GENEReviews

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Cerebrotendinous Xanthomatosis

[*Cerebral Cholesterinosis, CTX*]

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Summary

Disease characteristics. Cerebrotendinous xanthomatosis (CTX) is a lipid storage disease characterized by infantile-onset diarrhea, childhood-onset cataract, adolescent- to young adult-onset tendon xanthomas, and adult-onset progressive neurologic dysfunction (dementia, psychiatric disturbances, pyramidal and/or cerebellar signs, and seizures). Chronic diarrhea from infancy may be the earliest clinical manifestation. In approximately 75% of affected individuals, cataracts are the first finding, often appearing in the first decade of life. Xanthomas appear in the second or third decade; they occur on the Achilles tendon, the extensor tendons of the elbow and hand, the patellar tendon, and the neck tendons. Xanthomas have been reported in the lung, bones, and central nervous system. Some individuals show mental impairment from early infancy, whereas the majority have normal or only slightly subnormal intellectual function until puberty; dementia with slow deterioration in intellectual abilities occurs in the 20s in over 50% of individuals. Neuropsychiatric symptoms such as behavioral changes, hallucinations, agitation, aggression, depression, and suicide attempts may be prominent. Pyramidal signs (i.e., spasticity) and/or cerebellar signs are almost invariably present between age 20 and 30 years. Other findings include extrapyramidal manifestations (dystonia and atypical parkinsonism), seizures, and peripheral neuropathy.

Diagnosis/testing. CTX is diagnosed by clinical features and biochemical testing. The biochemical abnormalities that distinguish CTX from other conditions with xanthomas include: high plasma and tissue cholestanol concentration, normal-to-low plasma cholesterol concentration; decreased chenodeoxycholic acid; increased concentration of bile alcohols and their glyconjugates; and increased concentrations of cholestanol and apolipoprotein B in cerebrospinal fluid. *CYP27A1* is the only gene known to be associated with cerebrotendinous xanthomatosis. Molecular genetic testing of the *CYP27A1* gene is clinically available.

Management. Long-term treatment of individuals with CTX with chenodeoxycholic acid (CDCA) normalizes bile acid synthesis, normalizes plasma and CSF concentration of cholestanol, and improves neurophysiologic findings; however, CDCA is only available in Italy. Inhibitors of HMG-CoA reductase alone or in combination with CDCA are also effective

in decreasing cholestanol concentration and improving clinical signs; however, they may induce muscle damage. Cataract extraction is typically required in at least one eye by age 50 years.

Genetic counseling. CTX 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 is available if the mutations have been identified in the proband. Prenatal testing is available if both mutations have been identified.

Diagnosis

Clinical Diagnosis

Cerebrotendinous xanthomatosis (CTX), a lipid storage disease, is suspected in individuals with the following:

- Infantile-onset diarrhea
- Childhood-onset cataract
- Adolescent- to young adult-onset tendon xanthomas
- Adult-onset progressive neurologic dysfunction (dementia, psychiatric disturbances, pyramidal and/or cerebellar signs, and seizures)

MRI. MRI shows bilateral hyperintensity of the dentate nuclei and cerebral and cerebellar white matter.

Testing

For laboratories offering biochemical testing see Testing.

CTX is caused by deficiency of the mitochondrial enzyme sterol 27-hydroxylase with resulting cholestanol and cholesterol accumulation in virtually every tissue.

Biochemical testing. The main laboratory abnormalities that distinguish CTX from other conditions with xanthomas include the following:

- **High** plasma and tissue **cholestanol** concentration
- **Normal to low** plasma **cholesterol** concentration
- Markedly **decreased** formation of **chenodeoxycholic acid** resulting from impaired primary bile acid synthesis
- **Increased concentration of bile alcohols** and their glyconjugates in bile, urine, and plasma
- Increased concentration of cholestanol and apolipoprotein B in cerebrospinal fluid (CSF) resulting from **changes in the blood-brain barrier**

See Table1.

Table 1. Biochemical Abnormalities in Cerebrotendinous Xanthomatosis

Analyte	Source	Concentration		Availability
		In CTX	Normal	
Cholestanol	Plasma	Up to 5-10 times normal	330±30 µg/dL	Clinical Testing
Bile alcohols	Urine	14,000±3500 nmol/L	Not detectable	
	Plasma	Up to 500-1000 times normal values	8.48±3.67	

Other laboratory abnormalities that are observed but not diagnostic include:

- Increased plasma lactate concentration
- Increased brain lactate concentration (by MR spectroscopy)

Enzyme assay. Sterol 27-hydroxylase enzymatic activity in fibroblasts, liver, and leukocytes is markedly reduced in affected individuals.

Note: Measurement of enzyme activity is no longer necessary for diagnosis.

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. *CYP27A1* is the only gene known to be associated with CTX.

Other loci. No locus heterogeneity has been identified [Lee et al 2001].

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal testing

Clinical testing

- **Sequence analysis** of *CYP27A1* detects mutations in 90%-100% of affected individuals.

Research testing. Approximately 6% of mutations are deletions (see Table 3) that require special methods of detection available on a research basis only.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Cerebrotendinous Xanthomatosis

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	*CYP27A1* sequence variants	90%-100% [1]	Clinical Testing
Duplication/deletion testing	*CYP27A1* deletions	~6%	Research only

1. Per laboratories listed in the GeneTests Laboratory Directory January 2006

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

Testing Strategy

1. Sequence analysis
2. Measurement of plasma cholestanol concentration for clinical and metabolic correlation or if sequence analysis is not available

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *CYP27A1*.

Clinical Description

Natural History

Cerebrotendinous xanthomatosis (CTX) is suspected in individuals with infantile-onset diarrhea, childhood-onset cataract, adolescent- to young adult-onset tendon xanthomas, and adult-onset progressive neurologic dysfunction (dementia, psychiatric disturbances, pyramidal and/or cerebellar signs, and seizures). Intrafamilial variability is considerable [Dotti et al 1996; Nagai et al 1996; Verrips, Hoefsloot et al 2000; Federico & Dotti 2003; Moghadasian 2004].

A distinction can be made between systemic signs and neurologic signs, described in detail below:

Systemic signs

- **Enterohepatic system.** Chronic diarrhea from infancy may be the earliest clinical manifestation of CTX [Cruysberg et al 1991, Cruysberg 2002]. Gallstones have been reported on occasion.
- **Eye.** In approximately 75% of affected individuals, cataracts are the first finding, often appearing in the first decade of life. In 25% of individuals, cataracts are first observed after the age of 40 years. Cataracts may be visually significant opacities requiring lensectomy or visually insignificant cortical opacities. The appearance can include irregular cortical opacities, anterior polar cataracts, and dense posterior subcapsular cataracts [Cruysberg et al 1995].

  Other findings include palpebral xanthelasmas [Van Bogaert et al 1937, Philippart & Van Bogaert 1969], optic nerve atrophy [Schimschock et al 1968], and proptosis [Morgan et al 1989]. In 13 individuals reported by Dotti et al (2001) ranging in age from 32 fto 54 years, all had cataracts, approximately 50% had optic disk paleness, 30% had signs of premature retinal senescence with retinal vessel sclerosis, 15% had cholesterol-like deposits along vascular arcades, and 15% had myelinated nerve fibers.
- **Xanthomas.** These appear in the second or third decade. In addition to the classic xanthomatas of the Achilles tendon, xanthomas also occur on the extensor tendons of the elbow and hand, the patellar tendon, and the neck tendons. Xanthomas have been reported in the lung, bones, and central nervous system (CNS).
- **Cardiovascular system.** Premature atherosclerosis and coronary artery disease have been reported [Schimschock et al 1968, Fujiama et al 1991, Kerleau et al 1993,

Valdivielso et al 2004, Frih-Ayed et al 2005]; however, occurrence of atherosclerosis in CTX homozygotes has been attributed to factors other than mutation of *CP27A1* [Leitersdorf et al 1994].

Dotti et al (1998) described lipomatous hypertrophy of the atrial septum.

- **Skeleton.** Bone involvement is characterized by granulomatous lesions in the lumbar vertebrae and femur, osteopenia and increased risk of bone fractures, and impaired adsorption of radiocalcium, which improves with chenodeoxycholic acid treatment [Berginer et al 1993, Federico et al 1993]. Osteopenia is evident by total body densitometry in untreated individuals. Individuals may have marked thoracic kyphosis.
- **Endocrine abnormalities.** Hypothyroidism has occasionally been reported [Philippart & Van Bogaert 1969, Bouwes Bavinck et al 1986, Idouji et al 1991].
- **Premature aging.** Early-onset cataract, osteopenia with bone fractures and loss of teeth, atherosclerosis, and neurologic impairment with dementia and/or parkinsonism, associated with the characteristic facies, suggest a generalized premature aging process [Dotti et al 1991].
- **Histologic changes.** Histologic liver findings include electron-dense amorphous material surrounded by smooth endoplasmic reticulum [Salen et al 1978] and abnormalities in mitochondria with paracrystalline inclusions and increased number of peroxisomes [Federico 1989]. Xanthomas are characterized by birefringent crystalline material surrounded by numerous multinucleate giant cells with foamy cytoplasm.

Neurologic signs

- **Mental retardation or dementia** following slow deterioration in intellectual abilities occurs in the 20s in over 50% of individuals [Verrips, van Engelen, ter Laak et al 2000]. Some individuals show mental impairment from early infancy, whereas the majority have normal or only slightly subnormal intellectual function until puberty. In the spinal form, intellect is almost always normal.
- **Neuropsychiatric symptoms** such as behavioral changes, hallucinations, agitation, aggression, depression, and suicide attempts may be prominent.
- **Pyramidal signs (i.e., spasticity) and/or cerebellar signs** are almost invariably present between age 20 and 30 years. A spinal form, in which spastic paraparesis is the main clinical symptom, was described by Van Bogaert (1962) and more recently by Verrips, Nijeholt et al (1999).
- **Extrapyramidal manifestations** including dystonia and atypical parkinsonism have been reported on occasion [Fiorelli et al 1990, Rogelet et al 1992, Dotti et al 2000, Grandas et al 2002]. Although palatal myoclonus was observed in the first individual reported [Van Bogaert et al 1937], it was not observed in a large series of affected individuals [Dotti et al 2001].
- **Seizures** are reported in approximately 50% of individuals with CTX [Matsumuro et al 1990, Arlazoroff et al 1991, Dotti et al 1996].
- **Peripheral neuropathy** is evident on electrophysiologic studies [Ohnishi et al 1979, Argov et al 1986, Federico et al 1987, Ben Hamida et al 1991], which reveal decreased nerve conduction velocities (NCV) and abnormalities in somatosensory, motor, brainstem, and visual evoked potentials [Mondrelli et al 1992]. Clinical manifestations related to peripheral nerve involvement are distal muscle atrophy and pes cavus. Sensory abnormalities are rarely described.

- **Heterozygotes.** A symptomatic heterozygote carrier with biochemically proven CTX has been reported [Sugama et al 2001].
- **Neuropathology.** Classic CNS pathology findings in CTX include granulomatous and xanthomatous lesions in the cerebellar hemispheres, globus pallidus, and cerebellar peduncles. Demyelination and gliosis and involvement of the long tract of the spinal cord have been described [Van Bogaert et al 1937, Van Bogaert 1962]. Nerve biopsy reveals primary axonal degeneration, demyelination, and remyelination. Federico et al (1991) found mild myopathic changes of increased variability of fiber size with randomly distributed atrophic fibers. Ultrastructural abnormalities included mitochondrial subsarcolemmal aggregates and morphologic changes of these organelles [Federico et al 1991]. Reduced respiratory chain enzyme activity has been observed [Dotti et al 1995].
- **Neuroimaging.** Changes on CT and MRI include diffuse brain and cerebellar atrophy, white matter signal alterations, and bilateral focal cerebellar lesions [Berginer et al 1981, Waterreus et al 1987, Berginer et al 1994, Dotti et al 1994, De Stefano et al 2001]. MR spectroscopy shows decreased n-acetylaspartate and increased lactate indicative of widespread brain mitochondrial dysfunction [De Stefano et al 2001]. The quantitative assessment of brain damage in CTX with use of magnetization transfer MRI has recently been described [Inglese et al 2003].

Genotype-Phenotype Correlations

Several authors have attempted to correlate genotype to phenotype, but no correlation has been identified [Dotti et al 1996; Verrips, van Engelen, Wevers et al 2000]. The interaction of many genes and other factors may influence the clinical presentation.

Prevalence

The prevalence of CTX caused by the Arg362Cys mutation alone has recently been estimated at approximately one per 50,000 among Caucasians [Lorincz et al 2005]. Epidemiologic studies are lacking.

Series of affected individuals have been reported in Israel and the USA [Berginer et al 1984], Italy [De Stefano et al 2001, Dotti et al 2001], Japan [Kuriyama et al 1991], and the Netherlands [Waterreus et al 1987; Verrips, Hoefsloot et al 2000]. Affected individuals have been reported in Belgium [Van Bogaert et al 1937, Philippart & Van Bogaert 1969], Brazil [Canelas et al 1983], Canada [Pastershank et al 1974], France [Rogelet et al 1992], Iran [Farpour & Mahloudji 1975], Norway [Schreiner et al 1975], Tunisia [Ben Hamida et al 1991], Spain [Campdelacreu et al 2002], China [Ko & Lee 2001], and Sweden [Rystedet et al 2002].

Differential Diagnosis

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

Xanthomas. Differential diagnosis includes:

- Sitosterolemia, inherited sterol storage disease characterized by tendon xanthomas and by a strong predisposition to premature atherosclerosis. Serum concentration of plant sterols (sitosterol and campesterol) is increased. Primary neurologic signs and cataracts are not present. Spastic paraparesis may occur as a result of spinal cord compression by multiple intradural, extramedullary xanthomas [Hatanaka et al 1990].

- Hypercholesterolemia and hyperlipemia (especially type IIa), in which plasma cholestanol level is normal

When xanthomas are not evident, the differential diagnosis includes all forms of progressive mental deterioration [Gilad et al 1999; Verrips, van Engelen, ter Laak et al 2000].

Early-onset cataract. Cruysberg (2002) reports that CTX comprises the second-largest group of individuals with early-onset cataract and known neurologic disease. (Myotonic dystrophy type 1 is the largest group.) Unexplained juvenile-onset cataracts associated with infantile-onset chronic diarrhea and mental retardation or deterioration strongly suggest the possibility of CTX [Cruysberg et al 1991; Cruysberg et al 1995; Verrips, van Engelen, ter Laak et al 2000].

Management

Treatment of Manifestations

Clinical improvement of individuals with CTX following chenodeoxycholic acid treatment (CDCA, a drug extensively used in the treatment of bile acid metabolism with cholesterol gallstones) was first reported by Berginer et al (1984). Long-term CDCA treatment (750 mg/day in adults) normalizes bile acid synthesis (leading to disappearance of abnormal metabolites from serum, bile, and urine), normalizes plasma and CSF concentration of cholestanol by suppressing cholestanol biosynthesis, and improves neurophysiologic findings [Mondelli et al 1992, Mondelli et al 2001] and other clinical manifestations including osteoporosis [Federico et al 1993].

In a study of 11 years of treatment with CDCA, Mondelli et al (2001) reported that four months into treatment, nerve conduction velocities normalized and subsequently remained stable; motor evoked potentials (MEPs) and sensory evoked potentials (SEPs) improved slowly but continuously; and clinical manifestations stabilized, but neurologic deficits did not improve. The contrast between two untreated siblings whose symptoms progressed and a third treated sibling whose symptoms stabilized suggests that treatment is beneficial.

Although CDCA is considered the best treatment for CTX [Samenuk & Koffman 2001], it has recently ceased to be available as other more effective drugs for gallstones have appeared; its unavailability has left affected individuals without an essential drug for their disease, with the exception of affected individuals in Italy, who are closely monitored [Federico & Dotti 2001].

Inhibitors of HMG-CoA reductase alone or in combination with CDCA are also effective in decreasing cholestanol concentration and improving clinical signs [Peynet et al 1991; Verrips, Wevers et al 1999]. However, because of clinical evidence that HMG-CoA reductase inhibitors may induce muscle damage and even rhabdomyolysis, caution is required in the use of these drugs [Federico & Dotti 1994].

Other possible treatments include low-density lipoprotein (LDL) apheresis, but the results are controversial [Mimura et al 1993, Berginer & Salen 1994].

Liver transplantation, although never performed in individuals with CTX, remains a possibility.

Eyes. Cataract extraction is typically required in at least one eye by age 50 years.

Symptomatic treatments for epilepsy, spasticity, and parkinsonism have been utilized. Parkinsonism is poorly responsive to levodopa, whereas an antihistamine drug,

diphenylpyraline hydrochloride, had an excellent effect in three individuals [Ohno et al 2001].

Annual follow-up is recommended for the following:

- Neurologic and neuropsychologic evaluation
- Cholestanol plasma concentration
- Brain MRI
- Echocardiography
- Total body density (TBD)

Testing of Relatives at Risk

Early diagnosis of at-risk family members using biochemical testing, or molecular genetic testing if the two disease-causing mutations in the proband are known, allows initiation of treatment that may prevent or limit disease manifestations.

Therapies Under Investigation

Therapies with CDCA, simvastatin, and LDL apheresis have recently been reported [Dotti et al 2004].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Therapies with ursodeoxicolic acid, lovastatin, and cholestyramine have been reported to be ineffective [Tint et al 1989, Batta et al 2004].

Caution has been suggested with statines [Federico & Dotti 2001].

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

Cerebrotendinous xanthomatosis is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes, and, therefore, carry one mutant allele.
- Heterozygotes (carriers) are generally asymptomatic, although an increased incidence of cardiovascular disorders and gall stones has been observed in obligate carriers [personal observation].

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

Offspring of a proband. The offspring of an individual with CTX are obligate heterozygotes (carriers) for a disease-causing mutation in the *CYP27A1* gene.

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

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the family.

Related Genetic Counseling Issues

Disease manifestations in heterozygotes. An increased frequency of cardiovascular disorders and gallstones has been observed in families of affected individuals [personal observation].

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 

for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

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

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

Molecular Genetics

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

Table A. Molecular Genetics of Cerebrotendinous Xanthomatosis

Gene Symbol	Chromosomal Locus	Protein Name
CYP27A1	2q33-qter	Cytochrome P450 27

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 Cerebrotendinous Xanthomatosis

213700	CEREBROTENDINOUS XANTHOMATOSIS
606530	CYTOCHROME P450, SUBFAMILY XXVIIA, POLYPEPTIDE 1; CYP27A1

Table C. Genomic Databases for Cerebrotendinous Xanthomatosis

Gene Symbol	Entrez Gene	HGMD
CYP27A1	1593 (MIM No. 606530)	CYP27A1

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

Note: HGMD requires registration.

Normal allelic variants: Leitersdorf et al (1993) elucidated the genomic structure, containing nine exons and eight introns (18.6 kb of DNA).

Pathologic allelic variants: Cali et al (1991) described the first mutations in the *CYP27A1* gene. A review of reported mutations and molecular genetic testing in 32 families, of which 21 were Dutch, was reported by Verrips, Hoefsloot et al (2000). Many of the reported mutations involve splice sites and are predicted to affect mRNA stability or lead to the formation of abnormal mRNA with translation products that are devoid of an adrenodoxin-binding region (residues 351-356) and/or the heme-binding site (residue 453-464), important for enzyme activity. Apart from 19% nonsense mutations, leading to the formation of truncated peptides devoid of function, approximately 45% of mutations are missense mutations that are predicted to lead to the expression of an abnormal cytochrome P450 27 protein.

Table 3. Pathologic Allelic Variants

Pathologic Allelic Variants	Effect of Mutation	Abnormal Gene Product	Frequency of Allelic Variants in Affected Family
26-27insC (exon 1)	Frameshift	Truncated protein	7
11-21delTGGGCTGCGC (exon 1)			1
c.376delC (exon 2)			4
c.400C>T (exon 2)	Arg94Trp	Amino acid substitution	8
c.401G>A (exon 2)	Arg94Gln		5

c.G>A (exon 2)	Trp100X	Truncated protein	1
c.430C>T (exon 2)	Arg104Trp	Amino acid substitution	2
c.455G>A (exon 2)	Gly112Glu		1
c.456G>T (exon 2)	Gly112Gly	Alternative splicing	3
IVS2+1G>A (intron 2)	Abnormal pre-mRNA splicing		1
c.496C>T (exon 3)	Gln126X	Truncated protein	1
546-547delG (exon 3)	Frameshift		4
c.604G>T (exon 3)	Glu162X		6
c.667G>C (exon 3)	Ala183Pro	Amino acid substitution	12
c.712C>T (exon 4)	Arg198X	Truncated protein	1
c.766C>T (exon 4)	Gln216X		1
c.797A>G (exon 4)	Lys226Arg	Amino acid substitution	5
c.800G>A (exon 4)	Trp227X	Truncated protein	1
c.829C>T (exon 4)	Arg237X		6
c.840delT (exon 4)	Frameshift		6
IVS4+1G>A (intron 4)	Del exon 4		6
IVS4-1G>A (intron 4)	Abnormal pre-mRNA splicing		7
c.871A>T (exon 5)	Lys251X	Truncated protein	4
965-969delTGGCC (exon 5)	Frameshift		1
c.1037C>T (exon 5)	Thr306Met	Amino acid substitution	18
c.1082A>G (exon 6)	Asp321Gly		1
c.1172C>T (exon 6)	Pro351Leu		5
1201-1202delCT (exon 6)	Frameshift	Truncated protein	1
c.1204C>A (exon 6)	Arg362Ser	Amino acid substitution	2
c.1204C>T (exon 6)	Arg362Cys		26

c.1205G>A (exon 6)	Arg362His		4
IVS6+1G>A (intron 6)	Abnormal pre-mRNA splicing		15
IVS6-1G>T (intron 6)			1
c.1223C>G (exon 7)	Pro368Arg	Amino acid substitution	1
c.1230C>G (exon 7)	Asn370Lys		1
c.1234C>T (exon 7)	Arg372Trp		2
c.1235G>A (exon 7)	Arg372Gln		7
c.1243G>T (exon 7)	Glu375X	Truncated protein	2
IVS7+1G>A (intron 7)	Abnormal pre-mRNA splicing		16
IVS7+5G>T (intron 7)			3
IVS7-1G>A (intron 7)			2
c.1344C>T (exon 8)	Pro408Ser	Amino acid substitution	1
c.1423C>T (exon 8)	Gln428X	Truncated protein	1
c.1436G>C (exon 8)	Gly439Ala	Amino acid substitution	1
c.1441C>T (exon 8)	Arg441Trp		7
c.1442G>A (exon 8)	Arg441Gln		12
c.1456C>T (exon 8)	Arg446Cys		4
c.1456C>G (exon 8)	Arg479Gly		1
Exon 7 - exon 9 del	Abnormal mRNA	Truncated protein	7

[Cali & Russell 1991; Leitersdorf et al 1993; Kim et al 1994; Leitersdorf et al 1994; Meiner et al 1994; Reshef et al 1994; Segev et al 1995; Chen et al 1996; Garuti, Lelli, Barozzini, Dotti et al 1996; Garuti, Lelli, Barozzini, Tiozzo et al 1996; Okuyama et al 1996; Verrips et al 1996; Watts et al 1996; Ahmed et al 1997; Chen, Kubota, Ujike et al 1998; Garuti et al 1997; Verrips et al 1997; Chen et al 1997; Chen, Kubota, Teramoto et al 1998; Verrips, Nijeholt et al 1999; Wakamatsu et al 1999; Nakashima et al 1994; Verrips, Hoefsloot et al 2000; Lee et al 2001; Lamon-Fava et al 2002; Castelnovo et al 2003; Mak et al 2004; Guyant-Marechal et al 2005; Von Bahr et al 2005]

Normal gene product: The mature enzyme consists of 498 amino acids and contains putative binding sites for adrenodoxin and haem encoded by the region between exons 6 and 8.

Abnormal gene product: Inactive truncated sterol 27-hydroxylase protein leads to several metabolic derangements including increased cholestanol production and bile alcohols

[Bjorkhem & Boberg 1995]. Many mutations are predicted to produce an inactive protein without adrenodoxin and/or heme binding domains; many others produce a protein with no functional domains. The other mutations are pathogenic, probably because they change the stability of the protein structure.

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.

United Leukodystrophy Foundation (ULF)
2304 Highland Drive
Sycamore IL 60178
Phone: 800-728-5483; 815-895-3211
Fax: 815-895-2432
Email: office@ulf.org
www.ulf.org

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: 0800 652 3181 (toll free)
Email: info.svcs@climb.org.uk
www.climb.org.uk

References

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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Chapter Notes

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