



Carnitine Palmitoyltransferase II Deficiency

Synonym: CPT II Deficiency

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Summary

Clinical characteristics

Carnitine palmitoyltransferase II (CPT II) deficiency is a disorder of long-chain fatty-acid oxidation. The three clinical presentations are lethal neonatal form, severe infantile hepatocardiomyopathy form, and myopathic form (which is usually mild and can manifest from infancy to adulthood). While the former two are severe multisystemic diseases characterized by liver failure with hypoketotic hypoglycemia, cardiomyopathy, seizures, and early death, the latter is characterized by exercise-induced muscle pain and weakness, sometimes associated with myoglobinuria. The myopathic form of CPT II deficiency is the most common disorder of lipid metabolism affecting skeletal muscle and the most frequent cause of hereditary myoglobinuria. Males are more likely to be affected than females.

Diagnosis/testing

The diagnosis of CPT II deficiency is established in a proband by the finding of reduced CPT enzyme activity in muscle or the identification of biallelic pathogenic variants in *CPT2* on molecular genetic testing.

Management

Treatment of manifestations: High-carbohydrate (70%) and low-fat (<20%) diet to provide fuel for glycolysis; use of carnitine to convert potentially toxic long-chain acyl-CoAs to acylcarnitines; avoidance of known triggers.

Prevention of primary manifestations: Infusions of glucose during intercurrent infections to prevent catabolism; frequent meals; avoiding extended fasting and prolonged exercise.

Prevention of secondary complications: Providing adequate hydration during an attack of rhabdomyolysis and myoglobinuria to prevent renal failure.

Agents/circumstances to avoid: Valproic acid, general anesthesia, ibuprofen, and diazepam in high doses.

Evaluation of relatives at risk: If the pathogenic variants have been identified in an affected family member, molecular genetic testing of at-risk relatives can reduce morbidity and mortality through early diagnosis and treatment; if the pathogenic variants in the family are not known, screening for alterations in acylcarnitines may be of use in identifying other affected family members.

Genetic counseling

CPT II deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes (carriers) are usually asymptomatic; however, manifesting carriers have been reported. Prenatal testing for a pregnancy at increased risk for one of the severe forms of the disease is possible either by molecular genetic testing of *CPT2*, if the two pathogenic variants in the family are known, or by assay of CPT II enzyme activity.

Diagnosis

Suggestive Findings

Carnitine palmitoyltransferase II (CPT II) deficiency **should be suspected** in individuals with the following clinical features (by age) and supportive laboratory findings.

Clinical features (by age)

- **Lethal neonatal form** presents within days after birth. Characterized by:
 - Episodes of liver failure with hypoketotic hypoglycemia
 - Cardiomyopathy
 - Cardiac arrhythmias
 - Seizures and coma after fasting or infection
 - Facial abnormalities or structural malformations (e.g., cystic renal dysplasia, neuronal migration defects or brain dysgenesis)
- **Severe infantile hepatocardiomyopathy form** presents in the first year of life. Characterized by:
 - Liver failure
 - Cardiomyopathy
 - Seizures
 - Hypoketotic hypoglycemia
 - Peripheral myopathy
 - Attacks of abdominal pain and headache
- **Myopathic form** has variable onset (1st to 6th decade). Characterized by:
 - Recurrent attacks of myalgia accompanied by myoglobinuria precipitated by prolonged exercise (especially after fasting), cold exposure, or stress
 - Possible weakness during attacks
 - Usually no signs of myopathy (weakness, myalgia, elevation of serum creatine kinase [CK] concentration) between attacks

Supportive laboratory findings

- **High-performance liquid chromatography tandem mass spectrometry of serum/plasma acylcarnitines** (i.e, the acylcarnitine profile) that demonstrates an elevation of C12 to C18 acylcarnitines, notably of C16 and C18:1 (See Differential Diagnosis for other disorders with this acylcarnitine profile.)

Note: CPT II deficiency cannot be excluded based on acylcarnitine quantification in dried blood spots alone and investigation of plasma is recommended [de Sain-van der Velden et al 2013].

- **Serum CK concentration** more than fivefold of normal when heart or brain disease is excluded
 - Most individuals with the myopathic form of CPT II deficiency have normal serum CK concentration (<80 U/L) between attacks.
 - Permanent elevation of serum CK concentration (≤ 313 U/L) is observed in approximately 10% of affected individuals [Wieser et al 2003].

Establishing the Diagnosis

The diagnosis of CPT II deficiency **is established** in a proband by the finding of reduced CPT enzyme activity in muscle or by the identification of biallelic pathogenic (or likely pathogenic) variants in *CPT2* on molecular genetic testing (see Table 1).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *CPT2* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *CPT2* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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](#).

Table 1. Molecular Genetic Testing Used in Carnitine Palmitoyltransferase II Deficiency

Gene ¹	Method	Proportion of Probands with Pathogenic Variants ² Detectable by Method
CPT2	Sequence analysis ³	>95% ^{4, 5}
	Gene-targeted deletion/duplication analysis ⁶	None reported ⁷

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. The following pathogenic variants are found with the approximate stated frequency in individuals who have the myopathic form: p.Ser113Leu in 60%; p.Lys414ThrfsTer7 in 20%; p.Pro50His, p.Arg503Cys, p.Gly549Asp, p.Lys414ThrfsTer7, and p.Met214Thr in 15% [Taggart et al 1999, Thuillier et al 2003, Wieser et al 2003, Fanin et al 2012].

5. The severe infantile hepatocardiomyopathic form and the lethal neonatal form are associated with severe pathogenic variants including p.Lys414ThrfsTer7 [Vladutiu et al 2002b, Thuillier et al 2003].

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. No deletions or duplications involving *CPT2* as causative of CPT II deficiency have been reported.

CPT II Enzyme Activity

Affected individuals. Tests of total CPT enzyme activity (both CPT I and CPT II) rely on the basic reaction: palmitoyl-CoA + carnitine \leftrightarrow palmitoylcarnitine + CoA. Activity of CPT II represents only 20%-40% of total CPT activity. Measured enzyme activity is dependent on assay conditions, which have not been standardized, making comparisons of published data from different laboratories difficult:

- The "radio isotope exchange assay" described by Norum [1964] is still widely used.
- The "isotope forward assay" measures total CPT enzyme activity (CPT I and CPT II) by the incorporation of radio-labeled carnitine into palmitoylcarnitine [Zierz & Engel 1985]. Total CPT enzyme activity is normal in both affected individuals and controls. In this assay, CPT II enzyme activity is measured as the fraction that is not inhibited by malonyl-CoA.
- CPT II activity can also be determined spectroscopically [Motlagh et al 2016].

The lethal neonatal form and the severe infantile hepatocardiomyopathic form are associated with less than 10% of normal CPT II enzyme activity in lymphoblasts and skeletal muscle.

Although the CPT II enzyme defect in the myopathic form can be detected using other tissues (e.g., liver, fibroblasts, leukocytes), preparation of tissue for assay of CPT II enzyme activity is difficult, and comparison of CPT II enzyme activity in different tissues yields inconsistent results. Therefore, only muscle tissue is recommended for assay of enzyme activity for the myopathic form of CPT II deficiency.

Rettinger et al [2002] developed a tandem mass spectrometric assay (MS/MS) for the determination of CPT II enzyme activity based on the stoichiometric formation of acylcarnitine, which directly correlates with the CPT II enzyme activity. The assay allows unambiguous detection of individuals with the myopathic form of CPT II deficiency [Gempel et al 2002].

Clinical Characteristics

Clinical Description

Three carnitine palmitoyltransferase II (CPT II) deficiency phenotypes are recognized: a lethal neonatal form; a severe infantile hepatocardiomyopathy form; and a myopathic form, in which onset ranges from infancy to adulthood.

Lethal Neonatal Form

Liver failure, hypoketotic hypoglycemia, cardiomyopathy, respiratory distress, and/or cardiac arrhythmias occur. Affected individuals have liver calcifications and cystic dysplastic kidneys [Vladutiu et al 2002b, Sigauke et al 2003].

Neuronal migration defects including cystic dysplasia of the basal ganglia have been reported [Pierce et al 1999]. Among 19 individuals with the neonatal phenotype a characteristic pattern of malformations was seen. In addition to polycystic kidneys (found in 9 affected individuals), the following was also seen: hydrocephalus (in 8 individuals); cerebellar vermian hypoplasia (5); polymicrogyria, pachygyria and other neuronal migration defects (4); cerebral calcifications (3); cystic dysplasia of the brain (2); and agenesis of the corpus callosum (1) [Boemer et al 2016].

Prognosis is poor. Death occurs within days to months.

The lethal neonatal form is characterized by reduced CPT II enzyme activity in multiple organs, reduced serum concentrations of total and free carnitine, and increased serum concentrations of long-chain acylcarnitines and lipids.

Severe Infantile Hepatocardiomyopathy Form

This form is characterized by hypoketotic hypoglycemia, liver failure, cardiomyopathy, and peripheral myopathy.

Cardiac arrhythmias can result in sudden death during infancy [Vladutiu et al 2002b]. Sudden infant death also occurred in a boy age ten months during an acute illness. Post-mortem analysis revealed hepatomegaly and acylcarnitine profile compatible with CPT II deficiency [Bouchireb et al 2010]. Another instance of sudden infant death occurred in an infant age 13 days who was homozygous for the c.534_558del25insT pathogenic variant. The infant had a Dandy-Walker malformation [Yahyaoui et al 2011].

Myopathic Form

The myopathic form of CPT II deficiency is the most common disorder of lipid metabolism affecting skeletal muscle and is the most frequent cause of hereditary myoglobinuria.

In vivo investigation of fatty acid oxidation in CPT2-deficient persons by indirect calorimetry and stable isotope methodology shows an impaired oxidation of long chain fatty acids during low-intensity exercise, with normal oxidation at rest [Ørngreen et al 2005]. Clinically almost all individuals with the myopathic form experience myalgia. Approximately 60% have muscle weakness during the attacks. Occasionally, muscle cramps occur, although they are not typical of the disease. Myoglobinuria with brown-colored urine during the attacks occurs in approximately 75% of individuals.

Age at onset and age at diagnosis vary widely. Detailed clinical data obtained from 23 of 32 individuals with the myopathic form revealed age of onset ranging from one to 61 years; age at diagnosis ranged from seven to 62 years [Wieser et al 2003, Deschauer et al 2005]. In 70%, the disease started in childhood (age 0-12 years); in 26%, the first attacks occurred in adolescence (age 13-22 years); and in one individual, symptoms began in late adulthood (age 61 years).

Exercise is the most common trigger of attacks, followed by infections (~50% of affected individuals) and fasting (~20%). The severity of exercise that triggers symptoms is highly variable. In some individuals, only long-term exercise induces symptoms, and in others, only mild exercise is necessary.

Cold, general anesthesia, sleep deprivation, and conditions that are normally associated with an increased dependency of muscle on lipid metabolism are also reported as trigger factors.

Most individuals are mildly affected; some are even serious athletes [Deschauer et al 2005]. Affected individuals are generally asymptomatic with no muscle weakness between attacks. Some individuals have only a few severe attacks and are asymptomatic most of their lives, whereas others have frequent myalgia, even after moderate exercise, such that daily activities are impaired and disease may worsen.

End-stage renal disease caused by interstitial nephritis with acute tubular necrosis requiring dialysis occasionally occurs [Kaneoka et al 2005].

The preponderance of affected males is notable. In the series of 32 individuals of Wieser et al [2003], the ratio of males to females was nearly two to one (20/12); in a series published by Anichini et al [2011], the ratio of males to females was 7.3:1 (22/3); in earlier reports, ratios as high as five to one were reported. The reason for the preponderance of males is unknown; hormonal factors may play a role but cannot completely account for it [Vladutiu et al 2002a]. Females may be less likely to develop myoglobinuria and therefore remain undetected.

Genotype-Phenotype Correlations

A consistent genotype-phenotype correlation is found between *CPT2* missense pathogenic variants (including the common p.Ser113Leu) and the **myopathic form**; these are referred to as pathogenic variants that cause "mild" form of the disease. *CPT2* pathogenic null variants leading either to truncation of the protein or to mRNA degradation are referred to as pathogenic variants associated with the **lethal neonatal form**. However, several pathogenic variants are associated with both the mild and severe forms of CPT II deficiency, suggesting a role for other unknown modulators (intragenic variants; epigenetic or environmental factors) [Vladutiu et al 2000b, Musumeci et al 2007]. For a list of variants and their predicted phenotype, see Isackson et al [2008], Anichini et al [2011], and Fanin et al [2012].

Lethal neonatal form. Homozygosity for the severe pathogenic variants p.Pro227Leu, p.Lys414ThrfsTer7, and p.Lys642ThrfsTer6 [Isackson et al 2008] is associated with the lethal neonatal form. This subtype of the disease is also described in compound heterozygous states in combination with a pathogenic variant usually associated with mild disease (c.[1737delC];[520G>A]) [Semba et al 2008].

Severe infantile hepatocardiomyocardial form. Compound heterozygosity for pathogenic variants associated with mild and severe forms has been reported. A detailed analysis associated the following pathogenic variants with this type of the disease: p.Tyr120Cys, p.Arg151Gln, p.Asp328Gly, p.Arg382Lys, p.Arg503Cys, p.Tyr628Ser, and p.Arg631Cys [Vladutiu et al 2002b, Thuillier et al 2003, Isackson et al 2008, Fanin et al 2012].

Myopathic form. The variant p.Ser113Leu accounts for 60% of pathogenic alleles in the myopathic form of CPT II deficiency. In a series of 32 affected individuals, 14 were homozygous for this common allele [Wieser et al 2003]; 17 were compound heterozygous for this common pathogenic variant and a second pathogenic variant. Testing for the p.Ser113Leu variant alone would suggest the diagnosis in 31 out of 32 individuals.

In northern Europeans the pathogenic variants p.Ser113Leu, p.Pro50His, and p.Lys414ThrfsTer7 are most frequently found, whereas in the Japanese the variant p.Phe383Tyr appears to have the highest prevalence [Taggart et al 1999, Isackson et al 2008, Yasuno et al 2008].

Heterozygotes have a biochemically intermediate phenotype (with markedly reduced enzyme activity) but generally do not display symptoms. However, a few symptomatic heterozygotes have been reported [Taggart et al

1999, Olpin et al 2003, Rafay et al 2005, Fanin et al 2012]. Heterozygotes have also been shown to have impaired fat oxidation during exercise as compared to controls [Ørngreen et al 2005].

Histopathologic changes in asymptomatic carriers of CPT II deficiency (heterozygotes) and in affected individuals (homozygotes) are inconsistent. A recent study found histopathologic abnormalities quite frequently (in all but one heterozygote). Lipid accumulation, found in all homozygotes, was mild or absent in heterozygotes.

Prevalence

Some twenty families with the lethal neonatal form [Smeets et al 2003, Thuillier et al 2003, Isackson et al 2008, Semba et al 2008, Boemer et al 2016] have been described. Since pregnancies in which a fetus has severe cerebral malformations are frequently interrupted, CPT II deficiency or other fatty acid oxidation disorders may be missed and the prevalence higher than previously suspected.

Approximately 28 families with the severe infantile hepatocardiomyopathy form have been described.

Since the first description of the myopathic form of CPT II deficiency by DiMauro & DiMauro [1973], findings in more than 300 cases have been published [Thuillier et al 2003, Bonnefont et al 2004, Isackson et al 2006, Fanin et al 2012, Joshi et al 2013]. Symptoms of the myopathic form can be mild and physical impairment may not occur; thus, this form of CPT II deficiency may be under-recognized.

Genetically Related (Allelic) Disorders

One reported family presented with a slowly progressive mild myopathy characterized by progressive muscle weakness and myopathic symptoms caused by a heterozygous p.Arg503Cys pathogenic variant in *CPT2*. A son of this family survived an episode of malignant hyperthermia during surgery at age four years [Vladutiu et al 2000a].

Durka-Kęsy et al [2012] reported a case of myopathy related to CPT II deficiency. However the diagnosis of myopathy as well as that of CPT II deficiency appear to be of questionable validity [Durka-Kęsy et al 2012].

The polymorphism p.Phe352Cys in exon 4 of *CPT2* is found only in East Asians. It is thermolabile and reduces enzyme activity during high temperatures. Reports have associated this polymorphism with acute encephalopathy during infectious disease and sudden unexpected death in infancy [Shinohara et al 2011, Yamamoto et al 2014].

Differential Diagnosis

Elevated acylcarnitines. The differential diagnosis of an elevation of C12 to C18 acylcarnitines, notably of C16 and C18:1, includes glutaric acidemia type II (see [Multiple Acyl-CoA Dehydrogenase Deficiency](#)) and [carnitine-acylcarnitine translocase deficiency](#), which can be excluded by additional screening of urinary metabolites such as glutaric and 3-OH-glutaric acid.

Neonatal Form

Carnitine-acylcarnitine translocase (CACT) deficiency. The neonatal phenotype of CACT deficiency, one of the most severe and usually lethal mitochondrial fatty-acid oxidation abnormalities, is characterized by hypoketotic hypoglycemia, hyperammonemia, cardiac abnormalities, and early death. Tandem mass spectrometry shows increased concentration of 16-2 H3 palmitoylcarnitine, suggesting either CPT II deficiency or CACT deficiency. One report shows that heat-denaturing high-performance liquid chromatography (DHPLC) is of use for diagnosing CACT deficiency [Fukushima et al 2013]. CACT deficiency is an autosomal recessive condition caused by compound heterozygous or homozygous pathogenic variants in *SLC25A20*.

Note: The differentiation of CACT deficiency from CPT II deficiency continues to be difficult using current acylcarnitine profiling techniques either from plasma or blood spots, or in the intact cell system (fibroblasts/ amniocytes). Specific enzyme assays are required to unequivocally differentiate CACT enzyme activity from CPT II enzyme activity [Roe et al 2006].

Alternatively, molecular genetic testing could be used to distinguish between these two conditions.

Carnitine palmitoyltransferase 1A (CPT1A) deficiency is a disorder of long-chain fatty-acid oxidation in which clinical symptoms usually occur with a concurrent febrile or gastrointestinal illness when energy demands are increased. The recognized phenotypes are: acute fatty liver of pregnancy, in which the fetus has biallelic pathogenic variants in *CPT1A* that cause CPT1A deficiency; and hepatic encephalopathy, in which individuals (typically children) present with hypoketotic hypoglycemia and sudden onset of liver failure. Individuals with hepatic encephalopathy typically present with hypoglycemia, absent or low levels of ketones, and elevated serum concentrations of liver transaminases, ammonia, and total carnitine.

The ratio of free-to-total carnitine in serum or plasma on a newborn screen bloodspot may be elevated in CPT1A deficiency. CPT1 enzyme activity on cultured skin fibroblasts is 1%-5% of normal in most affected individuals. In individuals with an enzymatically confirmed diagnosis of CPT1A deficiency, the *CPT1A* pathogenic variant detection frequency using sequence analysis is greater than 90%. Inheritance is autosomal recessive.

Myopathic Form

The myopathic form of CPT II deficiency is the most common disorder of lipid metabolism affecting skeletal muscle and is the most frequent cause of hereditary myoglobinuria. If clinical history is suggestive of a metabolic myopathy, routine laboratory tests including measurement of concentrations of lactate, pyruvate, creatine kinase, amino acids, and free acylcarnitine in blood should be performed. Careful family history should be taken. In early reports, elevation of acylcarnitines, notably C16 and C18:1, suggestive of a defect in mitochondrial β -oxidation, was detected by screening for acylcarnitines [Chace 2001]. Differential diagnosis of this finding includes CPT II deficiency, glutaric acidemia II (see [Multiple Acyl-CoA Dehydrogenase Deficiency](#)), carnitine-acylcarnitine translocase deficiency, and *TANGO2*-related metabolic encephalopathy and arrhythmias (a condition characterized by metabolic encephalomyopathic crises, rhabdomyolysis, cardiac arrhythmias, and neurodegeneration and caused by pathogenic variants in *TANGO2*). Unlike CPT II deficiency, *TANGO2*-related metabolic encephalopathy and arrhythmias is frequently accompanied by cardiac arrhythmias, cognitive impairment, epilepsy, spasticity, and brain atrophy. Additional tests are necessary to reach a definite diagnosis [Albers et al 2001].

Rhabdomyolysis and/or myoglobinuria. Rhabdomyolysis is etiologically heterogeneous, most cases being apparently acquired – for example, as a result of mechanical or vascular damage. Recurrent rhabdomyolysis preceded by exercise or infection is more likely to have an underlying metabolic defect, and strategic diagnostic procedures are warranted. History and physical examination are likely to identify the acquired and drug-related forms. However, one has to bear in mind that sometimes myoglobinuria with episodes of dark urine is ignored, and pronounced muscle pain after only light exercise is not considered a sign of disease. Screening for metabolic disorders (carnitine profile, amino acids, tandem mass spectrometry) may point in specific directions. Muscle biopsy for histologic and biochemical analysis should be performed. However, in a significant proportion of individuals, no cause of rhabdomyolysis can be identified.

Acquired causes of rhabdomyolysis

- Excessive use of muscle force (e.g., sports, seizures, dystonia)
- Muscle damage (e.g., crush, cold, ischemia, embolism)
- Infections (bacterial/viral/fungal)

- Temperature changes
- Inflammatory myopathies (polymyositis, vasculitis)

Drug-related causes of rhabdomyolysis

- Induction of an autoimmune reaction (e.g., cyclosporine, penicillamine)
- Hypokalemia (amphotericin, caffeine)
- Membrane disruption (cimetidin, colchicine)
- Disturbance of Na/K ATPase (antidepressants, arsen, azathioprine, bezafibrates)
- Neuroleptic syndrome (all neuroleptics, lithium)
- Serotonergic syndrome (amphetamines, MAO-inhibitor, SSRI)

Metabolic-toxic causes of rhabdomyolysis

- Defects of glucose/glycogen metabolism (e.g., [McArdle disease](#), [Tarui disease \[OMIM 232800\]](#)). Deficiencies of the six enzymes involved in glycogen breakdown (phosphorylase, phosphorylase kinase, phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase) result in exercise intolerance and recurrent rhabdomyolysis.
- Defects of lipid metabolism (carnitine deficiency). Mitochondrial β -oxidation of long-chain fatty acids is a major source of energy production, particularly at times of stress or fasting. Skeletal muscle can use carbohydrates or lipids as fuel, depending on the degree of activity. At rest or during prolonged low-intensity exercise, approximately 70% of the energy requirement is met by the oxidation of long-chain fatty acids. Two defects of lipid metabolism primarily affecting the skeletal muscle are known: carnitine palmitoyltransferase II deficiency and [systemic primary carnitine deficiency](#) characterized by progressive proximal weakness and cardiomyopathy.
- Defects of oxidative phosphorylation (complex II deficiency, complex III defect, cytochrome *c* oxidase deficiency) (See [Mitochondrial Disorders Overview](#).)
- [TANGO2-related encephalopathy and arrhythmias](#)
- Malignant hyperthermia (See [Malignant Hyperthermia Susceptibility](#).)
- [Dystrophinopathies](#) (Duchenne muscular dystrophy, Becker muscular dystrophy)
- Myoadenylate deaminase deficiency (MAD) (OMIM 615511)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with carnitine palmitoyltransferase II (CPT II) deficiency, the following are recommended:

- Neurologic examination
- Strength testing
- Review of dietary association of symptoms
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Current treatment for long-chain fatty-acid oxidation disorders:

- Avoid known triggers.
- Reduce the amount of long-chain dietary fat while covering the need for essential fatty acids.
- Provide carnitine to convert potentially toxic long-chain acyl-CoAs to acylcarnitines.

- Provide a large fraction of calories as carbohydrates to reduce body fat utilization and prevent hypoglycemia.
- Provide approximately one third of the calories as even-chain medium chain triglycerides (MCT). Metabolism of the eight to ten carbon fatty acids in MCT oil, for example, is independent of CPT I, carnitine-acylcarnitine translocase, CPT II, very long-chain acyl-CoA dehydrogenase (VLCAD), trifunctional protein, and long-chain hydroxy-acyl-CoA dehydrogenase deficiency (LCHAD) enzyme activities.

Prevention of Primary Manifestations

Appropriate measures include the following:

- Infusions of glucose during intercurrent infections to prevent catabolism
Note: Oral glucose cannot achieve this effect.
- High-carbohydrate (70%) and low-fat (<20%) diet to provide fuel for glycolysis
- Frequent meals and avoidance of extended fasting
- Avoidance of prolonged exercise and other known triggers

Prevention of Secondary Complications

The most important aim while treating an individual with CPT II deficiency is to prevent renal failure during an episode of rhabdomyolysis and myoglobinuria. Therefore, sufficient hydration and, if necessary, dialysis must be performed immediately when renal failure is imminent.

Surveillance

Annual or more frequent monitoring to regulate medication and diet is indicated.

Agents/Circumstances to Avoid

Extended fasting and prolonged exercise are to be avoided.

Reports of medication-induced side effects in individuals with CPT II deficiency are rare. Relying mostly on case reports, the following agents should be avoided:

- Valproic acid [Kottlors et al 2001]
- General anesthesia
- Ibuprofen
- Diazepam in high doses [Bonnefont et al 1999]

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk relatives so that morbidity and mortality can be reduced by early diagnosis and treatment. In addition, predictive testing for at-risk asymptomatic family members may be advisable before general anesthesia. Complications of general anesthesia (including rhabdomyolysis and suxamethonium hypersensitivity in individuals with a variety of neuromuscular diseases and renal post-anesthetic failure in individuals with CPT II deficiency in particular) have been observed [Katsuya et al 1988, Wieser et al 2008].

- Molecular genetic testing is appropriate if the pathogenic variants in the family are known.

- If the pathogenic variants in the family are not known, screening for alterations in acylcarnitines may be of use to identify other affected family members.

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

Pregnancy Management

While a variety of maternal complications have been observed in association with other fatty acid oxidation disorders (severe preeclampsia; acute fatty liver of pregnancy; maternal liver disease; and hemolysis, elevated liver enzymes, and low platelets), none of these complications has been associated with CPT II deficiency [Preece & Green 2002, Shekhawat et al 2005].

Therapies Under Investigation

Promising results have been obtained with treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using anaplerotic odd-chain triglycerides [Roe et al 2002]. These results were confirmed in seven individuals with CPT II deficiency, who avoided rhabdomyolysis or hospitalization while on the triheptanoin (anaplerotic) diet. Affected individuals returned to normal physical activity including strenuous sports [Roe et al 2008].

Fibrates are a class of hypolipidemic drugs that increase high-density lipoprotein levels by mRNA upregulation of many lipid-metabolism genes through interaction with the steroid/thyroid transcription factor PPAR α . Studies have demonstrated that bezafibrate increases *CPT2* mRNA and normalizes enzyme activity in mild forms of CPT II-deficient cultured fibroblasts and myoblasts [Bonfont et al 2009]. In a trial including six affected individuals treated with bezafibrate, the level of fatty acid oxidation in muscle biopsies was elevated, accompanied by a significant increase in palmitoyl-L-carnitine oxidation, increased *CPT2* mRNA, and increased translated protein. A reduction of episodes of rhabdomyolysis could be observed, as well as amelioration of quality of life (measured by SF-36) as shown by an increase in physical activity and a decline in muscular pain [Bonfont et al 2009, Bonfont et al 2010]. Another study did not show beneficial effects of bezafibrate on fatty acid oxidation and other disease manifestations; this study, however, was heavily criticized for methodologic shortcomings [Ørngreen et al 2014, Bastin et al 2015]

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for information on clinical studies for a wide range of diseases and conditions.

Other

Carnitine supplementation is essentially a cure for the carnitine membrane transporter defect. While oral carnitine supplementation of 50 mg/kg/d is often prescribed in the treatment of other fat oxidation disorders, controlled trials of its effectiveness in CPT II deficiency are lacking. In addition, carnitine administration is controversial, given the possibility of accumulation of acyl-CoAs and consequent depletion of free CoA in the mitochondria [Yoshino et al 2003]. In acutely ill infants aggressive treatment with IV glucose and cardiac support is critical, and should be complemented with L-carnitine supplementation.

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

Carnitine palmitoyltransferase II (CPT II) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *CPT2* pathogenic variant).
- Heterozygotes (carriers) are generally asymptomatic; however, manifesting carriers for the p.Arg503Cys pathogenic variant have been reported [Vladutiu et al 2000a, Vladutiu 2001].
Anichini et al [2011] identified only one pathogenic variant in 5/18 individuals with CPT II deficiency. While failure to detect the second pathogenic variant is the likely explanation, these individuals may instead represent symptomatic heterozygotes.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are generally asymptomatic.

Offspring of a proband. The offspring of an individual with CPT II are obligate heterozygotes (carriers) for a pathogenic variant in *CPT2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CPT2* pathogenic variant.

Carrier (Heterozygote) Detection

Molecular genetic testing. Carrier testing should rely on molecular genetic methods if both *CPT2* pathogenic variants have been identified in an affected family member.

Biochemical testing

- No data regarding the use of MS/MS for carrier detection are available.
- Carriers can be detected by measuring enzyme activity in muscle homogenates. Two unaffected carriers (parents), each carrying the common *CPT2* p.Ser113Leu pathogenic variant (see Molecular Genetics), had normal total CPT II enzyme activity on routine testing, but intermediate activities of 30% and 44% after addition of malonyl-CoA and triton X, respectively [Wieser et al 2003].

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, clarification of carrier status, 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.

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).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *CPT2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CPT II deficiency are possible. Intrafamilial phenotypic homogeneity is a common feature in the lethal neonatal form and the severe infantile hepatocardiomyopathy form of CPT II deficiency; however, data on prediction of the phenotype from prenatal test results are sparse and genotype-phenotype correlations remain inexact [Thuillier et al 2003, Joshi et al 2014].

Biochemical testing. Prenatal diagnosis for pregnancies at 25% risk is possible by analysis of enzyme activity of CPT II in cultured amniocytes and in freshly sampled chorionic villi [Vekemans et al 2003]. Deficient CPT II enzyme activity should be confirmed in an affected family member (usually an affected sib) before prenatal testing can be performed using enzyme assay. Tandem mass spectrometry analysis of the acylcarnitine profile in amniotic fluid supernatant has been attempted. Results from one affected fetus were normal, possibly due to the low excretion and poor solubility of long chain acylcarnitines in fetal urine. Therefore, prenatal diagnosis of CPT II deficiency cannot be reliably achieved through acylcarnitine analysis of amniotic fluid [Boemer et al 2016].

Ultrasound examination. Brain and/or renal abnormalities on fetal ultrasonography in the midtrimester of pregnancy have been identified in fetuses subsequently diagnosed to have CPT II deficiency using biochemical or molecular genetic testing [Elpeleg et al 2001, Sharma et al 2003].

Differences in perspective may exist among medical professionals if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal 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](#).

- **British Inherited Metabolic Disease Group (BIMDG)**
TEMPLE (Tools Enabling Metabolic Parents LEarning)
United Kingdom
[CPT II Deficiency](#)
- **National Library of Medicine Genetics Home Reference**
[Carnitine palmitoyltransferase II deficiency](#)
- **FOD Family Support Group (Fatty Oxidation Disorder)**
Phone: 517-381-1940
Email: deb@fodsupport.org; fodgroup@gmail.com
www.fodsupport.org
- **Metabolic Support UK**
United Kingdom
Phone: 0845 241 2173
www.metabolicsupportuk.org

- **Muscular Dystrophy Association (MDA) - USA**
Phone: 833-275-6321
www.mda.org

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. Carnitine Palmitoyltransferase II Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>CPT2</i>	1p32.3	Carnitine O-palmitoyltransferase 2, mitochondrial	CPT2 database	CPT2	CPT2

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 Carnitine Palmitoyltransferase II Deficiency ([View All in OMIM](#))

255110	CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, MYOPATHIC, STRESS-INDUCED
600649	CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, INFANTILE
600650	CARNITINE PALMITOYLTRANSFERASE II; CPT2
608836	CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, LETHAL NEONATAL

Molecular Pathogenesis

The carnitine palmitoyltransferase enzyme system (CPT), in conjunction with acyl-CoA synthetase and carnitine-acylcarnitine translocase, mediates the entry of long-chain fatty acids (LCFA) into the mitochondrial matrix for β -oxidation. CPT II, encoded by *CPT2*, is located on the inner mitochondrial membrane. CPT I, another component of this system, is located on the outer membrane; one isoform of CPT I is associated with [carnitine palmitoyltransferase 1A deficiency](#).

Gene structure. *CPT2* spans 20 kb and contains five exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants (see Table 2). In persons of northern European heritage, two normal variants, p.Val368Ile and p.Met647Val, occur with a frequency of 0.5 and 0.25 respectively, exhibiting Hardy-Weinberg equilibrium. A third normal variant, p.Phe352Cys, occurs in the Japanese population [Wataya et al 1998].

Pathogenic variants (see Table 2). More than 90 *CPT2* pathogenic variants have been identified, the majority are predicted to produce amino acid substitutions or small deletions [Isackson et al 2006, Isackson et al 2008, Anichini et al 2011, Fanin et al 2012, Joshi et al 2013].

- A so-called "common" variant, p.Ser113Leu, is present in exon 3 of *CPT2*. This variant is identified in approximately 60% of all mutated alleles.
- p.Lys414ThrfsTer7 was found in subsequent studies in eight affected individuals and is therefore the second-most common variant [Taggart et al 1999].
- Interestingly, the p.Phe448Leu amino acid substitution alone has no functional consequence [Deschauer et al 2005]. However, it is always found on the same allele (*in cis*) with the p.Lys414ThrfsTer7 frameshift variant, which is pathogenic because it predicts a premature termination codon. The mode of action of this complex mutated haplotype p.[Lys414ThrfsTer7;Phe448Leu] remains unclear.

Table 2. CPT2 Variants Discussed in This GeneReview

Variant Classification	DNA Nucleotide Change	Predicted Protein Change (Alias ¹)	Reference Sequences
Benign	c.1055T>G ²	p.Phe352Cys	NM_000098.2 NP_000089.1
	c.1102G>A	p.Val368Ile	
	c.1939A>G	p.Met647Val	
Pathogenic	c.149C>A	p.Pro50His	
	c.338C>T	p.Ser113Leu	
	c.359A>G	p.Tyr120Cys	
	c.520G>A	p.Glu174Lys	
	c.534_558del25insT	p.Leu178_Ile186delinsPhe	
	c.641T>C	p.Met214Thr	
	c.680C>T	p.Pro227Leu	
	c.983A>G	p.Asp328Gly	
	c.1145G>A	p.Arg382Lys	
	c.1148T>A	p.Phe282Tyr	
	c.1238_1239delAG	p.Lys414ThrfsTer7 (Gln413fs)	
	c.[1238_1239del;1342T>C]	p.[Lys414ThrfsTer7;Phe448Leu] ³ (Gln413fs/Phe448Leu)	
	c.1342T>C	p.Phe448Leu	
	c.1507C>T	p.Arg503Cys	
	c.452G>A	p.Arg151Gln	
	c.1646G>A	p.Gly549Asp	
c.1737delC	p.Tyr579Ter		
c.1883A>C	p.Tyr628Ser		
c.1891C>T	p.Arg631Cys		
c.1923_1935del	p.Lys642ThrfsTer6 (Glu641fs) ⁴		

Variants listed in the table have been provided by the author. *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.

1. Variant designation that does not conform to current naming conventions

2. [rs2229291](#)

3. The two sequence variants are on the same allele (i.e., *in cis*); the p.Phe448Leu variant has no known functional significance.

4. Isackson et al [2008]

Normal gene product. CPT II has a molecular weight of 60-70 kd. The initial translation product contains 658 amino acids.

Abnormal gene product. It has been proposed that the pathologic findings likely result from altered regulatory properties of the enzyme system rather than from a lack of catalytic activity, since enzyme activity is normal in affected individuals as well as in controls under optimal assay conditions, but the enzyme is abnormally inhibited by malonyl-CoA, an intrinsic inhibitor of this system.

The crystal structure of rat carnitine palmitoyltransferase II has led to new insights into possible pathologic mechanisms. It was shown that the overall structure shows similarity to other carnitine acyltransferases with structural differences in the active sites, which may have an effect on substrate selectivity. Regarding the most frequently mutated residue, serine-113, Hsiao et al [2006] report: "The side chain hydroxyl of Ser113 has a long hydrogen-bond with the guanidinium group of Arg498, which in turn is ion-paired to Asp376, located four residues from the catalytic His372 residue. Therefore, the p.Ser113Leu variant may disturb this hydrogen-bonding and ion-pair network, and thereby indirectly affect the catalytic efficiency of the His372 residue."

Hsiao et al [2006] suggest that the p.Pro50His variant, which is 23 amino acids from the active site, results in an altered association of the enzyme with the mitochondrial membrane, thus impairing the transport of acylcarnitine substrate to the active site of CPT II.

Chapter Notes

Revision History

- 3 January 2019 (aa) Revision: *TANGO2*-related metabolic encephalopathy and arrhythmias added to Differential Diagnosis
- 16 March 2017 (ma) Comprehensive update posted live
- 15 May 2014 (me) Comprehensive update posted live
- 6 October 2011 (me) Comprehensive update posted live
- 25 June 2009 (me) Comprehensive update posted live
- 30 November 2006 (me) Comprehensive update posted live
- 27 August 2004 (me) Review posted live
- 7 October 2003 (tw) Original submission

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