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Carnitine Palmitoyltransferase II Deficiency

[*CPT II Deficiency*]

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Summary

Disease 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 hepatocardiomuscular form, and myopathic form that 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. Males are more likely to be affected than females.

Diagnosis/testing. Tandem mass spectrometric measurement of serum/plasma acylcarnitines is an initial screening test. Definitive diagnosis is usually made by detection of reduced CPT enzyme activity. Molecular genetic testing of *CPT2*, the only gene known to be associated with CPT II deficiency, provides additional means for noninvasive, rapid, and specific diagnosis. Such testing is clinically available.

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. *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 to avoid:* valproic acid, general anesthesia, ibuprofen, and diazepam in high doses. *Testing relatives at risk:* If the disease-causing mutations 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.

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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Heterozygotes (carriers) are usually asymptomatic; however, manifesting carriers have been reported. Prenatal diagnosis for pregnancies at 25% risk for one of the severe forms of the disease is possible either by molecular genetic testing of the *CPT2* gene if the two disease-causing mutations in the family are known or by assay of CPT II enzyme activity.

Diagnosis

Clinical Diagnosis

The three clinical presentations of carnitine palmitoyltransferase II (CPT II):

- **Lethal neonatal form, 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)
  - Onset within days after birth
- **Severe infantile hepatocardiomuscular form, characterized by:**
  - Liver failure
  - Cardiomyopathy
  - Seizures, hypoketotic hypoglycemia
  - Peripheral myopathy
  - Attacks of abdominal pain and headache
  - Onset in the first year of life
- **Myopathic form, characterized by:**
  - Recurrent attacks of myalgia accompanied by myoglobinuria precipitated by prolonged exercise (especially after fasting), cold exposure, or stress
  - Possible weakness during attacks
  - No signs (usually) of myopathy (weakness, myalgia, elevation of serum creatine kinase [CK] concentration) between attacks
  - Variable onset (first to sixth decade)

Testing

Tandem mass spectrometry (MS/MS) of serum/plasma acylcarnitines (i.e, the acylcarnitine profile). The finding suggestive of a defect in mitochondrial β-oxidation (and thus suspect for CPT II deficiency) is an elevation of C12 to C18 acylcarnitines, notably of C16 and C18:1. (See Differential Diagnosis for other disorders with this acylcarnitine profile.)

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 <—> 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 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 is measured as the fraction that is not inhibited by malonyl-CoA.

The lethal neonatal form and the severe infantile hepatocardiomuscular 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 enzyme assay 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 stoichometric 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.

Carriers

- 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.S113L mutation, had normal total CPT II enzyme activity on routine testing, but intermediate activities of 30% and 44% after addition of malonyl-CoA or Triton X respectively [Wieser et al 2003].
- When causative mutations are known, carrier testing should rely on molecular genetic methods.

For laboratories offering biochemical testing for CPT II, see Testing.

Serum CK concentration. Rhabdomyolysis of any etiology results in elevation of serum CK concentration. A more than fivefold increase in serum CK concentration indicates severe damage to muscle tissue 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; however, permanent elevation of serum CK concentration (≤313 U) is observed in about 10% of individuals [Wieser et al 2003].

Histologic investigation shows mild unspecific myopathic changes (atrophic fibers and increased variability in fiber size) in 50% of individuals with the myopathic form of CPT II deficiency; normal findings are present in 50% of affected individuals. Elevated storage of lipids in skeletal muscle is found in 11% of individuals [Engel 2004].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *CPT2* is the only gene associated with CPT II deficiency.

Molecular genetic testing: Clinical uses

- Diagnosis
- Carrier detection
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis**

  Lethal neonatal form. Homozygosity for the severe mutations p.R631C, p.D328G, or p.Y628S is associated with the lethal neonatal form [Taroni et al 1992, Bonnefont et al 1996, Thuillier et al 2003].

  Severe infantile hepatocardiomuscular form. Compound heterozygosity for a mild and a severe mutation has been reported with this form [Vladutiu, Quackenbush et al 2002; Thuillier et al 2003].

  Myopathic form

  - The mutation p.S113L accounts for 60% of mutant alleles in the myopathic form of CPT II deficiency. In a series of 32 affected individuals, 14 were homozygous for the common allele [Wieser et al 2003]; 17 were compound heterozygous for the common allele and a second abnormal allele. Testing for this mutation alone would suggest the diagnosis in 31 out of 32 individuals.
  - The second most common mutation is Q413fs (also written Q413fs/F448L), found in up to 20% of affected individuals [Taggart et al 1999].

- **Sequence analysis.** Sequence analysis, available on a clinical basis, detects rare or family-specific mutations.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Percent of Mutant Alleles		Test Availability
		Myopathic Form	Severe Infantile Hepatocardiomuscular Form/ Lethal Neonatal Form	
Targeted mutation analysis	p.S113L	~60% [1]	Limited data [2]	Clinical Testing
	Q413fs	~20% [1]		
	p.P50H, p.R503C, p.G549D, Q413fs, p.M214T	~15% [1]		
Sequence analysis	*CPT2* sequence variants	>95% [1]		

1. Taggart et al 1999, Thuillier et al 2003, Wieser et al 2003, communication with laboratories listed in GeneTests performing analysis
2. The severe infantile hepatocardiomuscular form and the lethal neonatal form are associated with severe mutations such as Q413fs [Vladutiu, Quackenbush et al 2002; Thuillier et al 2003]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

- Tandem mass spectrometry of serum/plasma acylcarnitines is recommended as an initial screening test.

- If the results suggest a defect of β-oxidation, molecular genetic testing for the more common *CPT2* mutations (p.S113L, Q413fs/F448L) is recommended.
- If molecular genetic testing does not reveal homozygosity or compound heterozygosity for the common *CPT2* allele, CPT II enzyme activity should be measured.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *CPT2*.

Clinical Description

Natural History

Three carnitine palmitoyltransferase II (CPT II) deficiency phenotypes are recognized: a lethal neonatal form; a severe infantile hepatocardiomuscular 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, Quackenbush et al 2002; Sigauke et al 2003].

Neuronal migration defects including cystic dysplasia of the basal ganglia have been reported [Pierce et al 1999].

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

Cardiac arrthymias can result in sudden death during infancy [Bonnefont et al 1996; Yamamoto et al 1996; Vladutiu, Quackenbush et al 2002].

Myopathic form. Almost all individuals with the myopathic form experience myalgia. About 60% have muscle weakness during the attacks. Occasionally, muscle cramps occur; however, they are not typical of the disease. Myoglobinuria with brown-colored urine during the attacks occurs in about 75% of individuals.

Age at onset and age at diagnosis vary widely. In a sample of 32 individuals with the myopathic form, detailed clinical data were obtained from 23 individuals [Wieser et al 2003, Deshauer et al 2005]. Age at onset ranged from one to 61 years; age at diagnosis ranged from seven to 62 years. In 70%, the disease started in childhood (0-12 years); in 26%, the first attacks occurred in adolescence (13-22 years); in one individual, symptoms began in late-adult life (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 (ESRD) caused by interstitial nephritis with acute tubular necrosis requiring dialysis occasionally occurs [Kaneoka et al 2005].

There is a marked preponderance of affected males. 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 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 explain the gender disproportion completely [Vladutiu, Bennett et al 2002]. Females may be less likely to develop myoglobinuria and therefore remain undetected.

Genotype-Phenotype Correlations

Consistent genotype-phenotype correlation can be found in that missense mutations are associated with the muscle form (including the common p.S113L mutation) and therefore called "mild mutations" and truncating mutations are frequently associated with the lethal neonatal forms and subsequently termed "severe" mutations.

For unknown reasons, compound heterozygosity for a "mild" and a "severe" mutation can be associated either with the mild muscle form or with the severe multisystemic infantile form [Bonnefont 1999, Vladutiu 2002].

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].

Prevalence

Thirteen families with the lethal neonatal form [Thuillier et al 2003] and about 20 families with the severe infantile hepatocardiomuscular form have been described. Since the first description of the myopathic form of CPT II deficiency in 1973 by DiMauro and DiMauro, findings in more than 200 cases have been published [Thuillier et al 2003]. Since symptoms of the myopathic form can be mild and physical impairment may not occur, this form of CPT II deficiency may be under-recognized.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Elevated acylcarnitines. The differential diagnosis of an elevation of C12 to C18 acylcarnitines, notably of C16 and C18:1, includes glutaricacidemia type II (see Organic Acidemias) and carnitine-acylcanitine 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 carnitine-acylcarnitine translocase (CACT) deficiency is one of the most severe and usually lethal mitochondrial fatty-acid oxidation abnormalities, 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.

Note: The differentiation of carnitine-acylcarnitine translocase deficiency (CACT) 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). Therefore, specific enzyme assays are required to unequivocally differentiate CACT from CPT II [Roe et al 2006].

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 three recognized phenotypes are hepatic encephalopathy, in which children present with hypoketotic hypoglycemia and sudden onset of liver failure; adult-onset myopathy, seen in one individual of Inuit origin; and acute fatty liver of pregnancy, in which the fetus is homozygous for a mutation in *CPT1A*, the gene associated with CPT1A deficiency.

The ratio of free-to-total carnitine in serum or plasma on a newborn screen bloodspot is elevated in CPT1A deficiency. CPT 1 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* mutation detection rate 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 should be performed, including measurement of concentrations of lactate, pyruvate, creatine kinase, amino acids, and free acylcarnitine in blood. 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, glutaricacidemia II, or carnitine-acylcarnitine translocase deficiency; 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 the result of acquired causes, such as 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 as 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 cases of rhabdomyolysis

- Induction of an autoimmune reaction (e.g., cyclosporine, penicillamine)
- Hypokalemia (amphotericin, caffeine)
- Membrane disruption (cemitidin, colchicine)
- Disturbance of Na/K ATPase (antidepressants, arsen, azathioprin, 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). Deficiencies of the six enzymes involved in glycogen breakdown (phosphorylase, phosphorylase kinase, phosphofructokinase, phosphoglycerate kinase, phosphyglycerate 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, about 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 primary carnitine deficiency characterized by progressive proximal weakness and cardiomyopathy.
- Defects of oxidative phosphorylation (complex II deficiency, complex III defect, cytochrome c oxidase deficiency)
- Malignant hyperthermia (see Malignant Hyperthermia Susceptibility)
- Dystrophinopathies (Duchenne muscular dystrophy, Becker muscular dystrophy)
- Myoadenylate deaminase deficiency (MAD)

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Neurologic examination
- Strength testing
- Review of dietary association of symptoms

Treatment of Manifestations

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

- 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 about 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

- Infusions of glucose during intercurrent infections to prevent catabolism
- High-carbohydrate (70%) and low-fat (<20%) diet to provide fuel for glycolysis
- Frequent meals and the avoidance of extended fasting
- Avoidance of prolonged exercise

Prevention of Secondary Complications

The most important aim while treating an individual with CPT II deficiency is to prevent renal failure during an attack 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
- Prolonged exercise

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 [Cornelio et al 1980]
- Ibuprofen [Ross & Hoppel 1987]
- Diazepam in high doses [Bonnefont et al 1999]

Testing of Relatives at Risk

It is appropriate to offer molecular genetic testing to at-risk relatives if the disease-causing mutations are identified in an affected family member, so that morbidity and mortality can be reduced by early diagnosis and treatment.

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].

Search ClinicalTrials.gov for access to 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. However, although it is often prescribed (oral carnitine supplementation 50 mg/kg/d) in the treatment of other fat oxidation disorders, no benefit has been observed.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 and therefore carry one mutant allele.
- Heterozygotes (carriers) are generally asymptomatic; however, manifesting carriers for the p.R503C mutation have been reported [Vladutiu et al 2000, Vladutiu 2001].

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are generally asymptomatic.

Offspring of a proband. The offspring of an individual with CPT II are obligate heterozygotes (carriers) for a disease-causing mutation in the *CPT2* gene.

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

Carrier Detection

Carrier testing is available once the mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Although only a few cases have been reported in the literature, prenatal diagnosis for pregnancies at 25% risk of resulting in an infant with the lethal neonatal form or severe infantile hepatocardiomuscular form of CPT II deficiency is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed. Intrafamilial phenotypic homogeneity is a common feature in the lethal neonatal form and the severe infantile hepatocardiomuscular form of CPT II deficiency; however, data on prediction of the phenotype from prenatal test results are sparse and genotype-phenotype correlations remain unclear [Thuillier et al 2003].

Note: Gestational age is expressed as menstrual weeks calculated from the first day of the last normal menstrual period or by ultrasound measurements.

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 sibling, before prenatal testing can be performed using enzyme assay.

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].

Requests for prenatal testing for the myopathic form of CPT II deficiency have not been reported. Differences in perspective may exist among medical professionals if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see 

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Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Carnitine Palmitoyltransferase II Deficiency

Gene Symbol	Chromosomal Locus	Protein Name
CPT2	1p32	Carnitine O-palmitoyltransferase 2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Carnitine Palmitoyltransferase II Deficiency

255110	CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, LATE-ONSET
600649	CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, INFANTILE
600650	CARNITINE PALMITOYLTRANSFERASE II; CPT2
608836	CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, LETHAL NEONATAL

Table C. Genomic Databases for Carnitine Palmitoyltransferase II Deficiency

Gene Symbol	Entrez Gene	HGMD
CPT2	1376 (MIM No. 600650)	CPT2

For a description of the genomic databases listed, click here.

Molecular Genetic 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 is located on the inner mitochondrial membrane; CPT I is located on the outer membrane and, in contrast to CPT II, has three isoforms encoded by different genes (a liver isoform, L-CPT I, and a muscle isoform, M-CPT I). In situ, the enzymes display different kinetic and regulatory properties, such as Km values for substrates and sensitivity to inhibition by malonyl-CoA, TG-CoA, and related compounds [Price et al 2002].

Normal allelic variants: *CPT2* spans 20 kb and contains five exons. In Caucasians, two polymorphisms, p.V368I and p.M647V, occur with a frequency of 0.5 and 0.25 respectively, exhibiting Hardy-Weinberg equilibrium. A third polymorphism, p.F352C, occurs in the Japanese population [Wataya et al 1998].

Pathologic allelic variants: A total of 60 disease-causing mutations have been identified to date in CPT II; 41 of these are predicted to produce amino acid substitution/deletions [Isackson et al 2006].

A so-called "common" mutation is present in exon three of CPT2 at amino acid position 113, resulting in the exchange of a serine to a leucine. This mutation is identified in about 60% of all mutant alleles. Q413fs was found in subsequent studies in eight affected individuals and is therefore the next common mutation [Taggart et al 1999]. Analysis of 32 individuals by direct sequencing of the entire CPT2 gene led to the description of four novel mutations: p.M214T, p.F479Y, Q413fs, and 515del4 [Taggart et al 1999, Deschauer et al 2002, Wieser et al 2003].

Interestingly, the F448L mutation is always associated with the 35 amino acids located upstream of the Q413fs deletion mutation, resulting in a termination codon six amino acids

downstream, which would leave the F448L mutation without functional importance. However, experiments proving that the enzyme is truncated have not yet been conducted and it is well known that the efficiency of any codon (stop codon in this case) is heavily influenced by its context. The mode of action of this complex mutant haplotype still remains enigmatic.

Normal gene product: Within species, CPT I but not CPT II seems to be conserved across tissue lines. The size of monomeric CPT I ranges from 86 kd in rat skeletal muscle to 90-94 kd in rat liver. 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.

Reporting of 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 of substrate selectivity. Regarding the most frequently mutated residue, p.S113, Hsiao et al (2006) report: "The side chain hydroxyl of Ser113 has a long hydrogen-bond with the gaunidinium group of Arg498, which in turn is ion-paired to Asp376, located four residues from the catalytic His372 residue. Therefore, the S113L mutation 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.P50H mutation, 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.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Carnitine palmitoyltransferase II deficiency

Association for Neuro-Metabolic Disorders (ANMD)
PO Box 0202/L3220
1500 Medical Center Drive
Ann Arbor MI 48109-0202
Phone: 313-763-4697
Fax: 313-764-7502

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: (+44) 0870 7700 326

Fax: (+44) 0870 7700 327
Email: steve@climb.org.uk
www.climb.org.uk

FOD (Fatty Oxidation Disorder) Family Support Group
2041 Tomahawk
Okemos MI 48864
Phone: 517-381-1940
Email: deb@fodsupport.org
www.fodsupport.org

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Revision History

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