Very Long-Chain Acyl-CoA Dehydrogenase (*ACADVL*) Deficiency

Indications for Ordering

- Abnormal newborn screen suggestive of very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
- Diagnostic testing for individual with clinical and/or biochemical evidence of VLCAD deficiency
- Carrier testing for reproductive partner of an individual affected with, or a carrier of, VLCAD deficiency

Test Description

- Bidirectional sequencing of the entire coding region and intron-exon boundaries of the *ACADVL* gene
- Multiplex ligation-dependent probe amplification (MLPA) to detect large *ACADVL* coding region deletions/duplications

Tests to Consider

Diagnostic issues

Biochemical studies can be completely normal if obtained while the patient is metabolically stable; molecular testing or functional studies are needed for definitive diagnosis

Biochemical tests

- Acylcarnitine Quantitative Profile, Plasma 0040033
- Carnitine Panel 0081110
- Organic Acids, Urine 0098389

Molecular tests

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (*ACADVL*) Sequencing and Deletion/Duplication 2004212

- Preferred molecular test to diagnose or rule out VLCAD deficiency following clinical and/or biochemical presentation

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (*ACADVL*) Sequencing 2002001

- Acceptable molecular test to diagnose or rule out VLCAD deficiency following clinical and/or biochemical presentation
- Detects most pathogenic variants

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence – ~1/40,000 newborns in U.S.

Clinical presentation

- Varies in severity and age of onset
  - Hypoketotic hypoglycemia, hepatomegaly, hepatic failure, and fasting-induced coma
- Newborn acute disease
  - Hypoglycemia, arrhythmia, Reye-like symptoms, hypertrophic cardiomyopathy, and sudden infant death
  - Morbidity and mortality – high for acute presentation in newborn
- Infancy or early childhood – milder
  - Resembles medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
  - Fasting intolerance and Reye-like syndrome triggered by prolonged fasting or illness
  - Increased liver function tests and elevated creatine phosphokinase (CPK)
- Adolescent or adult onset
  - Resembles carnitine palmitoyltransferase 2 (CPT2) deficiency
  - Myopathy, exercise-induced rhabdomyolysis, and myoglobinuria

Pathophysiology

- VLCAD enzyme
  - Involved in mitochondrial beta-oxidation of long-chain fatty acids
  - Fuels hepatic ketogenesis during periods of high energy demand (depleted hepatic glycogen stores)
- VLCAD deficiency leads to the accumulation of very long-chain fatty acids

Genetics

Gene – *ACADVL*

Inheritance – autosomal recessive

Variants

- Variants throughout the *ACADVL* gene
  - Some genotype-phenotype correlation may exist

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - Sequencing and deletion/duplication – >90%
  - Sequencing alone – 90%
- Analytical sensitivity and specificity – 99%

Results

- 2 pathogenic *ACADVL* gene variants on opposite chromosomes
  - Predicts VLCAD deficiency
- 1 pathogenic variant
  - Individual is at least a carrier for VLCAD deficiency
- Lack of gene variant reduces likelihood of VLCAD deficiency or carrier state
- Variants of unknown clinical significance may be identified

Limitations

- The following are not detected
  - Regulatory region and deep intronic variants
  - Deletions/duplications in exon 2 of *ACADVL*
- Diagnostic errors may occur due to rare sequence variations

References

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