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Carnitine Palmitoyltransferase 1A Deficiency

Synonyms: CPT1A Deficiency, Hepatic Carnitine Palmitoyltransferase 1 Deficiency

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Summary

Clinical characteristics

Carnitine palmitoyltransferase 1A (CPT1A) deficiency is a disorder of long-chain fatty acid oxidation. Clinical manifestations usually occur in an individual with a concurrent febrile or gastrointestinal illness when energy demands are increased; onset of symptoms is usually rapid. The recognized phenotypes are: acute fatty liver of pregnancy, in which the fetus has biallelic pathogenic variants in *CPT1A* that causes 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. Between episodes of hepatic encephalopathy, individuals appear developmentally and cognitively normal unless previous metabolic decompensation has resulted in neurologic damage.

Diagnosis

The diagnosis of CPT1A is established in a proband by the detection of biallelic pathogenic variants in *CPT1A* on molecular genetic testing or diminished carnitine palmitoyltransferase 1 (CPT 1) enzyme activity on cultured skin fibroblasts when molecular genetic testing is not definitive. Residual enzyme activity is 1%-5% in most individuals with CPT1A deficiency.

Management

Treatment of manifestations: Prompt treatment of hypoglycemia with intravenous fluid containing 10% dextrose; the dextrose infusion should be maintained past the time that the blood glucose concentration has normalized in order to replete hepatic glycogen stores. Affected individuals, parents/guardians, and health care providers need to have readily available emergency treatment protocols for catastrophic metabolic crises.

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Prevention of primary manifestations: To prevent hypoglycemia, infants should eat frequently during the day and have cornstarch continuously at night; fasting should not last more than 12 hours during illness, surgery, or medical procedures; adults need a high-carbohydrate, low-fat diet to provide a constant supply of carbohydrate energy and medium-chain triglycerides to provide approximately one third of total calories (C6-C10 fatty acids do not require the carnitine shuttle for entry into the mitochondrion).

Prevention of secondary complications: Prevention of hypoglycemia reduces the risk for related neurologic damage.

Surveillance: Individuals with CPT1A deficiency should have testing of liver enzymes (AST, ALT, alkaline phosphatase) and liver function (including PT and PTT) at clinic appointments, even when asymptomatic, and during periods of reduced caloric intake and febrile illness.

Agents/circumstances to avoid: Prolonged fasting; potentially hepatotoxic agents such as valproate and salicylate.

Evaluation of relatives at risk: Regardless of age, each sib of a proband should be evaluated for CPT1A deficiency by either molecular genetic testing (if both pathogenic variants have been identified in the proband) or by enzyme analysis in cultured skin fibroblasts.

Pregnancy management: Heterozygous pregnant women should be monitored for acute fatty liver of pregnancy.

Genetic counseling

CPT1A deficiency is inherited in an autosomal recessive manner. Heterozygotes (carriers) are asymptomatic, although heterozygous pregnant women may be at risk of developing acute fatty liver of pregnancy if the fetus has CPT1A deficiency. At conception, each sib of an affected individual has 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. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible by biochemical testing if the enzyme defect has been confirmed in an affected family member or by molecular genetic testing if both pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Carnitine palmitoyltransferase IA (CPT IA) deficiency **should be suspected** in an individual with the following prenatal history, newborn screening results, postnatal clinical features, and supportive laboratory findings:

Prenatal history. Maternal acute fatty liver of pregnancy. CPT1A deficiency in a fetus can lead to the following maternal findings during pregnancy:

- Hypoglycemia
- Abnormal liver enzymes
- Hyperammonemia
- Abnormal hepatic synthetic function resulting in bleeding diathesis

Newborn screening results. Increased ratio of free carnitine to the sum of C16:0 (palmitoylcarnitine) plus C18 acylcarnitines (C18:1, oleic acid and C18:2 linoleic acid) on a newborn screen blood spot [Fingerhut et al 2001, Sim et al 2001]. See ACMG ACT Sheet.

Postnatal clinical findings

- Hepatic encephalopathy (similar to that seen in Reye syndrome) precipitated by fasting or fever (See **Supportive laboratory findings**.)

- Rapid onset of symptoms in association with a relatively common infectious disease, such as a febrile or gastrointestinal illness

Supportive laboratory findings

- **Hypoketotic hypoglycemia**, defined as low blood glucose concentration (<40 mg/dL) in the absence of ketone bodies in the urine
- **Elevated liver enzymes.** AST and ALT that are two- to tenfold the upper limit of normal
- **Hyperammonemia.** Plasma ammonia concentrations usually 100-500 µmol/L (normal: <70 µmol/L)
- **Elevated total serum carnitine** in the range of 70-170 µmol/L (normal total serum carnitine: 25-69 µmol/L). The elevation of total carnitine and hypoketotic hypoglycemia should increase suspicion specifically for CPT1A deficiency.
- **Elevated ratio of C0/C16+C18 acylcarnitines.** CPT1A deficiency is charaterized by marked reduction in the synthesis of all acylcarnitine species and increased levels of free carnitine (C0) (see ACMG ACT Sheet).
- **Urine organic acids** that demonstrate elevated dodecanedioic acid during acute crisis and for several days following [Korman et al 2005]. The authors have also observed C12 dicarboxylic acid elevation during acute crisis in individuals subsequently diagnosed with CPT1A deficiency [Bennett, personal unpublished observation].

Establishing the Diagnosis

The diagnosis of CPT1A **is established** in a proband by the detection of biallelic pathogenic variants in *CPT1A* on molecular genetic testing (see Table 1) or diminished carnitine palmitoyltransferase 1 (CPT 1) enzyme activity measured on cultured skin fibroblasts when molecular genetic testing is not definitive.

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

- **Single-gene testing.** Sequence analysis of *CPT1A* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found. Note: Targeted analysis may be considered first for the following pathogenic variants:
  - p.Pro479Leu in populations with a very high frequency of this allele, including: infants who test positive for CPT1A deficiency in the state of Alaska newborn screening program, the Canadian First Nations population in Nunavut (i.e., Inuit) [Collins et al 2010], the Greenland Inuit [Rajakumar et al 2009], and Siberians [Clemente et al 2014]. Most affected individuals in these populations are homozygous for this variant [Park et al 2006].
  - p.Gly710Glu, which is common in the Hutterite population [Prasad et al 2001]
- **A multigene panel** that includes *CPT1A* 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 1A Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
CPT1A	Sequence analysis [3]	>90% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Rare [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. Sequence analysis also detects the common p.Gly710Glu pathogenic variant in the Hutterite population [Prasad et al 2001] and the p.Pro479Leu pathogenic variant in the Inuit population [Brown et al 2001].
5. In individuals with enzymatic confirmation of CPT1A deficiency
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.
7. Exon and multiexon deletions have been rarely reported [Gobin et al 2002].

Carnitine palmitoyltransferase 1 (CPT 1) enzyme activity on cultured skin fibroblasts. Residual enzyme activity is 1%-5% in most individuals with CPT1A deficiency.

Clinical Characteristics

Clinical Description

Carnitine palmitoyltransferase I (CPT I) is a mitochondrial membrane protein that converts long-chain fatty acyl-CoA molecules to their corresponding acylcarnitine molecules. The resulting acylcarnitines are then available for transport into the mitochondrial matrix where they can undergo fatty acid oxidation. Mitochondrial fatty acid oxidation by the liver provides an alternative source of fuel when glycogen reserves are significantly reduced, most often due to fasting or other intercurrent illness. The pathway fuels ketogenesis for metabolism in peripheral tissues that cannot oxidize fatty acids.

Clinical symptoms usually occur in an individual with a concurrent febrile or gastrointestinal illness when energy demands are increased. The precipitating illness may be a relatively common infectious disease, but the onset of symptoms is usually rapid and should alert the clinician to the possibility of a fatty acid oxidation defect.

Carnitine palmitoyltransferase 1A (CPT1A) deficiency is a disorder of long-chain fatty acid oxidation.

Fetal CPT1A deficiency has been associated with acute fatty liver of pregnancy [Innes et al 2000]. A heterozygous female carrying an affected fetus is at risk of developing this obstetric complication. A number of other fetal fatty acid oxidation defects also carry a similar risk to the heterozygous mother of developing acute fatty liver of pregnancy, typically in the third trimester, prompting further investigation of the newborn for a fatty acid oxidation defect in this situation.

Hepatic encephalopathy. Although some neonates present with "physiologic" hypoglycemia of the newborn, most individuals with CPT1A deficiency present with fasting-induced hepatic encephalopathy in early childhood. This is a potentially fatal presentation; children who recover are at risk for recurrent episodes of life-threatening illness.

Survival through infancy without symptoms has been reported; initial presentation may occur later in life with similar life-threatening acute hepatic illness. For example, death as a result of rapid-onset hepatic failure in

CPT1A deficiency occurred in an individual age 17 years despite the early recognition of a fatty acid oxidation defect [Brown et al 2001].

Between episodes of metabolic decompensation, individuals appear developmentally and cognitively normal unless previous metabolic decompensation has resulted in neurologic damage.

Recognition of CPT1A deficiency and initiating management to prevent lipolysis reduces the episodes of decompensation [Stoler et al 2004, Stanley et al 2014].

Long-term liver damage as a result of recurring hepatosteatosis has not been reported.

Some individuals with the hepatic encephalopathy phenotype have also had renal tubular acidosis.

Unlike with other long-chain fatty acid oxidation defects, cardiac or skeletal muscle involvement is not common [Bonnefont et al 2004, Stanley et al 2014].

Genotype-Phenotype Correlations

The p.Pro479Leu pathogenic variant observed in the Inuit, which has high residual enzymatic activity (15%-20%), does not appear to cause acute hepatic failure as do the other pathogenic variants associated with the more severe phenotype [Brown et al 2001]. However, evidence suggests that infants who are homozygous for the variant have impaired fasting tolerance [Gillingham et al 2011] and increased risk of infant mortality [Gessner et al 2010]. In a study using whole-genome high-coverage sequence data of Arctic populations, this *CPT1A* variant was identified as deleterious and associated with increased infant mortality in circum-Arctic populations [Clemente et al 2014].

Nomenclature

The disorder has been previously described as non-ketotic hypoglycemia, hepatic CPT deficiency, hepatic CPT1, and L-CPT1 deficiency.

Prevalence

CPT1A deficiency caused by variants other than p.Pro479Leu appears to be very rare in the general population, with fewer than 60 affected individuals reported.

Improved detection of CPT1A deficiency in the newborn period may increase the detection rate for the disorder [Sim et al 2001]. The number of non-Inuit diagnoses in the Region 4 Stork (R4S) newborn screening collaborative for 2015 was five cases, giving an estimated prevalence of 1:500,000 to 1:1,000,000 newborns [Piero Rinaldo, personal communication].

The frequency of homozygosity for the p.Pro479Leu pathogenic variant is very high in the native Alaskan population (1.3:1,000 live births) when ascertained by expanded newborn screening (available through Alaska Division of Public Health). Given the high residual enzyme activity associated with this allele, p.Pro479Leu homozygosity is generally regarded as non-pathogenic but may still be associated with increased infant mortality [Clemente et al 2014] (see Genotype-Phenotype Correlations).

The carrier rate for the p.Gly710Glu pathogenic variant in the Hutterite population may be as high as 1:16 [Prasad et al 2001].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *CPT1A*.

Differential Diagnosis

The absence (or paucity) of ketone bodies during a period of hypoglycemia should increase suspicion for one of the disorders of fatty acid oxidation or the carnitine cycle, including carnitine palmitoyltransferase 1A (CPT1A) deficiency.

Because the CPT1A enzyme is primarily expressed in liver, CPT1A deficiency is clinically more closely related to fatty acid and ketogenesis disorders with hepatic phenotypes. These include the following:

- Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
- 3-hydroxy-3-methylglutaryl (HMG)-CoA synthase deficiency (OMIM 605911)
- HMG-CoA lyase deficiency

In the absence of muscle or heart manifestations, the acute hepatic presentation of CPT1A deficiency cannot be clinically distinguished from other defects of long-chain fatty acid oxidation and conditions that present as a Reye-like illness. These include the following:

- Carnitine palmitoyltransferase II (CPT II) deficiency
- Carnitine-acylcarnitine translocase (CACT) deficiency
- Very-long-chain acyl-CoA dehydrogenase deficiency
- Mitochondrial trifunctional protein deficiency including long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (See Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency.)
- Urea cycle disorders
- Organic acidurias such as methylmalonic and propionic acidemia
- Disorders of oxidative phosphorylation (See Mitochondrial Disorders Overview.)
- Disorders of gluconeogenesis (including glycogen storage disease type I)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with carnitine palmitoyltransferase 1A (CPT1A) deficiency, the following evaluations are recommended:

- In affected individuals who have profound and/or prolonged exposure to hypoglycemia: a complete neurologic evaluation to detect secondary neurologic damage
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Guidelines for the treatment of CPT1A deficiency can be found at newbornscreening.info and MedlinePlus.

When individuals present with acute hypoglycemia, sufficient amounts of intravenous fluid containing 10% dextrose should be provided as quickly as possible to correct hypoglycemia and to prevent lipolysis and subsequent mobilization of fatty acids into the mitochondria.

Because individuals presenting with profound hypoglycemia have little to no residual hepatic glycogen, treating physicians should continue the glucose infusion beyond the time that blood glucose concentration has normalized in order to provide sufficient substrate for glycogen synthesis.

A letter should be provided to affected individuals (or their parents/guardians) and involved health care providers alerting them to the potentially catastrophic metabolic crises for which these individuals are at risk and explaining the appropriate emergency treatment.

Prevention of Primary Manifestations

A high-carbohydrate diet (70% of calories) that is low in fat (<20% of calories) is generally recommended to provide a constant supply of carbohydrate energy, particularly during illness. Restriction of dietary fat intake is somewhat controversial when affected individuals are well. If the physician chooses to recommend a low-fat diet when the affected individual is well, supplementation with essential fatty acids is necessary.

Provision of approximately one third of total calories as medium-chain triglycerides is recommended during periods of illness. C6-C10 fatty acids do not require the carnitine shuttle for entry into the mitochondrion.

Frequent feeding is recommended, particularly for infants, given their limited glycogen reserves. Cornstarch feedings given overnight provide a constant source of slow-release carbohydrate to prevent hypoglycemia during sleep.

Older children should not fast for more than 12 hours and for a shorter time if evidence of a febrile or gastrointestinal illness exists.

Adults should be aware of the risks of fasting and they and their primary care physician should be aware of the risks during surgery when both metabolic stress and fasting occur.

Brief hospital admission for administration of intravenous dextrose-containing fluid should be considered in individuals with known CPT1A deficiency who are required to fast more than 12 hours because of illness or surgical or medical procedures.

Prevention of Secondary Complications

Prevention of hypoglycemia reduces the risk of related neurologic damage.

Surveillance

At clinic appointments and during periods of reduced caloric intake and febrile illness that could precipitate metabolic decompensation, individuals with CPT1A deficiency should undergo liver function testing whether they are symptomatic or not. Tests should include liver enzymes, AST, ALT, alkaline phosphatase (ALP), and functional liver tests (including the blood-clotting tests PT and PTT).

Agents/Circumstances to Avoid

Prolonged fasting should be avoided, especially during a febrile or gastrointestinal illness.

Potentially hepatotoxic agents such as valproate and salicylate should not be given, even though adverse effects of pharmacologic agents have not been reported in individuals with CPT1A deficiency.

Evaluation of Relatives at Risk

Because presentation in later childhood is possible, it is appropriate to evaluate each sib of a proband, regardless of age, in order to identify as early as possible those who would benefit from initiation of preventive measures.

Evaluations can include:

- Molecular genetic testing if the *CPT1A* pathogenic variants in the family are known.
- Enzyme analysis in cultured skin fibroblasts if the pathogenic variants in the family are not known.

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

Pregnancy Management

Although data are limited, it is prudent to counsel unaffected female carriers regarding the risk for obstetric complications.

Women who have had one child with CPT1A deficiency following an uneventful pregnancy remain at risk for acute fatty liver of pregnancy in subsequent pregnancies with an affected fetus.

Pregnant females who are heterozygous for a *CPT1A* pathogenic variant should be monitored for acute fatty liver of pregnancy. In any pregnancies that follow identification of a child with CPT1A deficiency, liver function testing should be performed at each prenatal visit during the first two trimesters and more frequently during the third trimester when the risk for acute fatty liver of pregnancy is greatest. Management by a team comprising a maternal-fetal medicine specialist and a medical/biochemical geneticist is highly recommended.

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

Carnitine palmitoyltransferase 1A (CPT1A) 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 *CPT1A* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic. Pregnant female carriers may be at risk of developing acute fatty liver of pregnancy if the fetus has CPT1A deficiency.

Sibs of a proband

- At conception, each sib of an affected individual has 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. Pregnant females who are heterozygous for a *CPT1A* pathogenic variant may be at risk of developing acute fatty liver of pregnancy if the fetus has CPT1A deficiency.

Offspring of a proband

- The offspring of an individual with CPT1A deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *CPT1A*.
- In populations with a high carrier rate and/or a high rate of consanguinity, it is possible that the reproductive partner of the proband may be affected or a carrier. Thus, the risk to offspring is most accurately determined after molecular genetic testing and/or biochemical testing of the proband's reproductive partner.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CPT1A* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CPT1A* 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, 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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *CPT1A* pathogenic variants have been identified in an affected family member, prenatal testing and preimplantation genetic testing for a pregnancy at increased risk for CPT1A deficiency are possible options.

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 1 DEFICIENCY

- **MedlinePlus**
  Carnitine palmitoyltransferase I 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. Carnitine Palmitoyltransferase 1A Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CPT1A	11q13.3	Carnitine O-palmitoyltransferase 1, liver isoform	CPT1A database	CPT1A	CPT1A

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 1A Deficiency (View All in OMIM)

255120	CARNITINE PALMITOYLTRANSFERASE I DEFICIENCY
600528	CARNITINE PALMITOYLTRANSFERASE I, LIVER; CPT1A

Molecular Pathogenesis

The so-called carnitine shuttle mediates transport of long-chain fatty acyl species from the cytosol into the mitochondria for energy production by β-oxidation. Carnitine palmitoyltransferase I (CPT I) on the outer mitochondrial membrane converts long-chain acyl-CoAs to their acylcarnitine equivalents, which are transported into the inner mitochondrial compartment by carnitine-acylcarnitine translocase and then reconverted to the acyl-CoA species by CPT II at the inner mitochondrial membrane [McGarry & Brown 1997]. CPT I is thus the rate-limiting factor for entry of long-chain fatty acids into the mitochondria for β-oxidation.

In the reduced activity of CPT I caused by biallelic pathogenic variants of *CPT1A*, fatty acids cannot enter the mitochondria for energy production (see Figure 1); the result is a clinical and biochemical phenotype of fasting intolerance.

Of the three CPT I family members, CPT1A is expressed in liver, kidney, leukocytes, and skin fibroblasts; CPT1B is expressed in muscle; and CPT1C is brain specific. Pathogenic variants in *CPT1A* and *CPT1C* have been associated with genetic disease. A dominantly inherited pathogenic variant in *CPT1C* has recently been associated with and is likely to be causative of spastic paraplegia 73 (OMIM 616282), a condition with no similarity to CPT1A deficiency [Rinaldi et al 2015].

Gene structure. *CPT1A* spans more than 60 kb of genomic DNA, of which 18 exons (2-19) are transcribed. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Outside the Hutterite and Inuit populations, all pathogenic variants characterized to date have been within single families (see Table 2 [pdf]) and many span the catalytic region. These include 15 pathogenic missense variants (listed in Table 3) as well as insertions and deletions [Gobin et al 2002, Bonnefont et al 2004, Stoler et al 2004, Korman et al 2005]. Approximately 50% of individuals characterized to date are homozygous for a unique pathogenic variant.

Table 3. Selected *CPT1A* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.96T>G	p.Tyr32Ter	NM_001876.3 NP_001867.2
c.298C>T	p.Gln100Ter	
c.367C>T	p.Arg123Cys	
c.478C>T	p.Arg160Ter	
c.912C>G	p.Cys304Trp	
c.941C>T	p.Thr314Ile	
c.946C>G	p.Arg316Gly	
c.1027T>G	p.Phe343Val	
c.1069C>T	p.Arg357Trp	
c.1079A>G	p.Glu360Gly	
c.1241C>T	p.Ala414Val	
c.1361A>G	p.Asp454Gly	
c.1395G>T	p.Gly465Trp	
c.1425G>A	p.Trp475Ter	
c.1436C>T	p.Pro479Leu	
c.1451T>C	p.Leu484Pro	
c.1493A>G	p.Tyr498Cys	
c.1494T>A	p.Tyr498Ter	
c.1600delC	p.Leu534Ter (Leu534fsTer)	
c.1737C>A	p.Tyr579Ter	
c.2126G>A	p.Gly709Glu	
c.2129G>A	p.Gly710Glu	

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

Normal gene product. *CPT1A* encodes a 773-amino acid polypeptide, which is expressed in liver, kidney, leukocytes, and skin fibroblasts. Two transmembrane domains exist and both the N and C termini are likely to be in the cytosolic compartment.

Abnormal gene product. Immunoblot analysis suggests that most of the pathogenic variants result in very low to undetectable enzymatic activity and no detectable protein product [Brown et al 2001, Gobin et al 2002].

The p.Pro479Leu variant results in high residual enzyme activity and a detectable protein of normal size and amount on western blot analysis. It is believed that the product of the p.Pro479Leu allele affects malonyl-CoA interaction with CPT1A.

Chapter Notes

Author History

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- 14 January 2005 (mb) Original submission

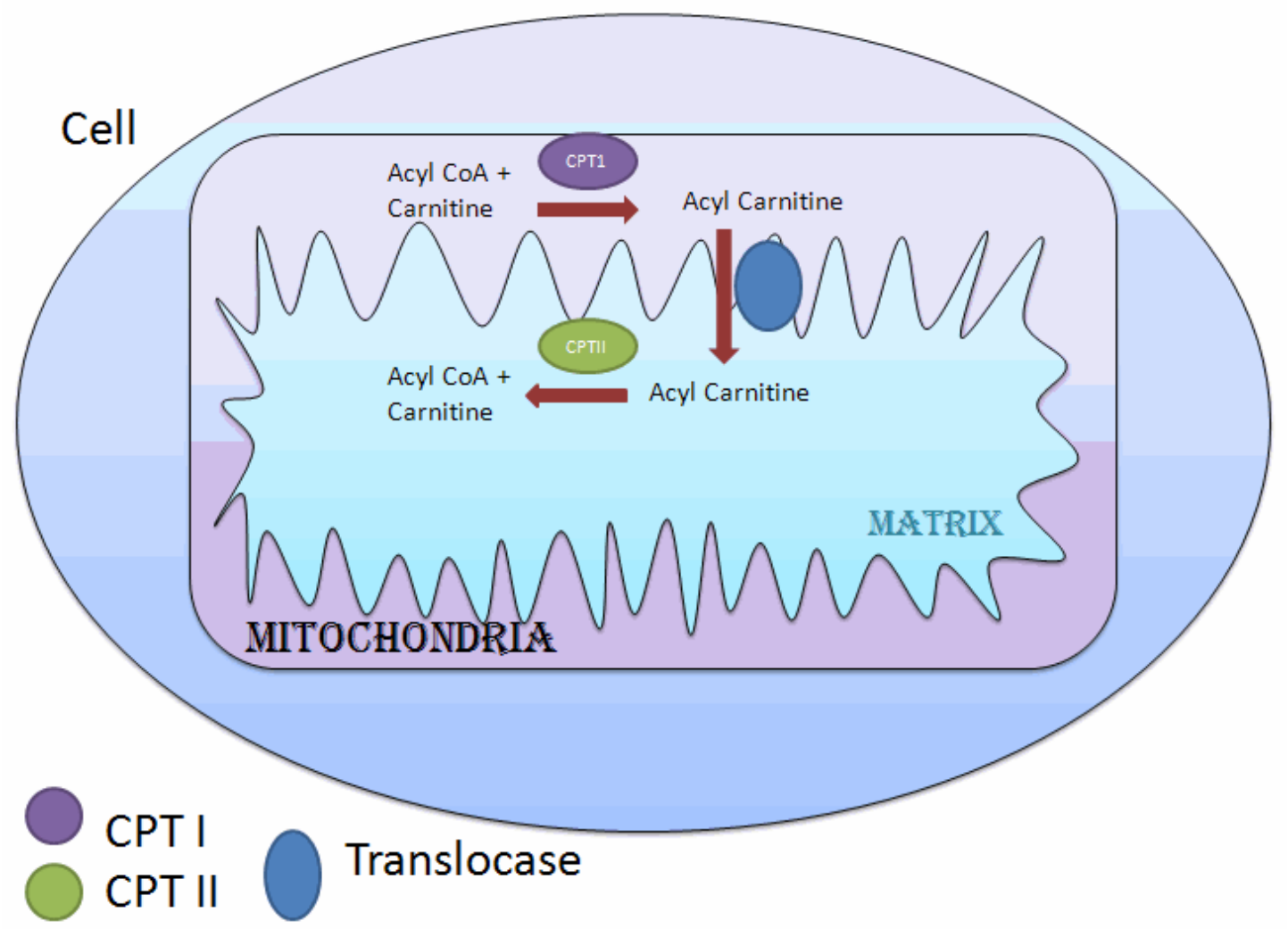

Figure 1. The carnitine shuttle

Acyl-CoAs are converted to acylcarnitines by carnitine palmitoyltransferase 1, translocated into the mitochondrial matrix by carnitine:acylcarnitine translocase, and reconverted to acyl-CoAs and free carnitine by carnitine palmitoyltransferase 2.

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