

# Primary Carnitine Deficiency (SLC22A5) Sequencing and Deletion/Duplication

## FOR DIAGNOSIS OF CARNITINE DEFICIENCY DUE TO MUTATIONS IN THE SLC22A5 GENE ENCODING THE OCTN2 CARNITINE TRANSPORTER

### Disease Overview

- Carnitine is essential for the transfer of long-chain fatty acids across the inner mitochondrial membrane for  $\beta$ -oxidation.
- The carnitine cycle is comprised of several enzymes encoded by different genes (carnitine palmitoyl transferase 1, carnitine-acylcarnitine translocase, and carnitine palmitoyl transferase 2) and a transporter, OCTN2. Inherited defects at any step may result in similar biochemical abnormalities and overlapping clinical phenotypes.
- The OCTN2 carnitine transporter plays an important role in the reabsorption of carnitine into the kidneys. A dysfunctional transporter will cause loss of carnitine in the urine and defective fatty acid metabolism.
- Mutations in the *SLC22A5* gene encoding the OCTN2 carnitine transporter result in primary carnitine deficiency characterized by low plasma carnitine (free carnitine  $<5 \mu\text{M}$ , normal  $25\text{--}50 \mu\text{M}$ ), decreased intracellular carnitine accumulation, and increased urinary carnitine excretion.
  - Diagnosis is confirmed by reduced carnitine transporter activity ( $<10$  percent of normal) in skin fibroblasts.
  - Carriers of a single *SLC22A5* gene mutation may have slightly decreased plasma carnitine levels and will have approximately 30–50 percent of normal fibroblast carnitine transport activity.
- Fatty acid accumulation in the liver, skeletal muscle, and heart tissues during fasting results in disease symptoms due to a lack of carnitine transporters.
- The clinical phenotype of primary carnitine deficiency is variable and may present in infancy to adulthood with metabolic or cardiac features:
  - Metabolic presentation, common before the age of 2, is characterized by hypoketotic hypoglycemia and loss of consciousness triggered by periods of fasting, hepatomegaly, Reye syndrome, and sudden death. Hyperammonemia with variably elevated liver function tests and mildly elevated creatine kinase levels may also be present.
  - Cardiac presentation is more prevalent in older patients. Common findings include cardiac and/or skeletal myopathy, hypotonia, and enlarged heart.
  - Affected individuals may be asymptomatic until experiencing prolonged periods of fasting, or they may experience mild developmental delay.
  - Carriers may experience cardiac hypertrophy in middle age, possibly posing a health risk.
- Determination of the specific carnitine cycle defect is

essential, as primary carnitine deficiency responds to carnitine supplementation of 100–400 mg/kg/day if started before irreversible organ damage is present. Long-term prognosis is favorable if lifelong carnitine supplementation is maintained.

### Epidemiology

- Incidence: one in 40,000 for European, Caucasian, and Japanese; lower in other populations.
- Carrier frequency: one in 100 for European, Caucasian, and Japanese populations.

### Genetics

- Autosomal recessive.
- Most *SLC22A5* mutations are rare; thus, affected individuals are typically compound heterozygotes.
- Carnitine transport activity correlates with the severity of the *SLC22A5* gene mutation; however, age of onset and clinical presentation cannot be accurately predicted from genotype.

### Indications for Ordering

- Positive newborn screen (low free carnitine) suggestive of primary carnitine deficiency.
- Diagnostic confirmation in a symptomatic individual with decreased plasma carnitine levels.
- Carrier screening for the reproductive partner of a confirmed *SLC22A5* mutation carrier.
- Diagnostic testing for mothers whose newborn had a positive newborn screen suggestive of primary carnitine deficiency (extremely low serum carnitine levels in newborns that respond to carnitine supplementation may reveal primary carnitine deficiency in the mother).

### Contraindications

Prenatal testing.

### Additional Ordering Notes

If there is a family history of primary carnitine deficiency and the specific familial mutations have already been identified, testing can be performed on at-risk family members by contacting ARUP's genetic counselor and requesting a custom sequencing test for the familial mutation(s) only.

### Interpretation

- The detection of two known pathogenic *SLC22A5* gene mutations predicts primary carnitine deficiency.
- When one or no mutations are detected in a clinically-affected individual, measuring carnitine transport activity in fibroblasts is recommended for diagnostic confirmation.
- When one deleterious mutation is detected in a clinically unaffected individual, the individual is predicted to be at least a carrier.
- Gene sequencing may reveal novel mutation(s); thus, the determination of clinical significance (benign or pathogenic) may be unclear.

### Methodology

- Bi-directional sequencing of the entire coding region and intron/exon boundaries of the *SLC22A5* gene.
- Multiplex ligation-dependent probe amplification (MLPA) to identify large deletions/duplications in the *SLC22A5* gene.
- Clinical sensitivity may be as high as 95 percent for sequencing and deletion/duplication; ~80 percent for sequencing alone; and as high as 10–15 percent for deletion/duplication analysis.
- Analytical sensitivity and specificity are 99 percent.

### Limitations

- Gene mutations causing enzymatic deficiencies of carnitine palmitoyl transferase 1, carnitine-acylcarnitine translocase, or carnitine palmitoyl transferase 2 are not detected by this assay.

- Regulatory region mutations and deep intronic mutations will not be detected.
- Rare diagnostic errors may occur due to primer-site mutations.

### Related Tests

- [Carnitine, Free \(0080065\)](#)
- [Carnitine, Total \(0080067\)](#)
- [Carnitine, Free & Total \(includes esterified carnitine\) \(0080068\)](#)
- [Carnitine Panel \(0081110\)—free, total, and esterified carnitine; acylcarnitine](#)
- [Carnitine Transport, Fibroblasts \(0080512\)](#)
- [Familial Mutation, Targeted Sequencing \(2001961\)](#)—targeted sequencing for specific *SLC22A5* gene mutation(s) previously identified in a family member

### References

1. Longo N, Amat di San Filippo C, Pasquali M. Disorders of carnitine transport and the carnitine cycle. *Am J Med Genet C Semin Med Genet* 2006;142(2):77–85.
2. Schimmenti LA, et al. Expanded newborn screening identifies maternal primary carnitine deficiency. *Molec Genet Metab* 2007;90(4):441–5.
3. Dobrowolski SF, et al. Validation of dye-binding/high-resolution thermal denaturation for the identification of mutations in the *SLC22A5* gene. *Hum Mutat* 2005;25(3):306–13.
4. Wang Y, et al. Phenotype and genotype variation in primary carnitine deficiency. *Genet Med* 2001;3:387–92.

## Test Information

<b>0051682</b>	<b>Carnitine Deficiency, Primary, <i>SLC22A5</i> Full Gene Sequencing</b>
<b>2004199</b>	<b>Primary Carnitine Deficiency (<i>SLC22A5</i>) Deletion/Duplication</b>
<b>2004203</b>	<b>Interferon Primary Carnitine Deficiency (<i>SLC22A5</i>) Sequencing and Deletion/Duplication</b>

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).