

Primary Carnitine Deficiency (*SLC22A5*) Full Gene Sequencing

*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 β -oxidation.
- The carnitine cycle is comprised of several enzymes (carnitine palmitoyl transferase 1, carnitine-acylcarnitine translocase, and carnitine palmitoyl transferase 2) and a transporter, OCTN2, encoded by different genes. 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 in 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 results in primary carnitine deficiency characterized by low plasma carnitine (free carnitine $<5 \mu\text{M}$, normal 25–50 μM), 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.

Contraindications

- Prenatal testing.
- Carrier screening for individuals with a previously identified familial *SLC22A5* mutation. Please order Familial Mutation, Targeted Sequencing (ARUP test #2001961).
- Diagnostic testing or carrier screening for parents of an affected newborn with two identified mutations (extremely low serum carnitine levels in newborns that respond to carnitine supplementation may reveal primary carnitine deficiency in the mother). Please order Familial Mutation, Targeted Sequencing (ARUP test #2001961) for the identified mutation(s).

Additional Ordering Notes

- If there is a positive family history of primary carnitine deficiency, please provide information on the relationship of the proband to the individual being tested, as well as the proband's specific mutations.
- The patient's previous laboratory plasma carnitine and carnitine transport activity results should be provided for the most accurate result interpretation.

Interpretation

- The detection of two known deleterious *SLC22A5* gene mutations predict 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 deleterious) may be unclear.

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.
- Large deletions, deep intronic mutations, and promoter mutations in the *SLC22A5* gene will not be detected.
- Analytical sensitivity may be compromised by rare primer-site mutations.

Methodology

- PCR followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *SLC22A5* gene.
- Clinical and analytical sensitivity are 82 and 99 percent, respectively.

Related Tests

- Carnitine, Free (0080065)
- Carnitine, Total (0080067)
- Carnitine, Free & Total (Includes Carnitine, Esterified) (0080068)
- Carnitine Panel (0081110)—free, total and esterified carnitine; acylcarnitine
- Carnitine Transport, Fibroblasts (0080512)
- Carnitine Deficiency, Primary (*SLC22A5*) Familial Mutation, Targeted Sequencing (2001961)

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

0051682

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For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.