GENEReviews

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Rhizomelic Chondrodysplasia Punctata Type 1

[*RCDP 1*]

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Summary

Disease characteristics. Rhizomelic chondrodysplasia punctata type 1 (RCDP1) classic type, a peroxisome biogenesis disorder (PBD), is characterized by proximal shortening of the humerus and to a lesser degree the femur (rhizomelia), punctate calcifications in cartilage with epiphyseal and metaphyseal abnormalities (chondrodysplasia punctata, or CDP), coronal clefts of the vertebral bodies, and cataracts that are usually present at birth or appear in the first few months of life. Birth weight, length, and head circumference are often at the lower range of normal; postnatal growth deficiency is profound. Mental deficiency is severe, and the majority of chidren develop seizures. Most affected children do not survive the first decade of life; a proportion die in the neonatal period. A milder phenotype in which all affected individuals have congenital cataracts and chondrodysplasia is now recognized; some do not have rhizomelia, and some have less severe mental and growth deficiency.

Diagnosis/testing. The diagnosis of RCDP1 is based on clinical findings and confirmed by clinically available biochemical or molecular genetic testing. Biochemical tests of peroxisome function include: red blood cell concentration of plasmalogens, plasma concentration of phytanic acid, and plasma concentration of very long chain fatty acids (VLCFA), which has consistently predicted the *PEX7* receptor defect in RCDP1. *PEX7*, which encodes the receptor for a subset of peroxisomal matrix enzymes, is the only gene known to be associated with RCDP1.

Management. Management of RCDP1 is supportive and limited by the multiple handicaps present at birth and poor outcome. Cataract extraction may restore some vision. Physical therapy is recommended to improve contractures; orthopedic procedures may improve function in some individuals. Surveillance includes monitoring of growth and development and regular assessments for seizure control, vision, hearing, contractures, and orthopedic complications.

Genetic counseling. Rhizomelic chondrodysplasia punctata type 1 is inherited in an autosomal recessive manner. At conception, each sib of a proband has a 25% chance of inheriting both mutant alleles and being affected, a 50% chance of inheriting one mutant allele and being an unaffected carrier, and a 25% chance of inheriting both normal alleles. Once the mutations have been identified in an affected family member, molecular genetic testing for carrier testing of at-risk relatives and prenatal testing for pregnancies at increased risk is available on a clinical basis. Prenatal diagnosis by assay of plasmalogen biosynthesis is also clinically available for pregnancies at 25% risk for RCDP1.

Diagnosis

Clinical Diagnosis

Classic RCDP1 is recognized **in the neonatal period** by the presence of:

- Cataracts;
- Skeletal features. Classic findings include the following:
  - Rhizomelia (proximal shortening of the long bones)
  - Chondrodysplasia punctata (CDP): punctate calcifications observed in radiographs in the epiphyseal cartilage at the knee, hip, elbow, and shoulder that can be more extensive, involving the hyoid bone, larynx, costochondral junctions, and vertebrae. Metaphyseal abnormalities may be present.
  - Radiolucent coronal clefts of the vertebral bodies on lateral spine radiographs that represent unossified cartilage

Classic RCDP1 is recognized **in childhood** by the presence of:

- Congenital cataracts;
- Severe mental deficiency;
- Profound growth retardation;
- Resolution of the punctate calcifications leaving abnormal epiphyses and flared and irregular metaphyses after age one to three years;
- Possible calcification of the intervertebral discs.

Milder RCDP1 phenotype is recognized by:

- Congenital cataracts;
- Chondrodysplasia;
- Variable rhizomelia;
- Milder mental and growth deficiency.

Testing

Biochemical tests. Three biochemical tests of peroxisome function are routinely used to confirm the diagnosis of RCDP1:

- Red blood cell concentration of plasmalogens (Table 1)
- Plasma concentration of phytanic acid (Table 2)
- Plasma concentration of very long chain fatty acids (VLCFA).

The finding of a deficiency of plasmalogens in red blood cells, increased plasma concentration of phytanic acid, and normal plasma concentration of very long chain fatty acids has consistently predicted the *PEX7* receptor defect in RCDP1.

These assays are extremely specialized and are reliably performed in only a few laboratories worldwide. For laboratories offering biochemical testing, see Testing.

Table 1. Values for Red Blood Cell Plasmalogens (Dimethylacetals) in RCDP1

C16 Saturated Dimethylacetals (DMA) to C16 Saturated Fatty Acid		
	Mean	**Range**
Normal	0.077 ± 0.009	0.051-0.090
Abnormal (RCDP1)		0.001-0.025 [1]
C18 Saturated DMA to C18 Saturated Fatty Acid		
	Mean	**Range**
Normal	0.167 ± 0.015	0.137-0.255
Abnormal (RCDP1)		0.001-0.050

Values are expressed as a ratio of C16 or C18 dimethylacetyls to fatty acid molecules.

1. Values are for the classic RCDP1 phenotype; individuals with a mild RCDP1 phenotype may fall outside this range.

Table 2. Plasma Concentration of Phytanic Acid in RCDP1

	Mean	Range
Normal	0.80 µg/mL ± 0.40	0-2.5 µg/mL [1]
Abnormal (RCDP1)		As high as 300 µg/mL

1. Plasma concentration of phytanic acid varies with dietary intake of animal fat. It can be normal in infants with RCDP1 because breast milk is low in phytanic acid and most formulas use vegetable fat.

Assays in cultured skin fibroblasts

- Defective plasmalogen biosynthesis, defective phytanic acid (PA) oxidation, and normal VLCFA oxidation are confirmed in cultured fibroblasts.
- The absence of processed thiolase is determined in some laboratories.
- The fibroblast assays allow more complete characterization of peroxisomal functions and are critical in establishing the diagnosis in individuals with milder forms of RCDP1, whose plasmalogen levels may not be markedly abnormal.

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *PEX7*, which encodes the receptor for a subset of peroxisomal matrix enzymes, is the only gene known to be associated with RCDP1.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical method

- **Sequence analysis.** Sequence analysis of all ten exons of the *PEX7* gene and flanking intronic regions from genomic DNA in 133 individuals with RCDP1 from the United

States and the Netherlands identified 97% of mutant alleles [Braverman et al 2002, Motley et al 2002]. Both alleles were identified in 94% of affected individuals and a single allele in 6%. Note: In all individuals with biochemically confirmed RCDP1, at least one mutant *PEX7* allele was identified.

- L292X was the most common, accounting for 51% of alleles.
- IVS9+1G>A, G217R, and A218V together accounted for 17% of alleles.

Table 3 summarizes molecular genetic testing for this disorder.

Table 3. Molecular Genetic Testing Used in Rhizomelic Chondrodysplasia Punctata Type 1 (RCDP1)

Test Method	Mutations Detected	Mutation Detection Rate [1]		Test Availability
		Two mutations	One mutation	
Sequence analysis	*PEX7* sequence variants	94%	6%	Clinical Testing

1. Braverman et al 2002, Motley et al 2002

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

Testing Strategy for a Proband

1. When the diagnosis of RCDP is considered, blood should be sent first for measurement of plasmalogen, phytanic acid and very long chain fatty acid concentrations.
2. When abnormalities are identified in #1, the diagnosis is confirmed by enzymatic assays in cultured fibroblasts.
3. Molecular genetic testing is used to identify the two disease-causing alleles in the proband, establishing genotype-phenotype correlations and enabling prenatal diagnosis and carrier testing of at-risk relatives.

Genetically Related (Allelic) Disorders

Defects in *PEX7* can result in at least two phenotypes distinct from RCDP1:

- Isolated congenital cataracts
- A disorder similar to adult Refsum disease

In both disorders, plasmalogen biosynthesis is nearly normal, although phytanic acid oxidation is severely reduced [Moser et al 1995, Braverman et al 2002, van den Brink et al 2003].

Clinical Description

Natural History

Classic RCDP1—The characteristic clinical features observed in RCDP1 are skeletal abnormalities, cataracts, growth retardation, and mental deficiency. The majority of individuals do not survive beyond the first decade of life and a proportion of individuals die in the neonatal period. In a review of 69 individuals with RCDP diagnosed by the Peroxisomal Diseases Laboratory at the Kennedy Krieger Institute, 60% of individuals survived the first year and 39% the second; a few survived beyond age ten years [Moser et al 1996]. In a review of 35 individuals with RCDP1 who were older than one month of age, White et al (2003) reported 90% survival at one year of age, 50% survival to age six years, and approximately 20% survival at age 12 years. Most deaths were secondary to respiratory complications.

Skeletal findings. Infants with RCDP1 have bilateral shortening of the humerus and to a lesser degree the femur. They typically have contractures and stiff, painful joints, causing irritability in infancy. Cartilaginous structures of the face are affected, resulting in frontal bossing and a short, saddle nose.

Cataracts. Bilateral cortical cataracts develop in virtually all affected individuals. They are usually present at birth or appear in the first few months of life and are progressive.

Growth retardation. Although birth weight, length, and head circumference are often at the lower range of normal, postnatal growth deficiency is profound.

Mental deficiency. Developmental quotients are below 30. Early developmental skills such as smiling and recognizing voices are achieved by most children with RCDP, but at delayed ages. Skills usually achieved in normal children beyond six months of age are never seen [White et al 2003].

The majority of children develop seizures.

Routine brain imaging is normal or has shown cerebral and cerebellar atrophy with enlargement of the ventricles and CSF spaces [Gilbert et al 1976, Wardinsky et al 1990, Powers et al 1999]. MR imaging and MR spectroscopy have shown delayed myelinization, signal abnormalities in supratentorial white matter, decreased choline-to-creatine ratios, and increased levels of mobile lipids, thought to reflect the deficiency of plasmalogens, which are substantial components of myelin [Alkan et al 2003, Bams-Mengerink et al 2006].

Other. Most children with RCDP1 have recurrent respiratory tract infections caused by neurologic compromise, aspiration, immobility, and a small chest with restricted expansion.

Radiologic and MRI evidence of multilevel cervical stenosis with or without compression of the spinal cord has been observed. Spinal cord compression may complicate the neurologic picture, which often includes spastic quadriplegia [Khanna et al 2001].

Ichthyotic skin changes are noted in fewer than one-third of individuals.

About 5-10% of individuals have a cleft of the soft palate.

Other malformations observed in individuals with RCDP1 include congenital heart disease and ureteropelvic junction (UPJ) obstruction.

Mild RCDP1—Only a few individuals with milder forms of RCDP1 have been described. All have had chondrodysplasia and cataracts but variable expression of punctate calcifications, rhizomelia, growth retardation, and mental deficiency [Poll-The et al 1991, Gray et al 1992, Smeitink et al 1992, Nuoffer et al 1994, Barth et al 1996, Braverman et al 2002, Bams-Mengerink et al 2006]. One child, presenting with developmental delay and poor growth, subsequently developed retinitis pigmentosa and peripheral neuropathy, features overlapping those of adult Refsum disease [Braverman et al 2002]. Thus, it is likely that a continuum of phenotypes will emerge within the RCDP group. Molecular analysis of *PEX7* may identify individuals with unusual phenotypes.

Genotype-Phenotype Correlations

The degree of plasmalogen deficiency correlates directly with phenotypic severity:

- Individuals in the milder RCDP group exhibit intermediate defects in fibroblast plasmalogen synthesis and RBC plasmalogen concentrations that are approximately

30% of the mean in controls and more than two standard deviations above the mean in children with classic RCDP.

- Individuals with more variant phenotypes have near-normal plasmalogen biochemistry.
- Defects in phytanic acid oxidation are severe in all *PEX7* defects.

Some correlations between the predicted severity of *PEX7* mutations and phenotype have emerged:

- All individuals homozygous for the L292X mutation studied thus far have had classic RCDP1.
- In individuals who are compound heterozygotes for L292X and another mutation, the effect of the other allele is important in determining the phenotype. Several *PEX7* alleles that are associated with either a milder RCDP phenotype, adult Refsum disease, or isolated congenital cataracts have been identified. It is predicted that these encode either residual amounts of a normal Pex7 protein or a defective protein with residual function [Braverman et al 2002, Motley et al 2002, van den Brink et al 2003].

Nomenclature

RCDP1 is one of two groups of peroxisome biogenesis disorders (PBD). The other PBD group is the Zellweger syndrome spectrum.

Although individuals with RCDP1 have a perturbation in matrix protein import consistent with a peroxisomal assembly defect, they have a biochemical, cellular, and clinical phenotype distinct from PBD of the Zellweger syndrome spectrum.

Prevalence

The prevalence of RCDP1 is estimated to be lower than 1/100,000 [Stoll et al 1989]. The disorder is pan ethnic. The high frequency of the L292X allele is secondary to a founder effect in Caucasians of Northern European descent [Braverman et al 2000].

Differential Diagnosis

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

The classic RCDP1 phenotype can be mimicked by isolated deficiencies of either of two peroxisomal enzymes involved in plasmalogen biosynthesis, as well as by severe Conradi-Hünermann syndrome. In addition, several different disorders, described below, have similar punctate cartilaginous changes and various combinations of limb asymmetry, short stature, mental retardation, cataracts, and skin changes. The radiologic finding of chondrodysplasia punctata (CDP) has been observed in various metabolic disorders, skeletal dysplasias, chromosome abnormalities, and teratogen exposures. Exhaustive classifications of CDP have been published [Wulfsberg et al 1992, Poznanski 1994].

- **Rhizomelic chondrodysplasia punctata, type 2 (RCDP2) and type 3 (RCDP3).** RCDP2 is caused by deficiency of the peroxisomal enzyme dihydroxyacetone phosphate acyltransferase, or DHAPAT (OMIM 602744). RCDP3 is caused by deficiency of the peroxisomal enzyme alkyl-dihydroxyacetone phosphate synthase, or ADAPS (OMIM 600121). The clinical phenotypes resemble that seen in RCDP1, emphasizing the role of plasmalogen deficiency in determining the RCDP phenotype. RCDP2 and RCDP3 are inherited in an autosomal recessive manner and are rarer than

RCDP1. The specific enzyme defect is confirmed by measurement of the enzyme activity in cultured skin fibroblasts.

- **X-linked recessive chondrodysplasia punctata, or brachytelephalangic type (CDPX1)** is caused by defects in arysulfatase E (ARSE), a vitamin K-dependent enzyme (OMIM 302950). Affected males have hypoplasia of the distal phalanges without limb shortening or cataracts. The diagnosis is confirmed by molecular genetic testing. Contiguous gene deletions involving *ARSE* result in more complex phenotypes, including ichthyosis and corneal opacities resulting from steroid sulfatase deficiency.
- **Warfarin embryopathy and other vitamin K deficiencies** [including vitamin K epoxide reductase deficiency (OMIM 277450)] are phenotypically similar to CDPX1.
- **X-linked dominant chondrodysplasia punctata, or Conradi-Hünermann syndrome (CDPX2)** is usually lethal in males (OMIM 302960). It is caused by defects in sterol-Δ8-isomerase, which catalyzes an intermediate step in the conversion of lanosterol to cholesterol. Lyonization in females results in phenotypic variability and asymmetric findings. Cataracts are sectorial and limb shortening is rhizomesomelic and usually asymmetric. Severely affected infants have bilateral findings resembling those of RCDP1. The diagnosis is confirmed by measuring the plasma concentration of sterols, which show accumulation of the precursors 8(9)-cholestenol and 8-dehydrocholesterol.
- **Chondrodysplasia punctata, tibia-metacarpal type** (OMIM 118651) and **humero-metacarpal type** [Fryburg & Kelly 1996] are inherited in an autosomal dominant manner. The gene defect(s) is (are) unknown. Affected individuals have short metacarpals with shortening of various long bones. No cataracts or skin changes are present.
- **Maternal systemic lupus erythematosis (SLE)** (OMIM 152700) can cause CDP with rhizomelic limb shortening.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Full skeletal survey
- Ophthalmologic examination
- Growth parameters
- Developmental assessment
- MR imaging of brain with MR spectroscopy

Treatment of Manifestations

Management is supportive and limited because of the multiple handicaps present at birth and poor outcome.

Cataract extraction may preserve some vision.

Physical therapy is recommended to assist in the improvement of contractures; orthopedic procedures have improved function in some individuals.

Prevention of Primary Manifestations

Dietary restriction of phytanic acid to avoid the consequences of phytanic acid accumulation over time may benefit individuals with milder forms of RCDP.

Prevention of Secondary Complications

Poor feeding and recurrent aspiration necessitate the placement of a gastrostomy tube; despite improved nutrition, linear growth is not enhanced.

Individuals with RCDP1 require good pulmonary toilet and careful attention to respiratory function. Influenza and RSV vaccines should be provided.

Surveillance

Based on a retrospective review of the natural history of 35 individuals with RCDP, White et al (2003) provide health supervision guidelines for primary caretakers of children with RCDP, including:

- Growth curves that allow weight comparisons to help determine the need for gastrostomy;
- The ages at which developmental milestones are achieved to provide realistic expectations;
- Recommendations for medical assessments including seizure control, vision, hearing, orthopedic care, and prevention of respiratory infections and contractures.

Therapies Under Investigation

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

Other

Data suggest that oral plasmalogen supplementation using alkylglycerol sources can increase tissue plasmalogen concentrations in rodents and red blood cell (RBC) plasmalogen concentrations in individuals with Zellweger syndrome spectrum disorders [Das et al 1992]. Anecdotal reports of alkylglycerol supplementation in a few individuals with classic RCDP1 have not indicated dramatic clinical benefit; however, alkylglycerol supplementation has not yet been studied in a systematic fashion.

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

RCDP1 is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a proband are obligate heterozygotes (carriers) and therefore carry one mutant allele.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of inheriting both mutant alleles and being affected, a 50% chance of inheriting one mutant allele and being an unaffected carrier, and a 25% chance of inheriting both normal alleles.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. Affected individuals do not reproduce.

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

Carrier Detection

- Carriers cannot be identified by biochemical methods.
- Carrier testing of at-risk relatives using molecular genetic techniques is available on a clinical basis once the mutations have been identified in an affected family member.

Related Genetic Counseling Issues

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

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

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Biochemical testing. Prenatal diagnosis for pregnancies at 25% risk for RCDP1 is also available by assay of plasmalogen biosynthesis in cultured chorionic villi obtained by CVS at

about 10-12 weeks' gestation or in cultured amniocytes obtained by amniocentesis usually performed at about 15-18 weeks' gestation.

The determination of enzyme activity of alkyl-dihydroxyacetone phosphate synthase (ADAPS) and the subcellular localization of peroxisomal thiolase have also been performed successfully on uncultured chorionic villi.

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

Ultrasound examination. Rhizomelia and punctate calicifications have been noted on ultrasound examination as early as 18-19 weeks [Sastrowijoto et al 1994, Krakow et al 2003]. Others have reported these findings along with bilateral cataracts at 32 weeks, and epiphyseal stippling shown four weeks later. [Basbug et al 2005]; However, the diagnosis of RCDP was not verified after delivery in all cases.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see 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 Rhizomelic Chondrodysplasia Punctata Type 1

Gene Symbol	Chromosomal Locus	Protein Name
PEX7	6q22-q24	Peroxisomal targeting signal 2 receptor

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 Rhizomelic Chondrodysplasia Punctata Type 1

215100	RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 1; RCDP1
601757	PEROXISOME BIOGENESIS FACTOR 7; PEX7

Table C. Genomic Databases for Rhizomelic Chondrodysplasia Punctata Type 1

Gene Symbol	Entrez Gene	HGMD
PEX7	5191 (MIM No. 601757)	PEX7

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

Molecular Genetic Pathogenesis

Role of the peroxisome targeting signal 2 receptor, Pex7, in peroxisome assembly. Peroxisomal matrix enzymes are synthesized on free polyribosomes and directed to the peroxisome by cytosolic receptors. The peroxisome targeting signal 1 receptor (encoded by PEX5) binds a C-terminal peroxisome targeting signal, PTS1, present on most matrix proteins. Pex7 binds an N-terminal PTS2, present on three. The two receptors themselves interact and carry their protein cargo to the peroxisome membrane; the matrix proteins are then translocated inside, the import complex is disassembled, and the receptors are recycled for another round of import. This import process, along with the formation of new peroxisomes and division of existing ones, is termed peroxisome biogenesis. More than 20 proteins are required for

peroxisome biogenesis; collectively they are called peroxins and they are encoded by *PEX* genes.

Metabolic pathways dependent on Pex7. The three PTS2 proteins transported to the peroxisome by Pex7 are alkyl-dihydroxyacetone phosphate synthase (ADHAPS or AGPS), phytanoyl-CoA hydroxylase (PhyH), and peroxisomal 3-ketoacyl-CoA thiolase.

- **ADHAPS** catalyzes the initial steps of plasmalogen biosynthesis in a complex with the PTS1 protein, dihydroxyacetone phosphate acyltransferase (DHAPAT). Plasmalogens are a class of membrane phospholipids, in which the fatty acid at the sn-1 position is replaced by a fatty alcohol in vinyl ether linkage to the glycerol backbone. Plasmalogens are present in significant proportions in plasma membranes and myelin, and their specific functions are now being investigated. These compounds may protect against oxidative damage, be required for membrane fusion and fission processes, and function as lipid messengers [Brites et al 2004]. Since isolated defects in DHAPAT or ADHAPS also result in RCDP (RCDP types 2 and 3), plasmalogen deficiency must play a major role in the pathogenesis of this disorder.
- **PhYH** catalyzes the initial step in the catabolism of phytanic acid, a 16-carbon methyl-branched fatty acid of dietary origin. Isolated defects in PhYH cause adult Refsum disease.
- **Peroxisomal thiolase** catalyzes the last step in beta oxidation of very long straight chain fatty acids. Beta oxidation is normal in RCDP1, presumably because the thiolase activity of sterol carrier protein-X, a PTS1 protein, compensates for this deficiency.

Normal allelic variants: The *PEX7* gene contains ten exons that span 91 kb of genomic DNA. No normal allelic variants have been identified in the coding sequence.

Pathologic allelic variants: Approximately 43 unique *PEX7* mutations have been identified thus far. The majority are missense, nonsense, or splice site mutations, small insertions, or deletions. L292X accounts for 51% of alleles; less common alleles are IVS9+1G>C, G217R, A218V, and Y40X.

Alleles associated with milder RCDP phenotypes, variant phenotypes, or adult Refsum disease are either missense alleles located on the surfaces of the Pex7 protein and thus unlikely to disrupt its structural integrity (S25F, H285R, T14P), or 'leaky' alleles, potentially able to generate residual amounts of normal Pex7 protein (-45C>T, IVS3-10A>G) and re-initiate translation in frame (52insGGGACGCC) or at a downstream methionine residue (12_18dupGTGCGGT) [Braverman et al 2002, Motley et al 2002, van den Brink et al 2003].

Normal gene product: Pex7, the peroxisome-targeting signal 2 receptor, is a 323-amino acid protein with serial WD40 repeats. These repeat domains fold into blades of a propeller-like structure, which resembles a torus on its side and provides several surfaces for protein interactions [Braverman et al 2002]. Pex7 is a receptor for a subclass of peroxisomal matrix enzymes and binds the PTS2 signal at the N-terminus of these proteins. Pex7 carries its cargo to the peroxisome membrane by virtue of its interaction with Pex5.

Abnormal gene product: Defects in Pex7 result in deficient activity of all PTS2 enzymes, but other peroxisomal functions remain intact. Fibroblast assays show that PTS2 proteins remain cytosolic in individuals with RCDP1 and are likely degraded, but PTS1 proteins are imported into peroxisomes normally. Peroxisome morphology is normal in fibroblasts but abnormal in liver, according to several case reports.

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.

RCDP Family Support Group
137 - 25th Avenue
Monroe WI 53566
Phone: 608-325-2717
www.peroxisome.org/Layperson/RCDPlptext.html

Little People of America (LPA)
5289 NE Elam Young Parkway Suite F-100
Hillsboro OR 97124
Phone: 888-LPA-2001 (888-572-2001); 503-846-1562
Fax: 503-846-1590
Email: info@lpaonline.org
www.lpaonline.org

International Skeletal Dysplasia Registry
Medical Genetics Institute
8700 Beverly Blvd.
West Tower Suite 665
Los Angeles CA 90048
Phone: 800-CEDARS-1 (800-233-2771)
Fax: 310-423-0462
www.csmc.edu

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

Published Statements and Policies Regarding Genetic Testing

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

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Suggested Readings

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Chapter Notes

Revision History

- 18 July 2006 (me) Comprehensive update posted to live Web site
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