Primary Carnitine Deficiency

Disease Overview

Carnitine is essential for the transfer of long-chain fatty acids across the inner mitochondrial membrane for beta (β) oxidation. The carnitine cycle is comprised of several enzymes and transporters encoded by different genes (carnitine palmitoyltransferase 1, carnitine-acylcarnitine translocase, carnitine palmitoyltransferase 2, and OCTN2 carnitine transporter). Inherited defects at any step may result in overlapping biochemical abnormalities and clinical phenotypes.

The OCTN2 carnitine transporter plays an important role in the renal reabsorption of carnitine, and its deficiency results in the loss of carnitine in the urine, with secondary deficiency in fatty acid oxidation.

Mutations in the *SLC22A5* gene encoding the OCTN2 carnitine transporter result in primary carnitine deficiency characterized by low plasma carnitine (free carnitine <5 µM; normal range, 25-50 µM), decreased intracellular carnitine accumulation, and increased urinary carnitine excretion.

Incidence

- 1/40,000 for European, Caucasian, and Japanese populations
- Carrier frequency – 1/100 for European, Caucasian, and Japanese populations

Clinical presentation – variable and may present in infancy to adulthood

- Childhood
  - Hepatic encephalopathy
  - Hypoketotic hypoglycemia
  - Reye syndrome
  - Sudden death
  - Hyperammonemia with variably elevated liver function tests and mildly elevated creatine kinase levels
  - Cardiac and/or skeletal myopathy
  - Cardiomegaly
  - Hypotonia
- Adulthood (can be asymptomatic)
  - Fatigue
  - Cardiac arrhythmias
  - Sudden death

Genetics

Gene – *SLC22A5*

Inheritance – autosomal recessive

Function/structure – codes for the OCTN2 carnitine transporter

Variants

- Carnitine transport activity correlates with severity of *SLC22A5* variants
- Genotype cannot accurately predict age of onset or clinical presentation

Diagnostic Testing

- Carnitine free and total in plasma and urine are the first-line tests for an individual with suspected primary carnitine deficiency
- Molecular testing (sequencing and deletion/duplication analysis of the *SLC22A5* gene) is recommended for diagnostic confirmation in individuals with clinical and/or biochemical presentation of primary carnitine deficiency

Individuals recommended for testing

- Follow-up of positive newborn screen suggestive of primary carnitine deficiency
- Diagnostic confirmation in individuals with clinical and/or biochemical presentation of primary carnitine deficiency

Tests to Consider

Biochemical tests – tandem mass spectrometry

Carnitine, Free & Total (Includes Carnitine, Esterified) 0080068 **and**
Carnitine, Free and Total, Urine 0081308

- Initial tests to diagnose or rule out primary or secondary carnitine deficiency
- Often ordered simultaneously

Acylcarnitine Quantitative Profile, Plasma 0040033 **and**
Organic Acids, Urine 0098389

- Order simultaneously to rule out secondary carnitine deficiency

Molecular tests

- Polymerase chain reaction followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *SLC22A5* gene
- Multiplex ligation-dependent probe amplification (MLPA)

Primary Carnitine Deficiency (*SLC22A5*) Sequencing and Deletion/Duplication 2004203

- Preferred molecular test to confirm a diagnosis of primary carnitine deficiency
- Carrier screening of reproductive partner of an individual who carries an *SLC22A5* variant

Primary Carnitine Deficiency (*SLC22A5*) Sequencing 0051682

- Molecular test to confirm diagnosis of or carrier status for primary carnitine deficiency
- Detects most pathogenic variants

Familial Mutation, Targeted Sequencing 2001961

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

Test Interpretation

Biochemical testing – Carnitine Free and Total, plasma and urine

- Primary carnitine deficiency is likely if
  - Low free and total carnitine in plasma/serum
  - Normal/elevated free and total carnitine in urine
  - Normal urine organic acids
  - Normal plasma acylcarnitine profile

Sensitivity/specificity

- Clinical sensitivity
  - Sequencing and deletion/duplication – up to 86%
  - Sequencing – up to 80%
  - Deletion/duplication – up to 5%
- Analytical sensitivity/specificity – 99%

Results

- Variant(s) detected
  - Two pathogenic *SLC22A5* variants on opposite chromosomes confirm primary carnitine deficiency
  - One pathogenic *SLC22A5* variant indicates individual is at least a carrier of primary carnitine deficiency
- Negative – no pathogenic variants detected
- Primary carnitine deficiency is less likely but not excluded
- Inconclusive – variants of uncertain clinical significance may be identified

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
  - Regulatory region variants
  - Deep intronic variants
  - Breakpoints of large deletions/duplications
  - Variants in genes other than *SLC22A5*

References

- Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. Biochim Biophys Acta. 2016;1863(10):2422-2435
- Longo N, Amat di San Filippo C, Pasquali M. Disorders of carnitine transport and the carnitine cycle. Am J Genet C Semin Med Genet. 2006;142(2):77-85