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Systemic Primary Carnitine Deficiency

Synonyms: Carnitine Transport Defect, Carnitine Uptake Defect, CDSP

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Summary

Clinical characteristics

Systemic primary carnitine deficiency (CDSP) is a disorder of the carnitine cycle that results in defective fatty acid oxidation. It encompasses a broad clinical spectrum including the following:

- Metabolic decompensation in infancy typically presenting between age three months and two years with episodes of hypoketotic hypoglycemia, poor feeding, irritability, lethargy, hepatomegaly, elevated liver transaminases, and hyperammonemia triggered by fasting or common illnesses such as upper respiratory tract infection or gastroenteritis
- Childhood myopathy involving heart and skeletal muscle with onset between age two and four years
- Pregnancy-related decreased stamina or exacerbation of cardiac arrhythmia
- Fatigability in adulthood
- Absence of symptoms

The latter two categories often include mothers diagnosed with CDSP after newborn screening has identified low carnitine levels in their infants.

Diagnosis/testing

Plasma carnitine levels are extremely reduced in CDSP. The diagnosis is established by identification of biallelic pathogenic variants in *SLC22A5* or demonstration of reduced fibroblast carnitine transport.

Management

Treatment of manifestations: Metabolic decompensation and skeletal and cardiac muscle function improve with 100-400 mg/kg/day oral levocarnitine (L-carnitine) if it is started before irreversible organ damage occurs. Hypoglycemic episodes are treated with intravenous dextrose infusion; cardiomyopathy requires management by specialists in cardiology.

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Prevention of primary manifestations: Maintain appropriate plasma carnitine concentrations with oral L-carnitine supplementation; prevent hypoglycemia with frequent feeding and avoiding fasting. Hospitalization for intravenous glucose administration for individuals who are required to fast for a procedure or who cannot tolerate oral intake due to illness such as gastroenteritis.

Prevention of secondary complications: Oral metronidazole and/or decreasing the carnitine dose usually results in the resolution of the fishy odor due to L-carnitine supplementation.

Surveillance: Echocardiogram and electrocardiogram: annually during childhood and less frequently in adulthood; monitor plasma carnitine concentration frequently until levels reach the normal range, then, measure three times a year during infancy and early childhood, twice a year in older children, and annually in adults; evaluate serum creatine kinase concentration and liver transaminases during acute illnesses.

Agents/circumstances to avoid: Fasting longer than age-appropriate periods.

Evaluation of relatives at risk: Measure plasma carnitine levels in sibs of an affected individual.

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

Genetic counseling

CDSP 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 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 a pregnancy at increased risk are possible if the *SLC22A5* pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Systemic primary carnitine deficiency (CDSP) **should be suspected** in the following clinical situations:

- Infant with positive newborn screening
- Infants with hypoketotic hypoglycemic episodes that may be associated with hepatomegaly, elevated transaminases, and hyperammonemia
- Children with skeletal myopathy and/or elevated serum concentration of creatine kinase (CK)
- Children with cardiomyopathy
- Adults with unexplained fatigability

Preliminary Testing

Newborn screening using tandem mass spectrometry (MS/MS) detects low levels of free carnitine (C0) and can identify infants with CDSP and mothers with CDSP. Because carnitine is transferred from the placenta to the fetus during pregnancy, an infant's carnitine levels during the neonatal period can reflect those of the mother. Thus, unaffected infants born to affected mothers can have low carnitine levels shortly after birth [Schimmenti et al 2007, El-Hattab et al 2010, Lee et al 2010].

The ACMG recommends that total and free carnitine be determined in infants who screen positive. Extremely reduced plasma free, acylated, and total (i.e., the sum of free and acylated) carnitine levels (i.e., <10% of controls) are diagnostic of this disorder [Longo et al 2006].

In addition, plasma carnitine levels should be measured in all mothers of infants found to have low free carnitine levels on newborn screening in order to determine if the mother (rather than the infant) has CDSP, or if both mother and infant have CDSP [Schimmenti et al 2007, El-Hattab et al 2010, Lee et al 2010].

Other presentations. In infants, children, and adults with other presentations plasma carnitine levels remain the mainstay of the initial laboratory diagnosis.

Of note, other biochemical studies may also have been done to address a broader differential diagnosis:

- **Plasma acylcarnitine profile.** Because of the low level of all acylcarnitine, this study may well be unsuccessful. If a profile can be generated, there is generally no specific elevation of any acylcarnitine species.
- **Urine organic acid analysis.** Nonspecific dicarboxylic aciduria, common in the acute decompensation of many fatty acid oxidation disorders, has been reported in some affected individuals with CDSP as well.

Establishing the Diagnosis

The diagnosis of CDSP **is established** in a proband by identification of biallelic pathogenic variants in *SLC22A5* on molecular genetic testing (see Table 1) or, if biallelic pathogenic variants cannot be identified, by use of a skin biopsy to assess carnitine transport in cultured fibroblasts.

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

- **Single-gene testing.** Sequence analysis of *SLC22A5* 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 *SLC22A5* 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.
- **More comprehensive genomic testing** (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes *SLC22A5*) fails to confirm a diagnosis in an individual with features of CDSP. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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

Table 1. Molecular Genetic Testing Used in Systemic Primary Carnitine Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
SLC22A5	Sequence analysis [3]	~70% [4]
	Gene-targeted deletion/duplication analysis [5]	6/96 [6]

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. In one study, *SLC22A5* sequencing performed in 70 infants with low carnitine levels detected by newborn screening identified two pathogenic variants in 23 infants and one pathogenic variant in 25 infants; no pathogenic variants were detected in 22 infants [Li et al 2010].
5. 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.
6. The Human Gene Mutation Database (HGMD) (www.hgmd.cf.ac.uk)

Fibroblast carnitine transport (uptake). Carnitine transport in skin fibroblasts from affected individuals is typically reduced below 10% of control rates [Longo et al 2006].

Clinical Characteristics

Clinical Description

The clinical manifestations of systemic primary carnitine deficiency (CDSP) can vary widely with respect to age of onset, organ involvement, and severity of symptoms. The CDSP phenotype encompasses a broad clinical spectrum including metabolic decompensation in infancy, cardiomyopathy in childhood, fatigability in adulthood, or absence of symptoms. CDSP has typically been associated with infantile metabolic presentation in about half of affected individuals and childhood myopathic presentation in the other half. However, adults with CDSP who have mild or no symptoms have been reported. Such milder phenotypes are expected to be underdiagnosed; therefore, it is difficult to determine the relative prevalence of different phenotypes associated with CDSP [Longo et al 2006, El-Hattab & Scaglia 2015].

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

Childhood myopathic (cardiac) presentation. The average age of myopathic presentation is between age two and four years, indicating that the myopathic manifestations of CDSP may develop over a longer period of time. Myopathic manifestations include dilated cardiomyopathy, hypotonia, skeletal muscle weakness, and elevated serum creatine kinase (CK). Death from cardiac failure can occur before the diagnosis is established, indicating that this presentation can be fatal if not treated. Older children with the infantile presentation may also develop myopathic manifestations including elevated CK, cardiomyopathy, and skeletal muscle weakness [Longo et al 2006, El-Hattab & Scaglia 2015].

Adulthood presentation. Several women have been diagnosed with CDSP after newborn screening identified low carnitine levels in their infants. About half of those women complained of fatigability, whereas the other half were asymptomatic. One woman was found to have dilated cardiomyopathy and another had arrhythmias [Schimmenti et al 2007, El-Hattab et al 2010, Lee et al 2010]. An asymptomatic adult male with CDSP has also been reported [Spiekerkoetter et al 2003].

Pregnancy-related symptoms. Pregnancy is a metabolically challenging state because energy consumption significantly increases. In addition, during pregnancy plasma carnitine levels are physiologically lower than those of non-pregnant controls. Affected women can have decreased stamina or worsening of cardiac arrhythmia during pregnancy, suggesting that CDSP may manifest or exacerbate during pregnancy [Schimmenti et al 2007, El-Hattab et al 2010].

Atypical manifestations. Other manifestations reported in individuals with CDSP include the following:

- Anemia [Cano et al 2008]
- Proximal muscle weakness and global developmental delays [Wang et al 2001]
- Respiratory distress [Erguven et al 2007]
- Arrhythmias and electrocardiographic abnormalities [Schimmenti et al 2007, Lee et al 2010], including long QT syndrome [De Biase et al 2012]

Heterozygous carriers. Heterozygous carriers are asymptomatic [Amat di San Filippo et al 2008].

Prognosis. Infantile metabolic and childhood myopathic presentations of CDSP can be fatal if untreated (see Management). The long-term prognosis is favorable as long as affected individuals remain on carnitine supplements. Repeated attacks of hypoglycemia or sudden death from arrhythmia have been described in affected individuals discontinuing carnitine supplementation [Longo et al 2006].

Genotype-Phenotype Correlations

Fibroblast carnitine transport is reduced in all affected individuals. However, it has been demonstrated that carnitine transport is higher in the fibroblasts of asymptomatic individuals than in the fibroblasts of symptomatic individuals. Nonsense and frameshift variants in *SLC22A5* are typically associated with lower carnitine transport and are more prevalent in symptomatic individuals whereas missense variants and in-frame deletions may result in protein with retained residual carnitine transport activity and are more prevalent in asymptomatic individuals [Rose et al 2012].

Prevalence

CDSP has a frequency of 1:20,000-1:70,000 in the United States [Magoulas & El-Hattab 2012], 1:40,000 in Japan [Koizumi et al 1999], and 1:120,000 in Australia [Wilcken et al 2003]. The disease is very common in the Faroe Islands, where the prevalence is 1:300 [Rasmussen et al 2014].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Systemic primary carnitine deficiency (CDSP) needs to be differentiated from secondary carnitine deficiency seen in the following situations [Flanagan et al 2010]:

- Inherited metabolic disorders including organic acidemias and fatty acid oxidation defects (e.g., very long-chain acyl-CoA dehydrogenase [VLCAD] deficiency, medium-chain acyl-CoA dehydrogenase [MCAD] deficiency, short-chain acyl-CoA dehydrogenase [SCAD] deficiency, carnitine-acylcarnitine translocase [CACT] deficiency, long-chain hydroxyacyl-CoA dehydrogenase [LCHAD] deficiency, and carnitine palmitoyltransferase II [CPT II] deficiency)
- Pharmacologic therapy (e.g., valproate, cyclosporine, pivampicillin)
- Malnutrition
- Hemodialysis and renal tubular dysfunction (e.g., renal Fanconi syndrome)
- Prematurity. Premature neonates may have mild reduction in plasma carnitine concentrations due to a lack of carnitine placental transfer in the third trimester and decreased tissue stores. Moreover, immature renal tubular function in premature neonates could lead to increased renal carnitine elimination [Li et al 2010, Clark et al 2014].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with systemic primary carnitine deficiency (CDSP), the following evaluations are recommended:

- Echocardiogram and electrocardiogram
- Serum creatine kinase (CK) concentration
- Liver transaminases
- Pre-prandial blood glucose concentration
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

L-carnitine supplementation. The main treatment for CDSP is oral levocarnitine (L-carnitine) supplementation. Typically, a high dose (100-400 mg/kg/day, divided in 3 doses) is required. Individuals with CDSP respond well if oral L-carnitine supplementation is started before irreversible organ damage occurs. Metabolic decompensation and skeletal and cardiac muscle function improve with L-carnitine supplementations.

Oral L-carnitine supplementation in infants with CDSP identified through newborn screening results in slow normalization of the plasma carnitine concentration. The carnitine dose needs to be adjusted according to the plasma carnitine concentrations, which should be measured frequently.

L-carnitine supplementation has relatively few side effects:

- High doses of oral L-carnitine can cause increased gastrointestinal motility, diarrhea, and intestinal discomfort.
- Oral L-carnitine can be metabolized by intestinal bacteria to produce trimethylamine, which has a fishy odor. Oral metronidazole at a dose of 10 mg/kg/day for 7-10 days and/or decreasing the carnitine dose usually results in the resolution of the odor [Longo et al 2006].

Note: (1) An unaffected infant born to a mother with CDSP can have low carnitine levels detected on newborn screening; in these infants oral L-carnitine supplementation is followed by a rise in plasma carnitine concentration within days or a few weeks [Schimmenti et al 2007, El-Hattab et al 2010]. (2) Asymptomatic adults with CDSP have been reported; however, the limited literature and the lack of follow up make it unclear whether these individuals have potential health risks. Because some fatty acid oxidation defects such as medium-chain acyl CoA dehydrogenase (MCAD) deficiency can remain asymptomatic until they results in sudden death

or another acute presentation during stress, it is prudent to treat asymptomatic individuals with CDSP with L-carnitine supplementation to prevent the possibility of decompensation during intercurrent illness or stress [El-Hattab et al 2010].

Other

- Hypoglycemic episodes are treated with intravenous dextrose infusion.
- Cardiomyopathy requires management by specialists in cardiology.

Prevention of Primary Manifestations

Maintaining appropriate plasma carnitine concentrations through oral L-carnitine supplementation (see Treatment of Manifestations) and preventing hypoglycemia (with frequent feeding and avoiding fasting) typically eliminate the risk of metabolic, hepatic, cardiac, and muscular complications.

Note: Hospitalization to administer intravenous glucose is recommended for individuals with CDSP who are required to fast because of medical or surgical procedures or who cannot tolerate oral intake because of an illness such as gastroenteritis.

Prevention of Secondary Complications

L-carnitine supplementation is well tolerated and has relatively few side effects: increased gastrointestinal motility, diarrhea, and a fishy odor. Oral metronidazole and/or decreasing the carnitine dose usually results in the resolution of the odor.

Surveillance

The following evaluations have been suggested [Magoulas & El-Hattab 2012]:

- Echocardiogram and electrocardiogram. Perform annually during childhood and less frequently in adulthood. Individuals with cardiomyopathy require management and follow up by specialists in cardiology.
- Plasma carnitine concentration. Monitor frequently until levels reach the normal range, thereafter, measure three times a year during infancy and early childhood, twice a year in older children, and annually in adults.
- Serum CK concentration and liver transaminases. Consider measuring during acute illnesses.

Agents/Circumstances to Avoid

Individuals with CDSP should avoid fasting longer than age-appropriate periods.

Evaluation of Relatives at Risk

Sibs of affected individuals should be tested by measuring plasma carnitine concentrations. If the carnitine levels are low, further evaluation for CDSP is recommended by molecular genetic testing if the *SLC22A5* pathogenic variants have been identified in the family or fibroblast carnitine transport assay.

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

Pregnancy Management

Pregnancy is a metabolically challenging state because energy consumption significantly increases. In addition, plasma carnitine levels are physiologically lower during pregnancy than those of non-pregnant controls. Affected women can have decreased stamina or worsening of cardiac arrhythmia during pregnancy, suggesting that

CDSP may manifest or exacerbate during pregnancy [Schimmenti et al 2007, El-Hattab et al 2010]. Therefore, all pregnant women with CDSP, including those who are asymptomatic, require close monitoring of plasma carnitine levels and increased carnitine supplementation as needed to maintain normal plasma carnitine levels.

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

Systemic primary carnitine deficiency (CDSP) 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 *SLC22A5* pathogenic variant). Occasionally an asymptomatic parent is found to have biallelic *SLC22A5* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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 and are not at risk of developing the disorder.

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

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

Carrier Detection

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

Biochemical testing. Heterozygous carriers usually have about 50% carnitine transport activity in fibroblasts and can have borderline low plasma carnitine levels. However, normal plasma carnitine levels have been reported in some heterozygous carriers. Because the diet, which provides about 75% of the daily requirement of carnitine, may play a role in modulating carnitine levels, plasma carnitine levels are not a reliable indicator for heterozygous carrier status; thus, either molecular testing of *SLC22A5* or fibroblast carnitine transport assay is needed to determine carrier status [El-Hattab et al 2010].

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

Once the *SLC22A5* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is a personal decision, discussion of these issues may be helpful.

Resources

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

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

Molecular Genetics

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

Table A. Systemic Primary Carnitine Deficiency: Genes and Databases

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

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

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

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

Molecular Pathogenesis

Carnitine is required for the transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix for beta-oxidation. During periods of fasting, fatty acids are the predominant substrate for energy production via oxidation in the liver, cardiac muscle, and skeletal muscle. Carnitine is transported inside the cells by an organic cation transporter (OCTN2) present in the heart, muscle, and kidney. OCTN2 is the protein product of *SLC22A5*. CDSP is a disorder of the carnitine cycle caused by the lack of functional OCTN2 resulting in urinary carnitine wasting, low plasma carnitine levels, and decreased intracellular carnitine accumulation.

Carnitine deficiency results in defective fatty acid oxidation. When fat cannot be utilized glucose is consumed without regeneration via gluconeogenesis, resulting in hypoglycemia. In addition, fats released from adipose tissue accumulate in the liver, skeletal muscle, and heart, resulting in hepatic steatosis and myopathy [Longo et al 2006, El-Hattab & Scaglia 2015].

Gene structure. *SLC22A5* comprises ten exons spanning approximately 3.2 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. To date more than 180 pathogenic variants have been reported in the *SLC22A5* database at ARUP Laboratories (see Table A).

About half of these pathogenic variants are missense variants. Nonsense variants, splice site variants, insertions, and small deletions comprise the remaining half of reported pathogenic variants.

Six large deletions involving *SLC22A5* have been described at the Human Gene Mutation Database (HGMD) (www.hgmd.cf.ac.uk).

Normal gene product. *SLC22A5* encodes the high-affinity sodium-dependent carnitine transporter, organic cation transporter 2 (OCTN2). OCTN2 is a transmembrane protein that comprises 557 amino acids; it includes 12 transmembrane domains and one ATP binding domain.

Abnormal gene product. *SLC22A5* pathogenic variants result in dysfunctional OCTN2 and decreased carnitine transport in various tissues.

Chapter Notes

Revision History

- 3 November 2016 (sw) Comprehensive update posted live
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