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Primary Carnitine Deficiency

Synonyms: Carnitine Deficiency, Carnitine Transport Defect (CTD), Carnitine Uptake Defect (CUD), Systemic Primary Carnitine Deficiency

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Summary

Clinical characteristics

Primary carnitine deficiency (PCD) is a disorder of the carnitine cycle that results in defective fatty acid oxidation. If untreated, it encompasses a broad clinical spectrum including: (1) metabolic decompensation in infancy typically presenting between age three months and two years with episodes of hypoketotic hypoglycemia, poor feeding, irritability, lethargy, hepatomegaly, elevated liver transaminases, and hyperammonemia triggered by fasting or common illnesses such as upper respiratory tract infection or gastroenteritis; (2) childhood myopathy involving heart and skeletal muscle with onset between age two and four years; (3) pregnancy-related decreased stamina or exacerbation of cardiac arrhythmia; (4) fatigability in adulthood; and (5) absence of symptoms. The latter two categories often include mothers diagnosed with PCD after newborn screening has identified low carnitine levels in their infants.

Diagnosis/testing

The diagnosis of PCD is established in a proband with consistent biochemical analyte findings and/or suggestive clinical and laboratory features by identification of biallelic pathogenic variants in *SLC22A5* on molecular genetic testing. In individuals with suspected PCD and negative molecular testing, a carnitine transport assay using cultured skin fibroblasts may be available.

Management

Targeted therapy: Metabolic decompensation and skeletal and cardiac muscle function improve with 100-200 mg/kg/day oral levocarnitine if it is started before irreversible organ damage occurs.

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Supportive care: Routine treatment includes preventing hypoglycemia with frequent feeding and avoidance of prolonged fasting; notifying designated metabolic center in advance of scheduled surgical or medical procedures; hospitalization for intravenous glucose administration for individuals who are required to fast for a procedure or who cannot tolerate oral intake due to illness such as gastroenteritis; implementing transitional care plan prior to adulthood. Emergency outpatient treatment includes levocarnitine and carbohydrate supplementation, antipyretics for fever, and antiemetics for occasional vomiting. Acute inpatient treatment includes high-calorie fluids, insulin as needed, intravenous or oral levocarnitine (100-200 mg/kg/day), evaluation of muscle and liver involvement by measuring serum creatine kinase concentration and liver transaminases, and evaluation by cardiologist with EKG and echocardiogram for cardiomyopathy.

Surveillance: Monitor plasma carnitine concentration frequently until levels reach normal range; once levels reach normal range, measure three times a year during infancy and early childhood, twice a year in older children, and annually in adults. Assess growth and development at each visit throughout childhood. Neuropsychological testing and quality of life assessment as needed. EKG and echocardiogram annually during childhood and less frequently in adulthood.

Agents/circumstances to avoid: Fasting longer than age-appropriate periods; catabolic illness; inadequate calorie provision during other stressors.

Evaluation of relatives at risk: Evaluation of all sibs of any age by molecular genetic testing if the *SLC22A5* pathogenic variants in the family are known or measurement of plasma-free carnitine concentration to identify as early as possible those who would benefit from institution of treatment and preventive measures.

Pregnancy management: Pregnant women with PCD require close monitoring of plasma carnitine levels and increased carnitine supplementation as needed to maintain plasma carnitine levels in the normal range.

Genetic counseling

PCD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SLC22A5* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *SLC22A5* pathogenic variants have been identified in an affected family member, molecular genetic carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

A diagnosis of primary carnitine deficiency (PCD) may be suspected due to an abnormal newborn screening result prior to onset of suggestive findings (see Scenario 1) or may be considered because of symptoms of PCD (see Scenario 2).

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for PCD is primarily based on use of dried blood spots collected between 24 hours and 72 hours after birth to quantify free carnitine (C0) concentration by tandem mass spectrometry. (For information on NBS by state in the United States, see www.newbornscreening.hrsa.gov.) Low concentration of free carnitine can identify (1) an infant with PCD, (2) a mother with PCD, or (3) both. NBS can identify a mother with PCD because transfer of carnitine across the placenta from an affected mother to her fetus results in a low plasma carnitine concentration in her newborn. Thus, an infant who does not have PCD but is born to a mother who has PCD can have low plasma carnitine concentrations shortly after birth, resulting in a false positive NBS result [Onuki et al 2023, van den Heuvel et al 2023].

Note: (1) NBS for PCD has low positive predictive value (e.g., 4.7% in California [Gallant et al 2017]). There are many factors that may affect NBS for PCD, including maternal carnitine deficiency, prematurity, pivalic acid-containing antibiotics, and some other inborn errors of metabolism. At least one country (New Zealand) has discontinued NBS for this disorder because of its very low sensitivity and positive predictive value [Wilson et al 2019]. (2) In the US, most NBS laboratories determine their own cutoff levels for test results that are considered to be out of range and require further laboratory testing because out-of-range NBS results individually are not entirely specific to PCD.

Positive NBS results (i.e., low blood concentrations of free carnitine) require evaluation of the newborn and mother as soon as possible and no later than three days after birth.

- See Table 1 and Establishing the Diagnosis on how to make an analyte diagnosis or confirm a diagnosis molecularly.
- For recommendations on presumptive treatment of affected newborns while awaiting diagnosis confirmation to prevent irreversible neurocognitive impairment, consult a metabolic specialist to discuss immediate treatment for PCD with oral levocarnitine supplementation and other recommended care.
- If a metabolic specialist is not available, begin treatment for PCD with oral levocarnitine supplementation (typically 100-200 mg/kg/day, divided in three doses; see Management) to prevent metabolic decompensation.

Table 1. Primary Carnitine Deficiency: Testing Recommended at the Time of Diagnosis of Low Carnitine Blood Levels via NBS

Laboratory Test	Results	Comments
Free & total blood & urine carnitine concentrations [1]	Extremely reduced plasma free, acylated, & total (i.e., the sum of free & acylated) carnitine concentrations (i.e., <10% of controls) are highly suggestive of PCD.	Plasma carnitine concentrations should be measured in all mothers of infants found to have low free carnitine levels on NBS to determine if the mother &/or infant have PCD.
Plasma acylcarnitine profile	Infants w/PCD have low plasma concentration of all acylcarnitines & therefore plasma acylcarnitine profile may not be successful. If a profile can be generated, there is typically no specific elevation of any acylcarnitine species.	Useful to rule out other causes of low free carnitine concentrations, incl organic acidemias & defects of fatty acid oxidation (See Differential Diagnosis.)
Urine organic acid analysis	Nondiagnostic for PCD	• Useful to rule out other causes of low carnitine levels, incl organic acidemias & defects of fatty acid oxidation (See Differential Diagnosis.) • Note: Nonspecific dicarboxylic aciduria occurs in some persons w/PCD & is common in fatty acid oxidation disorders w/acute decompensation.

PCD = primary carnitine deficiency

1. See ACMG C0 Algorithm (pdf). Because increased concentrations of these metabolites individually are not entirely specific to primary carnitine deficiency (PCD), follow-up testing is required to establish or rule out the diagnosis of PCD (see Establishing the Diagnosis). Measurement of blood glucose, electrolytes, blood gas, ammonia, liver transaminases, and creatine kinase may be performed to assess disease severity.

Scenario 2: Symptomatic Individual

A symptomatic individual can have either (1) typical findings associated with later-onset PCD or (2) untreated infantile-onset PCD resulting from any of the following: NBS not performed, false negative NBS result, clinical findings prior to receiving NBS result, or caregivers not adherent to recommended treatment after a positive NBS result. PCD **should be considered** in probands with the following clinical and laboratory findings and family history.

Clinical and supportive laboratory findings

- Episodes of hypoketotic hypoglycemia that may be associated with hepatomegaly, elevated liver transaminases, abnormal liver function tests, and hyperammonemia in infants
- Skeletal myopathy and/or elevated serum concentration of creatine kinase in children
- Cardiomyopathy in children
- Unexplained fatigability in adults
- Decreased plasma carnitine concentrations without an identified cause in individuals of any age

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Analyte Diagnosis

The biochemical diagnosis (in limited instances) **is established** in a proband by identification of extremely reduced plasma free, acylated, and total (i.e., the sum of free and acylated) carnitine concentrations (i.e., <10% of controls).

Molecular Genetic Diagnosis

The molecular genetic diagnosis of PCD **is established** in a proband with consistent analyte findings and/or suggestive clinical and laboratory features by identification of biallelic pathogenic (or likely pathogenic) variants in *SLC22A5* on molecular genetic testing (see Table 2).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SLC22A5* variants of uncertain significance (or of one known *SLC22A5* pathogenic variant and one *SLC22A5* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When NBS results and other laboratory findings suggest the diagnosis of PCD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel testing**.

- **Single-gene testing.** Sequence analysis of *SLC22A5* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; at least one large deletion has been identified [Li et al 2010].

  In individuals with suspected PCD and negative molecular testing, a carnitine transport assay using cultured skin fibroblasts may be available to confirm the diagnosis [Crefcoeur et al 2023].

- **An inborn errors of metabolism or metabolic myopathy multigene panel** that includes *SLC22A5* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Exome or genome sequencing can be used. Ordering a rapid turnaround time exome or genome sequencing is necessary when newborns or infants are critically ill. To date, the majority of *SLC22A5* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing [Frigeni et al 2017, Chen et al 2021, Lin et al 2021, Koleske et al 2022].

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in Primary Carnitine Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
SLC22A5	Sequence analysis [3]	~95% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Frigeni et al [2017] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Sequence analysis should include analysis of *SLC22A5* 5′ untranslated region (UTR). In a cohort of 236 individuals, pathogenic variant c.-149G>A in the 5′ UTR accounted for 14% of pathogenic variants [Ferdinandusse et al 2019].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

The clinical manifestations of primary carnitine deficiency (PCD) can vary widely with respect to age of onset, organ involvement, and severity. The broad clinical spectrum ranges from metabolic decompensation in infancy to cardiomyopathy in childhood, fatigability in adulthood, and absence of clinical manifestations. PCD has typically been associated with an infantile metabolic presentation that usually presents before age two years in

about half of untreated affected individuals. The remaining half have a childhood myopathic presentation that typically presents between ages two and four years with dilated cardiomyopathy, hypotonia, muscle weakness, and elevated creatine kinase (CK). However, adults with PCD and mild or no manifestations are likely underdiagnosed, making it difficult to determine the relative proportion of these presentations [El-Hattab & Scaglia 2015, Longo et al 2016].

Table 3. Primary Carnitine Deficiency: Select Features

Feature	Infantile Early Diagnosis & Treatment	Untreated Symptomatic Individual		
		Infantile onset	Childhood onset	Adult onset
Typical age at presentation/onset	Newborn	3 mos-2 yrs	2-4 yrs	Adulthood
Metabolic decompensation [1]	Rare w/appropriate treatment	+	+	±
Hepatomegaly		+	+	+
Cardio(myo)pathy		±	+	±
Neurologic manifestations		+	+	±

Based on El-Hattab & Scaglia [2015], Longo et al [2016], Crefcoeur et al [2022]
1. Hypoketotic hypoglycemia, hyperammonemia, elevated liver enzymes

Infantile Early Diagnosis and Treatment

Infants diagnosed with newborn screening (NBS) and treated early are usually asymptomatic, as manifestations can be prevented by maintaining normal plasma carnitine levels.

Infantile Metabolic (Hepatic) Presentation

Metabolic decompensation. Affected children can present between age three months and two years with episodes of metabolic decompensation triggered by fasting or common illnesses such as upper respiratory tract infection or gastroenteritis. These episodes are characterized clinically by poor feeding, irritability, lethargy, and hepatomegaly. Laboratory evaluations usually reveal hypoketotic hypoglycemia (hypoglycemia with minimal or no ketones in urine), hyperammonemia, and elevated liver transaminases. If affected children are not treated with intravenous dextrose infusion during episodes of metabolic decompensation (see Management), they may develop coma and die [Longo et al 2006, El-Hattab & Scaglia 2015].

Myopathic manifestations. Older children with the infantile presentation may also develop myopathic manifestations including elevated CK, cardiomyopathy, and skeletal muscle weakness [Longo et al 2006, El-Hattab & Scaglia 2015].

Neurologic manifestations. Muscular hypotonia, irritability, rigors, dystonia, and reduced consciousness secondary to metabolic decompensation are possible complications of PCD. Long-term clinical effects are related to the number and severity of metabolic decompensation episodes.

Growth. Growth (linear growth, head circumference, and weight) can be negatively impacted if untreated.

Childhood Myopathic (Cardiac) Presentation

Skeletal myopathy. Myopathic manifestations include hypotonia, skeletal muscle weakness, and elevated serum CK.

Cardiomyopathy. Dilated cardiomyopathy is often present. PCD is associated with shortening of the QT interval and can result in arrhythmia [Lodewyckx et al 2023]. Death from cardiac failure can occur before the diagnosis is established, indicating that this presentation can be fatal if not treated.

Metabolic decompensations also occur in childhood-onset PCD, with hypotonia, weakness, hypoketotic hypoglycemia, hyperammonemia, increased liver transaminases, and increased CK.

Growth. Growth (linear growth, head circumference, and weight) can be negatively impacted if untreated.

Adulthood Presentation

Adults can present with life-threatening symptoms after being asymptomatic [Crefcoeur et al 2022]. Cardiac arrythmias and sudden death can occur. Cardiomyopathy in individuals with PCD responds poorly to standard therapy, and without accurate diagnosis and carnitine supplementation, it can be fatal. PCD can result in shortening of the QT interval, inducing severe arrhythmia [Lodewyckx et al 2023].

One study from the Faroe Islands estimated an odds ratio (OR) of 54.3 for the association between sudden death and untreated PCD [Rasmussen et al 2014]. This indicates the importance of screening at-risk individuals and adherence to treatment with levocarnitine supplementation to prevent the possibility of decompensation during intercurrent illness or stress or even sudden death.

Several women have been diagnosed with PCD after NBS identified low carnitine levels in their infants. About half of those women reported fatigability, whereas the other half were asymptomatic. One woman had dilated cardiomyopathy, and another had arrhythmias [Schimmenti et al 2007, El-Hattab et al 2010, Lee et al 2010].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nonsense and frameshift variants in *SLC22A5* are more prevalent in symptomatic individuals. Missense variants are more prevalent in asymptomatic individuals [Rose et al 2012, Ji et al 2023].

Prevalence

PCD is very common in the Faroe Islands, where the reported prevalence is 1:300 [Rasmussen et al 2014]. The most prevalent pathogenic founder variant in this population is c.95A>G (p.Asn32Ser) (see Table 11).

NBS data estimated the incidence of PCD to be 1:348,333 in Australia and New Zealand, 1:121,609 in North America, 1:127,912 in Europe (excluding Denmark, Greenland, and the Faroe Islands) and 1:50,386 in Asia [Lefèvre et al 2023]. Some studies have suggested a higher prevalence in the Chinese population of 1:17,456 [Ji et al 2023].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC22A5*.

Differential Diagnosis

Primary carnitine deficiency (PCD) needs to be differentiated from secondary carnitine deficiency associated with other inherited metabolic disorders, including organic acidemias and fatty acid oxidation defects (see Table 4), and acquired conditions [Longo et al 2016].

Genetic disorders. Free and total carnitines, a plasma acylcarnitine profile, and urine organic acid analysis can be useful in differentiating fatty acid oxidation disorders and organic acidemias from PCD.

Table 4. Selected Autosomal Recessive Disorders Associated with Secondary Carnitine Deficiency in the Differential Diagnosis of Primary Carnitine Deficiency

Gene(s)	Disorder	Biochemical Phenotype
ACADM	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Elevated C8, C10, C10:1; increased excretion of dicarboxylic acids
ACADS	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	Elevated C4; increased excretion of ethylmalonic acid & dicarboxylic acids
ACADVL	Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency	Elevated C14:1, C14:2, C14, C12:1; increased excretion of dicarboxylic acids
CPT2	Carnitine palmitoyltransferase II deficiency	Elevated C16, C18:1; increased excretion of dicarboxylic acids
HADHA *HADHB*	Long-chain hydroxyacyl-CoA dehydrogenase (VCHAD) deficiency / trifunctional protein deficiency	Elevated C16-OH, C18-OH, C18:1-OH; increased excretion of 3-hydroxy-dicarboxylic acids
SLC25A20	Carnitine-acylcarnitine translocase deficiency	Elevated C16, C18:1; increased excretion of dicarboxylic acids

AR = autosomal recessive; CoA = coenzyme A; MOI = mode of inheritance

Acquired conditions

- Pharmacologic therapy (e.g., valproate, cyclosporine, pivampicillin)
- Malnutrition
- Hemodialysis and renal tubular dysfunction (e.g., renal Fanconi syndrome)
- Prematurity. Premature neonates may have mild reduction in plasma carnitine concentrations due to a lack of carnitine placental transfer in the third trimester and decreased tissue stores. Moreover, immature renal tubular function in premature neonates could lead to increased renal carnitine elimination [Li et al 2010, Clark et al 2014].

Management

No clinical practice guidelines for primary carnitine deficiency (PCD) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PCD, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Primary Carnitine Deficiency: Recommended Evaluations Following Initial Diagnosis

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist	Transfer to specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended)
Cardiology	Echocardiogram & electrocardiogram
Laboratory tests	• CK & liver transaminases • Post-prandial blood glucose concentration • Plasma free/total carnitine concentration following initiation of treatment
Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assess parental / affected person's coping skills & resources as needed

Table 5. continued from previous page.

Evaluation	Comment
Genetic counseling by genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of PCD to facilitate medical & personal decision making

CK = creatine kinase; MOI = mode of inheritance; PCD = primary carnitine deficiency
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Targeted therapy for PCD involves oral carnitine supplementation to prevent carnitine deficiency (see Table 6).

Table 6. Primary Carnitine Deficiency: Targeted Therapy

Treatment	Dosage	Considerations/Other
Oral levocarnitine supplementation	100-200 mg/kg/day divided 3x/day [1]	The weight-based carnitine dose needs to be adjusted according to plasma carnitine concentrations, which should be measured frequently.

1. High doses of oral levocarnitine can cause increased gastrointestinal motility, diarrhea, and intestinal discomfort. Oral levocarnitine can be metabolized by intestinal bacteria to produce trimethylamine, which has a fishy odor. Oral metronidazole at a dose of 10 mg/kg/day for 7-10 days and/or decreasing the carnitine dose usually results in the resolution of the odor [Longo et al 2016].

Oral levocarnitine supplementation in infants with PCD identified through newborn screening (NBS) results in slow normalization of the plasma carnitine concentration.

Metabolic decompensation and skeletal and cardiac muscle function improve with levocarnitine supplementation. Individuals with PCD respond well if oral levocarnitine supplementation is started before irreversible organ damage occurs.

Supportive Care

One of the most important components of preventing carnitine deficiency is education of parents and caregivers such that diligent observation and management can be administered expediently in the setting of intercurrent illness or other catabolic stressors (see Table 7 and Table 8). Essential information including written treatment protocols should be provided before inpatient emergency treatment might be necessary.

Table 7. Primary Carnitine Deficiency: Routine Outpatient Treatment of Manifestations

Principal Concern	Treatment	Considerations/Other
Prevent carnitine deficiency by maintaining normal blood carnitine concentration	Oral levocarnitine (See Targeted Therapy.)	

Table 7. continued from previous page.

Principal Concern	Treatment	Considerations/Other
Prevent hypoglycemia	To reduce risk of metabolic, hepatic, cardiac, & muscular complications: • Frequent feeds • Avoid fasting	• Written protocols for outpatient routine & emergency treatment should be provided to parents, primary care providers, teachers, & school staff. [1, 2] • Emergency letter/card should be provided summarizing key info, principles of emergency treatment, & contact information for primary treating metabolic center. • For any planned travel or vacations, consider contacting center of expertise near destination prior to travel dates.
Prevent complications during surgery or procedure (incl dental procedures)	• Notify designated metabolic center in advance of procedure to discuss perioperative mgmt w/surgeons & anesthesiologists. [1, 2] • Hospitalization to administer IV glucose is recommended for persons w/PCD who are required to fast because of medical or surgical procedures or who cannot tolerate oral intake because of illness such as gastroenteritis.	• Consider placing a "flag" in affected person's medical record such that all care providers are aware of diagnosis & need to solicit opinions & guidance from designated metabolic specialists in the setting of certain procedures. • Emergency surgeries/procedures require planning input from physicians w/expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional mgmt).
Consider transition from pediatric to adult-centered multidisciplinary care, depending on age	As a lifelong disorder w/varying implications according to age, a smooth transition of care from pediatric setting to adult setting for long-term mgmt is ideal. [3, 4]	Unfortunately, standardized procedures for transitional care do not exist for PCD due to the absence of multidisciplinary outpatient departments.

IV = intravenous; PCD = primary carnitine deficiency

1. Essential information including written treatment protocols should be provided *before* inpatient emergency treatment might be necessary.

2. Perioperative/perianesthetic management precautions may include evaluation at specialist anesthetic clinics for affected individuals deemed to be high risk for perioperative complications. Note: Hospitalization to administer IV glucose is recommended for individuals with PCD who are required to fast because of medical or surgical procedures or who cannot tolerate oral intake because of an illness such as gastroenteritis.

3. Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with PCD together with pediatric metabolic experts, dietitians, psychologists, and social workers.

4. As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise with metabolic diseases with sufficient resources is essential.

Emergency outpatient treatment. Parents or local hospitals should immediately inform the specialized metabolic center when the following occurs:

- Fever
- Vomiting/diarrhea or other manifestations of intercurrent illness
- New neurologic findings

Table 8. Primary Carnitine Deficiency: Emergency Outpatient Treatment

Indication	Treatment	Consideration/Other
Catabolism caused by infection, fever, vomiting, or diarrhea	• If affected person is not vomiting, carnitine & feeds may be given orally. • Carbohydrate supplementation orally or via tube feeding [1] • Increase carnitine supplementation. • Assess serum CK concentration & liver transaminases during acute illness.	• Trial of outpatient treatment at home for up to 12 hrs • Reassessment (~every 2 hrs) for clinical changes [2] • Hospitalization to administer IV glucose is recommended for persons w/PCD who cannot tolerate oral intake because of vomiting.
Fever	Administration of antipyretics (acetaminophen, ibuprofen)	
Occasional vomiting	Antiemetics [3]	

Based on British Inherited Metabolic Diseases Group emergency management recommendations for PCD
CK = creatine kinase; IV = intravenous; PCD = primary carnitine deficiency
1. Stringent guidelines to quantify carbohydrate/caloric requirements are available to guide dietary recommendations in the outpatient setting, with some centers recommending frequent provision of carbohydrate-rich, protein-free beverages every two hours, with frequent reassessment.
2. Alterations in mentation/alertness, fever, and enteral feeding tolerance, with any new or evolving clinical features discussed with the designated center of expertise for inherited metabolic diseases
3. Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to hospital.

Table 9. Primary Carnitine Deficiency: Acute Inpatient Treatment

Indication	Treatment	Consideration/Other
Increased catabolism (due to fever, perioperative/peri-interventional fasting periods, repeated vomiting/ diarrhea), hypoglycemia	• Administration of high-calorie fluids &, if needed, insulin • Levocarnitine supplementation (100 mg/kg divided q.i.d. PO or IV)	
Clinical myalgia, muscle tenderness, &/or urinary discoloration	• Administration of high-energy fluids &, if needed, insulin • Levocarnitine supplementation (100 mg/kg divided q.i.d. PO or IV)	Plasma CK &/or urinalysis may be indicated for assessment of rhabdomyolysis.
New or evolving neurologic symptoms (e.g., muscular hypotonia, irritability, rigors, dystonia, reduced consciousness)	• Administration of high-energy fluids &, if needed, insulin • Levocarnitine supplementation (100 mg/kg divided q.i.d. PO or IV)	
Hepatic involvement	• Administration of high-energy fluids &, if needed, insulin • Levocarnitine supplementation (100 mg/kg divided q.i.d. PO or IV)	Monitor for evidence of liver damage (measurement of liver transaminases)
Cardiomyopathy	• Eval by cardiologist • EKG • Echocardiogram	

CK = creatine kinase; IV = intravenous; PO = *per os* (orally); q.i.d = four times a day

Surveillance

In addition to regular evaluations by a metabolic specialist and metabolic dietician, the evaluations summarized in Table 10 are recommended to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations.

Table 10. Primary Carnitine Deficiency: Recommended Surveillance

Concern	Evaluation	Frequency
Carnitine deficiency	Measurement of plasma free/total carnitine by experienced metabolic physician w/adjustments in carnitine supplementation based on age, weight, & diet	Frequently until levels reach normal range; then every 4 mos during infancy & early childhood, every 6 mos in older children, & annually in adults
Growth	Measurement of height, weight, & head circumference	At each visit throughout childhood, esp if poorly treated or untreated
Development	Assessment of developmental milestones	At each visit throughout childhood
Cognition	Neuropsychological testing using age-appropriate standardized assessment testing	As needed
Quality of life	Assess quality of life using standard questioning or specific assessment tools for affected persons & parents/caregivers	
Cardiac	• EKG • Echocardiogram	• Annually during childhood; less frequently in adulthood • Note: In those nonadherent w/carnitine supplementation, consider more frequent monitoring.
Family/ Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Agents/Circumstances to Avoid

Avoid the following:

- Prolonged fasting beyond age-appropriate periods
- Catabolic illness (using measures to avoid intercurrent infection, such as being up to date on vaccinations with anticipation of likelihood of febrile illness post vaccination, wearing a mask in crowded environments, considering alternatives to daycare, recognizing symptoms early)
- Inadequate caloric provision during other stressors, especially when fasting is involved (surgery or procedure requiring fasting/anesthesia)

Evaluation of Relatives at Risk

Testing of all sibs of any age at increased risk of PCD is warranted to identify as early as possible those who would benefit from institution of treatment and preventive measures.

- If the *SLC22A5* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, measure plasma free carnitine concentrations. If the free carnitine concentrations are low, further evaluation for PCD is available using carnitine uptake studies in cultured skin fibroblasts [Crefcoeur et al 2023].

For at-risk newborn sibs when prenatal testing was not performed. In parallel with NBS, perform either molecular genetic testing for the familial *SLC22A5* pathogenic variants or plasma carnitines (free and total).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy is a metabolically challenging state for women with PCD because energy consumption significantly increases. In addition, plasma carnitine concentrations are physiologically lower in women with PCD during pregnancy than those of non-pregnant controls. Women with PCD can have decreased stamina or worsening of cardiac arrhythmia during pregnancy, suggesting that PCD may manifest or exacerbate during pregnancy [Schimmenti et al 2007, El-Hattab et al 2010]. Therefore, it is recommended that all pregnant women with PCD, including those who are asymptomatic, have close monitoring of plasma carnitine concentrations, followed by increased carnitine supplementation as needed to maintain normal plasma carnitine concentrations.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary carnitine deficiency (PCD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an *SLC22A5* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to determine the genetic status of the parents and allow reliable recurrence risk assessment.
- Occasionally an asymptomatic parent is found to have biallelic *SLC22A5* pathogenic variants. In this event, the asymptomatic parent should be referred to a specialist center with experience in management of inherited metabolic diseases for initiation of treatment and surveillance (see Management).
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity.
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC22A5* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with PCD are obligate heterozygotes (carriers) for an *SLC22A5* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC22A5* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *SLC22A5* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of known carriers and for the reproductive partners of individuals affected with PCD, particularly if both partners are of the same ancestry. A founder variant has been identified in the Faroe Islander population (see Table 11).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC22A5* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Primary carnitine deficiency

- **FOD Family Support Group (Fatty Oxidation Disorder)**
  Phone: 517-381-1940
  Email: deb@fodsupport.org; fodgroup@gmail.com
  fodsupport.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Primary Carnitine Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC22A5	5q31.1	Organic cation/ carnitine transporter 2	SLC22A5 database	SLC22A5	SLC22A5

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Primary Carnitine Deficiency (View All in OMIM)

212140	CARNITINE DEFICIENCY, SYSTEMIC PRIMARY; CDSP
603377	SOLUTE CARRIER FAMILY 22 (ORGANIC CATION TRANSPORTER), MEMBER 5; SLC22A5

Molecular Pathogenesis

Carnitine, required for the intracellular transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix for beta-oxidation, is transported into cells by OCTN2 (encoded by *SLC22A5*), the organic cation transporter present in the kidney, heart, and muscle and many other tissues. During periods of fasting, fatty acids are the predominant substrate for energy production via oxidation in the liver, cardiac muscle, and skeletal muscle. When OCTN2 is not working properly, carnitine is improperly transferred across the cell membrane, resulting in urinary carnitine wasting, low plasma carnitine concentration, and decreased intracellular carnitine accumulation. As the main function of carnitine is to transfer long-chain fatty acids from the cytoplasm into the mitochondria for beta-oxidation, carnitine deficiency results in defective fatty acid oxidation. When fat cannot be utilized glucose is consumed without regeneration via gluconeogenesis, resulting in hypoglycemia. In addition, fats released from adipose tissue accumulate in the liver, skeletal muscle, and heart result in hepatic steatosis and myopathy [Longo et al 2006, El-Hattab & Scaglia 2015].

Mechanism of disease causation. Loss of function

***SLC22A5*-specific laboratory technical considerations.** In one cohort of 236 individuals, a variant in the 5' untranslated region (UTR) (c.-149G>A) was identified in 57 individuals in whom only one or no *SLC22A5* pathogenic variant in the coding region was identified [Ferdinandusse et al 2019].

Table 11. *SLC22A5* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003060.4	c.-149G>A	--	Pathogenic variant in the 5' UTR [Ferdinandusse et al 2019]
NM_003060.4 NP_003051.1	c.95A>G	p.Asn32Ser	Founder pathogenic variant in the Faroe Islands [Rasmussen et al 2014]

UTR = untranslated region
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Revision History

- 5 December 2024 (gf) Comprehensive update posted live
- 3 November 2016 (sw) Comprehensive update posted live
- 26 June 2014 (me) Comprehensive update posted live
- 15 March 2012 (me) Review posted live
- 5 December 2011 (aeh) Original submission

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