions and

intron/exon boundaries of the *ACADS* gene.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly, Varies

Analytic Time

14 days

Maximum Laboratory Time

20 days

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81405-*ACADS (acyl-CoA dehydrogenase C-2 to C-3 short chain)* (eg, short chain acyl-CoA dehydrogenase deficiency), full gene sequence

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
SCADZ	SCAD Deficiency, Full Gene Analysis	In Process

Result ID	Test Result Name	Result LOINC Value
53123	Result Summary	50397-9
53124	Result	82939-0
53125	Interpretation	69047-9
53126	Additional Information	48767-8
53127	Specimen	31208-2
53128	Source	31208-2

Result ID	Test Result Name	Result LOINC Value
53129	Released By	18771-6