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Refsum Disease

Synonyms: Adult Refsum Disease, Refsum Syndrome

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Summary

Clinical characteristics. Refsum disease is characterized by anosmia and early-onset retinitis pigmentosa, which are both universal findings with variable combinations of neuropathy, deafness, ataxia, and ichthyosis. Onset of symptoms ranges from age seven months to older than age 50 years. Cardiac arrhythmia and heart failure caused by cardiomyopathy are potentially severe health problems which develop later in life.

Diagnosis/testing. The diagnosis of Refsum disease is suspected on the basis of clinical findings and a plasma phytanic acid concentration greater than 200 µmol/L in most affected individuals. Confirmation of the diagnosis requires either (1) molecular genetic testing to identify biallelic pathogenic variants in either *PHYH* (encoding phytanoyl-CoA hydroxylase), which accounts for more than 90% of Refsum disease, or *PEX7* (encoding the PTS2 receptor), which accounts for less than 10% of Refsum disease; or (2) enzyme analysis to identify deficiency of either phytanoyl-CoA hydroxylase enzyme activity or the peroxisome-targeting signal type 2 receptor.

Management. *Treatment of manifestations:* Dietary restriction of phytanic acid intake helps resolve ichthyosis, sensory neuropathy, and ataxia. Supportive treatment includes hydrating creams for ichthyosis and drugs for cardiac arrhythmias and cardiomyopathy. Plasmapheresis or lipid apheresis is used for acute arrhythmias or extreme weakness. A high-calorie diet prevents mobilization of phytanic acid into the plasma.

Agents/circumstances to avoid: Fasting and/or sudden weight loss; ibuprofen.

Evaluation of relatives at risk: Testing of sibs of a proband ensures early treatment to reduce plasma phytanic acid concentration before symptoms occur.

Genetic counseling. Refsum disease 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 relatives and prenatal diagnosis for pregnancies at increased risk are possible if the *PEX7* or *PHYH* pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Refsum disease, also referred to as "classic Refsum disease" (CRD) or "adult Refsum disease" (ARD), is suspected in individuals with late childhood-onset retinitis pigmentosa and variable combinations of the following clinical findings (listed in descending order of frequency):

- Anosmia
- Sensory motor neuropathy
- Hearing loss
- Ataxia
- Ichthyosis
- Short metacarpals and metatarsals present from birth (~35% of individuals)
- Cardiac arrhythmias and cardiomyopathy

It should be noted that: (1) the full constellation of signs and symptoms is rarely seen in an affected individual; (2) most features develop with age.

Establishing the Diagnosis

More than 90% of individuals with Refsum disease have deficiency of phytanoyl-CoA hydroxylase encoded by *PHYH* and fewer than 10% have a deficiency of the PTS2 receptor encoded by *PEX7* [Waterham & Wanders, unpublished observations].

Establishing the diagnosis first requires analysis of phytanic acid concentration in plasma or serum and then either molecular genetic testing or enzyme analysis (if molecular genetic testing is not available or results are ambiguous).

Analysis of phytanic acid concentration in plasma or serum. Associated laboratory findings are summarized in Table 1. Note that alpha-methylacyl-CoA racemase (AMACR) deficiency, the major disorder in the differential diagnosis of Refsum disease, is included in Table 1 for comparison (see Differential Diagnosis). When present, normal plasma phytanic acid levels essentially rule out the two forms of Refsum disease.

Table 1.

Comparison of Peroxisomal Metabolites in the Two Forms of Refsum Disease and AMACR Deficiency

	Forms of Refsum Disease		AMACR Deficiency	Normal
	Phytanoyl-CoA Hydroxylase Deficiency	PTS2 Receptor Deficiency		
Gene	*PHYH*	*PEX7*	*AMACR*	--
Plasma phytanic acid concentration [1]	>200 µmol/L [2]	>200 µmol/L [2]	>20 µmol/L	<10 µmol/L

	Forms of Refsum Disease		AMACR Deficiency	Normal
	Phytanoyl-CoA Hydroxylase Deficiency	PTS2 Receptor Deficiency		
Plasma pristanic acid concentration	<2 µmol/L	<2 µmol/L	>20 µmol/L	<3.0 µmol/L
Phytanic acid / pristanic acid ratio	Elevated	Elevated	Decreased	Normal
Plasma pipecolic acid concentration	Mildly elevated in 20%	Normal	Normal	Normal
Erythrocyte plasmalogen concentration [1]	Normal	Decreased to normal	Normal	Normal
Di- & trihydroxycholestanoic acid	Normal	Normal	Elevated	Normal

AMACR = α-methylacyl-CoA racemase. See Differential Diagnosis.

Plasma very-long-chain fatty acids (VLCFA) are normal in all three conditions.

1. Measured by gas chromatography
2. Plasma phytanic acid concentration may vary considerably because phytanic acid intake is dependent on local diet and may be deceptively low in populations with lower intakes of saturated fatty acids and cholesterol.

Molecular genetic testing to detect biallelic pathogenic variants in *PHYH* or *PEX7* is required to establish the diagnosis of Refsum disease (Table 2).

- One genetic testing strategy is **serial single-gene molecular genetic testing** in the order in which pathogenic variants most commonly occur (i.e., *PHYH*, then *PEX7).* Typically sequence analysis is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is identified.
- An alternative genetic testing strategy is use of a **multigene panel** that includes *PHYH* and/or *PEX7* and other genes of interest (see Differential Diagnosis). 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 at the most reasonable cost 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 2.

Molecular Genetic Testing Used in Refsum Disease

Gene [1]	Proportion of Refsum Disease Attributed t Mutation of This Gene [2]	Test Method

Gene [1]	Proportion of Refsum Disease Attributed t Mutation of This Gene [2]	Test Method
PHYH	>90%	Sequence analysis [3]
		Gene-targeted deletion/duplication analysis [4]
PEX7	<10%	Sequence analysis [3]
		Gene-targeted deletion/duplication analysis [4]

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.
2. Waterham & Wanders, unpublished observations
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

Studies of enzyme activity in fibroblasts distinguish between Refsum disease caused by *PHYH* or *PEX7* pathogenic variants and AMACR deficiency.

- **Deficiency of phytanoyl-CoA hydroxylase enzyme activity.** Phytanoyl-CoA hydroxylase catalyzes the conversion of phytanoyl-CoA into 2-hydroxyphytanoyl-CoA, a key step in the breakdown of phytanic acid via alpha-oxidation in peroxisomes. To assess activity of this enzyme, phytanic acid alpha-oxidation is first measured in cultured fibroblasts. If alpha-oxidation is deficient, the activity of the enzyme phytanoyl-CoA hydroxylase is measured.
- **Deficiency of the peroxisome-targeting signal type 2 (PTS2) receptor.** The PTS2 receptor plays a key role in peroxisome biogenesis by catalyzing the transport across the peroxisomal membrane of proteins equipped with a peroxisome-targeting signal type 2 (like phytanoyl-CoA hydroxylase). Abnormalities in fibroblasts of such individuals include the presence of an abnormal molecular form of peroxisomal thiolase (44 kd) and a partial deficiency of alkyldihydroxyacetonephosphate synthase [van den Brink et al 2003a].

Clinical Characteristics

Clinical Description

Onset of symptoms in "classic Refsum disease" (CRD) or "adult Refsum disease" (ARD) ranges from age seven months to after age 50 years. However, because the onset is insidious, it is difficult for many individuals to know exactly when symptoms first started. A few individuals remain asymptomatic until adulthood [Skjeldal et al 1987]. Early-onset disease is not necessarily associated with a poor prognosis for life span.

Retinitis pigmentosa is in most cases an early clinical feature, as is anosmia. Other findings that may occur in the following ten to 15 years in decreasing order of frequency [Skjeldal et al 1987]:

- Neuropathy
- Deafness
- Ataxia

- Ichthyosis

Wierzbicki et al [2002] documented in 15 individuals the cumulative incidence of the following features over many decades:

- Retinitis pigmentosa (15/15)
- Anosmia (14/15)
- Neuropathy (11/15)
- Deafness (10/15)
- Ataxia (8/15)
- Ichthyosis (4/15)

In a few instances, psychiatric disturbances have also been observed.

The four cardinal features, originally described by Refsum [1946] (retinitis pigmentosa, a chronic polyneuropathy, ataxia, and raised CSF protein concentration) are rarely seen in a single individual.

Some investigators distinguish between acute ARD and chronic ARD. In acute ARD, polyneuropathy, weakness, ataxia, sudden visual deterioration, and often auditory deterioration are often accompanied by ichthyosis, possibly cardiac arrhythmias, and elevated liver transaminases and bilirubin. Triggers for acute presentations include weight loss, stress, trauma, and infections. In contrast, in chronic ARD, RP is present, but the other features of ARD are subtle.

Ophthalmologic findings. Retinitis pigmentosa (pigmentary retinal degeneration, tapeto-retinal degeneration) is present in all individuals with biochemical findings of Refsum disease and therefore appears to be an obligatory finding; in a series of 17 individuals, retinitis pigmentosa was present in all [Skjeldal et al 1987].

Virtually every individual ultimately diagnosed to have Refsum disease experiences visual symptoms first. If a detailed past medical history is obtained, many individuals confirm the onset of night blindness in childhood. The delay between first ophthalmologic evaluation and diagnosis ranged between one and 28 years (mean = 11 years) in one study of 23 individuals [Claridge et al 1992].

Typically, individuals with Refsum disease experience night blindness years before the progressive changes of constricted visual fields and decreased central visual acuity appear. Because night blindness can be difficult to ascertain, particularly in children, electroretinography, which shows either a reduction or a complete absence of rod and cone responses, can help support the diagnosis in early stages (see Retinitis Pigmentosa Overview).

In general, individuals with retinitis pigmentosa due to Refsum disease keep some visual function until late in life albeit with severely concentrically constricted visual fields [Rüether et al 2010; Leroy, unpublished observations]

Anosmia. This is the absence of smell. Although the sense of smell and the sense of taste have their own specific receptors, they are intimately related. Both may be normal, reduced, or absent in individuals with Refsum disease. Studies by Wierzbicki et al [2002] have shown that anosmia is present in most, if not all, individuals with ARD/CRD. If smell is tested experimentally, all individuals with ARD/CRD have an abnormal smell test [Gibberd et al 2004].

Polyneuropathy. The polyneuropathy is a mixed motor and sensory neuropathy that is asymmetric, chronic, and progressive in untreated individuals. It may not be clinically apparent at the start of the illness. Initially, symptoms often wax and wane. Later, the distal lower limbs are affected with resulting muscular atrophy and weakness. Over the course of years, muscular weakness can become widespread and disabling, involving not only the limbs, but also the trunk.

Almost without exception, individuals with Refsum disease have peripheral sensory disturbances, most often impairment of deep sensation, particularly perception of vibration and position-motion in the distal legs.

Hearing loss. Bilaterally symmetric mild-to-profound sensorineural hearing loss affects the high frequencies or middle-to-high frequencies [Oysu et al 2001, Bamiou et al 2003]. Auditory nerve involvement (auditory neuropathy) may be evident on testing of auditory brain stem evoked responses (ABER) [Oysu et al 2001, Bamiou et al 2003]. Individuals with auditory nerve involvement may experience hearing difficulty even in the presence of a normal audiogram (see Hereditary Hearing Loss and Deafness).

Ataxia. Although cerebellar dysfunction is considered to be a main clinical sign of Refsum disease, onset is nevertheless relatively late, particularly when compared with the onset of retinopathy and neuropathy. Unsteadiness of gait is the main symptom related to cerebellar dysfunction. Ataxia is thus characteristically more marked than the degree of muscular weakness and sensory loss would indicate (see Hereditary Ataxia Overview).

Skeletal abnormalities. Short metacarpals and metatarsals are present in about 30% of affected individuals [Plant et al 1990]. Short metatarsals most often cause a rather typical dorsal displacement of the fourth digit of the foot.

Ichthyosis. Mild generalized scaling may occur in childhood, but usually begins in adolescence. This finding is present in a minority of affected individuals.

Cardiac arrhythmias. Cardiac arrhythmia and heart failure resulting from cardiomyopathy are frequent causes of death in Refsum disease.

Other laboratory findings

- **Elevated plasma concentration of pipecolic acid.** A few individuals with elevated plasma concentrations of both phytanic acid and pipecolic acid have been described [Tranchant et al 1993, Baumgartner et al 2000]. Subsequently, sequencing of *PIPOX* (encoding human L-pipecolic acid oxidase) [Ijlst et al 2000] in these individuals did not reveal any pathogenic variants [Waterham & Wanders, unpublished results], supporting the view that the accumulation of pipecolic acid in these patients is a secondary event related to phytanoyl-CoA hydroxylase deficiency but with an unclear mechanism.

  Baumgartner et al [2000] described an individual with psychomotor retardation and abnormally short metatarsals and metacarpals, but no other signs of classic Refsum disease. Phytanoyl-CoA hydroxylase enzyme activity was deficient; a homozygous deletion of *PHYH* causing a frameshift was identified. L-pipecolic acid concentration was elevated in plasma. Microscopy of the liver showed the presence of peroxisomes, although they were reduced in number and increased in size. These abnormal liver peroxisomes lacked catalase. Moreover, in fibroblasts, a mosaic pattern of cells with and without peroxisomes was found, in contrast to the peroxisomes in fibroblasts from individuals with classic Refsum disease who cannot be distinguished from controls by catalase immunofluorescence. Most likely, this individual is affected by two distinct genetic disorders with pathogenic variants in different genes, of which one is *PHYH* and the other remains to be identified. The latter gene may well be one of the *PEX* genes.

  Tranchant et al [1993] described three members of a family diagnosed with Refsum disease. Two had a significant increase of pipecolic acid concentration in plasma and a fourth individual, a brother, died at age 17 years from a progressive neurologic disorder with unusual clinical and neuropathologic abnormalities. Homozygosity mapping localized the gene to chromosome 10p. Subsequently these sibs were confirmed to have phytanoyl-CoA hydroxylase deficiency in fibroblasts and pathogenic variants in *PHYH* [Waterham & Wanders, unpublished observations]. Most likely, the mild accumulation of pipecolic acid in these individuals is the secondary result of the accumulation of phytanic acid. This hypothesis is supported by data of Wierzbicki et al [2002] showing elevated plasma pipecolic acid levels in 20% of individuals with Refsum disease.

- **CSF protein concentration** in individuals with Refsum disease is considerably higher than normal. In one Arab

family, CSF protein concentration was 101 mg/dL [Fertl et al 2001]. Normal CSF protein concentration in adults ranges from 15 to 50 mg/dL.

Genotype-Phenotype Correlations

More studies are needed to determine if Refsum disease caused by pathogenic variants in *PHYH* and Refsum disease caused by pathogenic variants in *PEX7* are phenotypically different. The Refsum disease phenotype caused by pathogenic variants in *PEX7* may be milder [Van den Brink et al 2003b], as exemplified by the patient described by Horn et al [2007].

Manifestations of Refsum disease may vary considerably among affected individuals in a family, i.e., among individuals with identical *PHYH* pathogenic variants. These phenotypic differences are comparable to those among affected individuals from different families. Consequently, no clear phenotype-genotype correlations have been identified as yet. Phenotypic variation may be related to the dietary intake of phytanic acid, which is thought to be the toxic compound.

Nomenclature

Adult Refsum disease was first described in 1946 by the Norwegian neurologist Sigwald Refsum as a distinct autosomal recessive neurologic entity, which he called heredopathia atactica polyneuritiformis.

In the literature, Refsum disease is also referred to as "classic Refsum disease" (CRD) or "adult Refsum disease" (ARD) to distinguish it from infantile Refsum disease (IRD), which belongs to the group of peroxisome biogenesis disorders, Zellweger syndrome spectrum. Distinction between so-called infantile Refsum disease IRD and classic Refsum disease is readily apparent on clinical grounds. IRD has a much earlier onset with cerebral and hepatic dysfunction, craniofacial dysmorphia, developmental delay, and death usually in infancy or early childhood. The only finding shared by IRD and CRD/ARD is the accumulation of phytanic acid in plasma and tissues. In CRD/ARD, phytanic acid metabolism is the only abnormality, whereas in IRD, a number of biochemical abnormalities result from the defect in peroxisome biogenesis. Thus, infantile Refsum disease is a poor designation, given the lack of resemblance to classic Refsum disease.

Prevalence

The prevalence of Refsum disease is probably very low. In the literature, no estimates of its prevalence have been reported. The fact that most individuals described in the literature have been identified in the United Kingdom and Norway, where awareness of Refsum disease is high, suggests that the true prevalence of Refsum disease may be much higher than currently reported. According to Wierzbicki (personal communication), the incidence is around one in 10^6 in the United Kingdom.

Genetically Related (Allelic) Disorders

PHYH. No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *PHYH*.

PEX7. Pathogenic variants in *PEX7* predominantly account for rhizomelic chondrodysplasia punctata type 1 (RCDP type I), a severe and often lethal disorder characterized by intellectual disability, rhizomelic shortening of the upper extremities, dwarfism, and cataract [Braverman et al 2002, Motley et al 2002]. Mild variants may account for Refsum disease.

Differential Diagnosis

Phytanic acid is also elevated in other peroxisomal disorders including:

- **Alpha-methylacyl-CoA racemase (AMACR) deficiency** (OMIM 614307). Although the predominant phenotype is adult-onset sensory motor neuropathy with or without associated pigmentary retinopathy [Ferdinandusse et al 2000], other presentations have been published as well which are dominated by early-onset liver failure with cholestasis, hepatomegaly, and elevated liver enzymes. This enzyme (encoded by *AMACR*) plays a key role in the breakdown of pristanic acid and the C27-bile acid intermediates di- and trihydroxycholestanoic acid. As a consequence of the impaired degradation of pristanic acid, both pristanic acid and phytanic acid accumulate with pristanic concentrations much more elevated than phytanic acid concentrations (see Table 1). AMACR deficiency and classic Refsum disease can be distinguished by screening peroxisome metabolites in the plasma, followed by fibroblast studies and molecular genetic testing. Inheritance is autosomal recessive.

- **Peroxisomal biogenesis disorders, Zellweger syndrome spectrum.** These disorders are characterized by a defect in peroxisome biogenesis and caused by pathogenic variants in one of the many *PEX* genes. Zellweger syndrome spectrum disorders can readily be distinguished from classic Refsum disease on clinical grounds. Furthermore, in addition to plasma phytanic acid concentration, additional peroxisomal abnormalities are found in plasma, including elevated very-long-chain fatty acids, pristanic acid concentration, and the bile acid intermediates di- and trihydroxycholestanoic acid. Inheritance is autosomal recessive.

- **Rhizomelic chondrodysplasia punctata type 1 (RCDP1),** caused by pathogenic variants in *PEX7*. Classic Refsum disease can be distinguished easily from RCDP type 1, although a few individuals with a mild form of RCDP type 1 with a Refsum-like phenotype have been described [van den Brink et al 2003a] (see Molecular Genetics for more details). In these individuals plasma phytanic acid concentration is also elevated. Inheritance is autosomal recessive.

Retinitis pigmentosa. Since visual deterioration is almost always the first symptom of Refsum disease, plasma phytanic acid concentration should be measured in *any* individual with retinitis pigmentosa, especially when combined with other features suggestive of Refsum syndrome, including anosmia, shortened metacarpals and metatarsals, and impaired hearing.

Retinitis pigmentosa and sensorineural hearing loss

- **Usher syndrome type I** is characterized by a congenital, bilateral, profound sensorineural deafness, vestibular areflexia, and adolescent-onset retinitis pigmentosa. Pathogenic variants in one of a minimum of nine different genes cause Usher syndrome type I. Inheritance is autosomal recessive.

- **Usher syndrome type II** is characterized by: congenital, bilateral, sensorineural hearing loss that is mild to moderate in the low frequencies and severe to profound in the higher frequencies; intact vestibular responses; and retinitis pigmentosa. Pathogenic variants in one of at least three genes (*USH2A*, *ADGRV1*, *DFNB31*) cause Usher syndrome type II. Inheritance is autosomal recessive.

- **Usher syndrome type III** (OMIM 276902, 614504) is characterized by progressive sensorineural hearing loss and adolescent-onset retinitis pigmentosa. Pathogenic variants in either *CLRN1* or *HARS* cause Usher syndrome type III. Inheritance is autosomal recessive.

Alström syndrome is characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing impairment, dilated or restrictive cardiomyopathy, the insulin resistance syndrome, liver involvement with cirrhosis, and multiple organ failure. Biallelic pathogenic variants in *ALMS1* are causative. Inheritance is autosomal recessive.

Bardet-Biedl syndrome (BBS) is characterized by rod-cone dystrophy (retinitis pigmentosa), obesity, hand and foot abnormalities including polydactyly (mostly but not exclusively postaxial), sensorineural hearing loss, diabetes mellitus, mental problems, and hypogonadism. The retinitis pigmentosa is generally more severe than that seen in Refsum disease. Pathogenic variants in one of at least 18 genes are associated with BBS. Inheritance is typically

autosomal recessive.

Kearns-Sayre syndrome (KSS) is defined by the triad of onset before age 20 years, pigmentary retinopathy, and progressive external ophthalmoplegia (PEO). In addition, affected individuals have at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration greater than 100 mg/dL, or cerebellar ataxia. Sensorineural hearing loss is seen in almost all affected individuals. Kearns-Sayre syndrome is caused by deletion of mitochondrial DNA (mtDNA) and, when inherited, is transmitted by maternal inheritance.

Ataxia. Friedreich ataxia is characterized by slowly progressive ataxia with mean onset between age ten and 15 years and usually before age 25 years. FRDA is typically associated with dysarthria, muscle weakness, spasticity in the lower limbs, scoliosis, bladder dysfunction, absent lower limb reflexes, and loss of position and vibration sense. Hearing loss is uncommon. Biallelic pathogenic variants in *FXN* are causative. Inheritance is autosomal recessive. (See also Hereditary Ataxia Overview.)

Ichthyosis. Sjögren-Larsson syndrome (OMIM 270200) is characterized by congenital ichthyosis and onset of ataxia in early childhood. Sjögren-Larsson syndrome is caused by biallelic pathogenic variants in *ALDH3A2*. Inheritance is autosomal recessive.

Increased CSF protein concentration. High CSF protein concentrations can be found in a variety of conditions.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Refsum disease, the following evaluations are recommended:

- **Ophthalmology.** Examination for retinitis pigmentosa/miosis, cataract, and visual fields [Claridge et al 1992]
- **Anosmia testing** using the procedure described by Gibberd et al [2004]
- **Neurology.** Ataxia, neuropathy, myography, and electrophysiologic assessment
- **Audiology.** Pure tone audiometry and possibly otoacoustic emission testing and auditory brain stem evoked response (ABER) testing if hearing difficulties are suspected but not identified on pure tone audiometry [Bamiou et al 2003]
- **Radiology.** Physical examination of hands, feet, and knees; radiologic assessment of hands and feet
- **Cardiology.** Cardiac evaluation including electrocardiography (ECG) and cardiac ultrasound examination
- **Other.** Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Chronic Treatment

The following are indicated:

- Dietary restriction of phytanic acid intake
- Avoidance of sudden weight loss
- Lifelong treatment with hydrating creams
- Regular care by a cardiologist for cardiac arrhythmias and cardiomyopathy in order to treat signs and symptoms properly with antiarrhythmic and cardiogenic supportive drugs

- Because the pupils do not dilate well if at all, other measures, such as use of iris hooks, may be necessary to allow sufficient pupillary enlargement during cataract surgery. In addition, an anterior chamber lens with iris fixation may be necessary because the brittleness of the zonular fibers holding the lens capsule may not allow positioning of an intraocular lens in the capsular bag after cataract removal, a complication observed in one patient [BP Leroy 2007, personal communication].

Treatment of Acute Presentation

Many acute features such as polyneuropathy, ataxia, ichthyosis, and cardiac arrhythmias resolve with reduction in plasma phytanic acid concentration (see Prevention of Primary Manifestations).

Plasmapheresis or lipapheresis can be used in the event of acute arrhythmias or extreme weakness because phytanic acid is transported on lipoproteins [Wierzbicki et al 1999]. During plasmapheresis, cardiac monitoring should be continuous and plasma glucose concentration should be kept high to prevent onset or exacerbation of arrhythmias.

A low phytanic acid diet can be given orally or by nasogastric tube. If oral intake is restricted, appropriate parenteral nutrition and fluid therapies are needed to maintain plasma glucose concentrations and prevent ketosis.

Prevention of Primary Manifestations

No curative therapy currently exists for Refsum disease.

By restricting dietary intake of phytanic acid or eliminating phytanic acid by plasmapheresis or lipid apheresis, plasma phytanic acid concentrations can be reduced by 50% to 70%, typically to about 100 to 300 µmol/L. This reduction in plasma phytanic acid concentration successfully resolves symptoms of ichthyosis, sensory neuropathy, and ataxia in approximately that order. However, it is uncertain whether treatment affects the progression of the retinitis pigmentosa, anosmia, and deafness [Gibberd & Wierzbicki 2000]. Although data are limited, it appears that despite strict dietary treatment the retinitis pigmentosa is very slowly progressive [BP Leroy, unpublished observations].

A high-calorie diet is necessary to avoid mobilization of stored lipids, including phytanic acid, into the plasma.

Postoperative care requires parenteral nutrition with solutions that do not contain phytanic acid, e.g., Intralipid® available in 10%, 20%, and 30% concentrations, which are all based on soybean oil and egg yolk phospholipid.

Prevention of Secondary Complications

Treatment of hypertension may help in delaying cardiomyopathy, which inevitably leads to arrhythmias. It is probably better to avoid amiodarone as an anti-arrhythmic drug, because of the risk of hyperthyroidism, which results in catabolism and increased phytanic acid release from tissues if not recognized in time. This complication was observed in one individual [BP Leroy 2007, personal communication].

Once cardiomyopathy has become difficult to treat, cardiac transplantation can be life-saving. One individual with *PHYH*-related Refsum disease and one with *PEX7*-related Refsum disease have successfully received a donor heart [BP Leroy 2007 & 2015, personal observations].

Surveillance

The following are appropriate:

- Measurement of plasma phytanic acid levels every three to six months and more frequently during illnesses or increased stress that may lead to a catabolic state
- Annual ophthalmologic examination to identify vision loss resulting from cataracts, which are treatable
- Annual cardiac examination to identify cardiomyopathy and concomitant arrhythmias

Agents/Circumstances to Avoid

Avoid the following:

- **All food products containing phytanic acid** such as ruminant (cow, sheep, and goat) products and certain fish (cod) products. Some nuts should also be avoided [Brown et al 1993].
- **Fasting** because stored lipids, including phytanic acid, are mobilized into the plasma
- **Ibuprofen** because it is metabolized by AMACR and may interfere with the metabolism of phytanic acid
- **Amiodarone** because of the risk that hyperthyroidism would induce enhanced catabolism, with consequent increase of plasma phytanic acid

Evaluation of Relatives at Risk

It is appropriate to evaluate sibs of a proband before symptoms of Refsum disease occur in order to institute early treatment to reduce plasma phytanic acid concentration. Evaluations include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Measurement of phytanic acid concentration in plasma or serum 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

Because of the tendency for pregnancy to induce catabolism, it is extremely important to manage plasma phytanic acid concentration during pregnancy in women with Refsum disease.

Fairly rapid reduction of visual fields has been observed during the third trimester of pregnancy [BP Leroy, unpublished observations], possibly due to increased plasma phytanic acid concentration resulting from increased catabolism.

Therapies Under Investigation

At present, the potential of enzyme replacement therapy (ERT) similar to that for lysosomal storage diseases (e.g., Hurler syndrome [see MPS I], Fabry disease, and Gaucher disease) is under investigation. This may eventually replace dietary restrictions and plasma- or lipapheresis.

In the long run, gene therapy may be the treatment of choice, but many issues need to be resolved before it can be applied.

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for access to information on clinical studies for a wide range of diseases and conditions.

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. —ED.

Mode of Inheritance

Refsum disease 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 *PEX7* or *PHYH* pathogenic variant).
- 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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier of a *PEX7* or *PHYH* pathogenic variant is 2/3.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with Refsum disease are obligate heterozygotes (carriers) of a *PEX7* or *PHYH* pathogenic variant.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier of a *PEX7* or *PHYH* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *PEX7* or *PHYH* pathogenic variants pathogenic variants in the family.

Biochemical testing is not accurate for carrier testing, as the biochemical findings (i.e., plasma phytanic acid concentration) in obligate heterozygotes (carriers) are near normal [Wierzbicki et al 2003].

Related Genetic Counseling Issues

See 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 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 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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *PEX7 or PHYH* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for Refsum disease

are possible.

Biochemical genetic testing. Prenatal diagnosis for pregnancies at 25% risk is possible by measurement of phytanic acid oxidation in fetal cells obtained by amniocentesis (usually performed at ~15-18 weeks' gestation) or chorionic villus sampling (usually performed at ~10-12 weeks' gestation).

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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.

- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Refsum Disease Information Page
- **NCBI Genes and Disease**
  Refsum disease
- **Foundation for Ichthyosis and Related Skin Types, Inc. (FIRST)**
  2616 North Broad Street
  Colmar PA 18915
  Phone: 215-997-9400
  Email: info@firstskinfoundation.org
  www.firstskinfoundation.org
- **Metabolic Support UK**
  5 Hilliards Court, Sandpiper Way
  Chester Business Park
  Chester CH4 9QP
  United Kingdom
  Phone: 0845 241 2173
  Email: contact@metabolicsupportuk.org
  www.metabolicsupportuk.org
- **Retinitis Pigmentosa International**
  PO Box 900
  Woodland Hills CA 91365
  Phone: 818-992-0500
  Fax: 818-992-3265
  Email: info@rpinternational.org
  www.rpinternational.org

- **United Leukodystrophy Foundation (ULF)**
  224 North Second Street
  Suite 2
  DeKalb IL 60115
  Phone: 800-728-5483 (toll-free); 815-748-3211
  Fax: 815-748-0844
  Email: office@ulf.org
  www.ulf.org

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.

Refsum Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PEX7	6q23.3	Peroxisomal targeting signal 2 receptor	dbPEX, PEX7 Gene Database PEX7 database	PEX7	PEX7
PHYH	10p13	Phytanoyl-CoA dioxygenase, peroxisomal	PHYH database	PHYH	PHYH

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 Refsum Disease (View All in OMIM)

266500	REFSUM DISEASE, CLASSIC
601757	PEROXISOME BIOGENESIS FACTOR 7; PEX7
602026	PHYTANOYL-CoA HYDROXYLASE; PHYH
614879	PEROXISOME BIOGENESIS DISORDER 9B; PBD9B

Molecular Genetic Pathogenesis

Pathogenic variants in *PHYH* and *PEX7* are known to cause Refsum disease by interfering with the alpha-oxidation of phytanic acid.

Alpha-oxidation of phytanic acid. Phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) is derived from dietary sources only, mainly from dairy and ruminant fats. Phytanic acid is a 3-methyl branched chain fatty acid, which cannot undergo straightforward beta-oxidation like other fatty acids since the presence of the methyl group at the 3 position blocks beta-oxidation. Nature has resolved this problem by creating an alpha-oxidation mechanism in which the terminal carboxyl group is released as CO_2. Accordingly, phytanic acid first undergoes alpha-oxidative chain shortening to produce pristanic acid (2,4,6,10-tetramethylpentadecanoic acid) and CO_2. All steps from phytanoyl-CoA

to pristanic acid occur in peroxisomes [Wanders et al 2001, Wanders et al 2011] (Figure 1):

- Activation of phytanic acid to phytanoyl-CoA
- Hydroxylation of phytanoyl-CoA to 2-hydroxyphytanoyl-CoA by the enzyme phytanoyl-CoA hydroxylase, encoded by *PHYH*. Phytanoyl-CoA hydroxylase is equipped with a PTS2 signal, and is targeted to the peroxisome by means of the PTS2 receptor, encoded by *PEX7*; see **Note:** (1).
- Conversion of 2-hydroxyphytanoyl-CoA into pristanal and formyl-CoA via the enzyme 2-hydroxyphytanoyl-CoA lyase encoded by 2-HPCL; see **Note:** (2)
- Conversion of pristanal into pristanic acid via an ill-defined aldehyde dehydrogenase [Jansen et al 2001]
- Conversion of pristanic acid into pristanoyl-CoA via the peroxisomal very-long-chain acyl-CoA synthetase (see Note 2), which has its catalytic site facing the lumen of the peroxisome [Smith et al 2000]

Note: (1) In case of a deficiency at the level of the PTS2 receptor, phytanoyl-CoA hydroxylase cannot be properly imported into the peroxisome, leading to its functional deficiency. (2) The other enzymes from the phytanic acid alpha-oxidation route, including 2-hydroxyphytanoyl-CoA lyase and very-long-chain acyl-CoA synthetase, are PTS1 proteins, which are targeted to the peroxisome by means of the PTS1 receptor, encoded by *PEX5*.

Beta-oxidation. Once pristanic acid has been activated to pristanoyl-CoA, it undergoes three cycles of beta-oxidation in the peroxisomes to generate 4,8-dimethylnonanoyl-CoA, which then is transported to mitochondria for final oxidation to CO_2 and H_2O in the form of its carnitine ester.

Note that unimpaired breakdown of phytanic acid is only possible if pristanic acid, the product generated from phytanic acid by alpha-oxidation, also undergoes unimpaired degradation. If pristanic acid oxidation is blocked, as in α-methylacyl-CoA racemase (AMACR) deficiency caused by pathogenic variants in *AMACR*, phytanic acid degradation is partially blocked, leading to elevated plasma phytanic acid concentration.

PHYH

Gene structure. *PHYH* comprises nine exons and spans 22 kb of genomic sequence. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Jansen et al [2004] described one sequence variant (c.636A>G; p.Thr212Thr) (see Table 3) with an incidence of around 10% in 93 control individuals that causes no amino acid change.

Pathogenic variants. Sequence analysis of *PHYH* has now been performed in 46 families and has revealed 32 different presumed pathogenic variants of which 20 (62.1%) are unique to one affected individual or family [Waterham & Wanders, unpublished data]. Of these 32 variants,

- Seventeen (53%) are missense variants.
- Six (19%) are deletions. All deletions are found in the first half of the coding sequence and all cause a frameshift.
- Three are insertions (9%). One causes a frameshift; the other, a three-nucleotide insertion, causes the insertion of a single amino acid into the PHYH protein.
- Six (19%) are splice site variants. Two splice site variants, c.135-2A>G and c.135-1G>C, lead to skipping of exon 3, which consists of 111 nucleotides. Either change causes an in-frame deletion of 37 internal amino acids, and an altered protein (p.Tyr46_Arg82del), which, when heterozygously expressed in *S. cerevisiae*, is clearly detectable by Western blot analysis, but completely lacks enzymatic activity [Jansen et al 2000]. Four splice site variants – c.497-2A>G, c.678+2T>G, c.678+5G>T, and c.679-1G>T – cause skipping of exon 6, which results

in a frameshift and a premature stop codon (p.Lys167GlyfsTer3).

Table 3.

Selected *PHYH* Variants

Variant Classification	DNA Nucleotide Change	Protein Amino Acid Change (Alias [1])	Reference Sequences
Benign	c.636A>G	p.=	NM_006214.3 NP_006205.1
Pathogenic	c.135-2A>G	p.Tyr46_Arg82del	
	c.135-1G>C	p.Tyr46_Arg82del	
	c.497-2A>G	p.Lys167GlyfsTer3 (Ala166fsTer3)	
	c.678+2T>G	p.Lys167GlyfsTer3 (Ala166fsTer3)	
	c.678+5G>T	p.Lys167GlyfsTer3 (Ala166fsTer3)	
	c.679-1G>T	p.Lys167GlyfsTer3 (Ala166fsTer3)	
	c.524A>G	p.His175Arg	
	c.526C>A	p.Gln176Lys	
	c.530A>G	p.Asp177Gly	
	c.610G>A	p.Gly204Ser	
	c.805A>C	p.Asn269His	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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. See Molecular Genetic Pathogenesis.

Abnormal gene product. The impact of any pathogenic variant in the phytanoyl-CoA hydroxylase gene can be assessed by evaluating the consequences of certain pathogenic variants on the stability and the catalytic activity of the hydroxylase upon expression. Interestingly, 15 of the 17 missense pathogenic variants identified in the phytanoyl-CoA hydroxylase are located in exon 6 and 7. Structure-function analysis has demonstrated that these exons code in part for the conserved beta-barrel core, which suggests that this structurally important element in the protein is susceptible to changes that directly cause loss of enzymatic activity. The effect of only very few of the missense pathogenic variants has been tested by expressing the mutated proteins and testing protein stability and enzyme activity. Mukherji et al [2001] have studied a few variants including p.His175Arg, p.Gln176Lys, and p.Asp177Gly. The amino acid triad p.His175, p.Gln176, p.Asp177 forms the iron-binding motif and pathogenic variants in these amino acids have been shown to cause a fully dysfunctional enzyme since the hydroxylase is completely dependent upon Fe^{2+} for the conversion of phytanoyl-CoA to 2-hydroxyphytanoyl-CoA. Two missense variants, p.Gly204Ser and p.Asn269His, cause the peculiar effect of uncoupling the hydroxylation of phytanoyl-CoA from the conversion of 2-oxoglutarate into succinate and CO_2. As demonstrated in expression studies, Mukherji et al [2001] found that no phytanoyl-CoA

was hydroxylated while decarboxylation of 2-oxoglutarate to succinate and CO_2 still took place, although at a much-reduced rate. This uncoupling is also observed in the case of the p.Gln176Lys substitution, which is also associated with a change in the iron-binding motif.

PEX7

Gene structure. *PEX7* comprises ten exons that span 91 kb of genomic DNA. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. So far, three individuals have been identified with mild pathogenic variants in *PEX7*.

The two individuals described by van den Brink et al [2003a] who were both compound heterozygous for pathogenic variants in *PEX7* had a p.Tyr40Ter nonsense pathogenic variant that introduces a premature stop codon in the N-terminal region of the protein. This pathogenic variant has also been found in classic RCDP type 1 with a severe clinical presentation [Motley et al 2002].

- In patient 1, the second allele was p.Gly7ValfsTer51, resulting from a seven-nucleotide duplication, predicted to cause a frame-shift leading to a premature stop codon at amino acid position 51. However, the duplication occurs between two in-frame initiation codons, which would suggest that use of the second ATG may produce a protein that lacks the first ten amino acids but retains partial peroxin 7 transport functions.
- In patient 2, the second allele was p.Thr14Pro, which is thought either to interfere with folding of the protein or to reduce the affinity for its binding partners [Braverman et al 2002].

Table 4.

Selected *PEX7* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.12_18dup	p.GLy7ValfsTer51	NM_000288.3 NP_000279.1
c.40A>C	p.Thr14Pro	
c.120C>G	p.Tyr40Ter	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The normal product is a 323-amino acid protein with six WD40 repeats. Each WD-repeat is composed of four beta-strands, which together make up one blade of a propeller. The overall structural appearance of a WD-repeat protein such as PEX7 with six such repeats, resembles that of a propeller with as many blades as the number of WD-repeats. Peroxisomal targeting signal 2 receptor, the protein encoded by *PEX7*, is a receptor for a subclass of peroxisomal matrix enzymes and targets these enzymes to the peroxisomal membrane.

Abnormal gene product. Defects in peroxisomal targeting signal 2 receptor 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 [Braverman et al 2002, Van den Brink et al 2003b].

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Chapter Notes

Revision History

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Figures

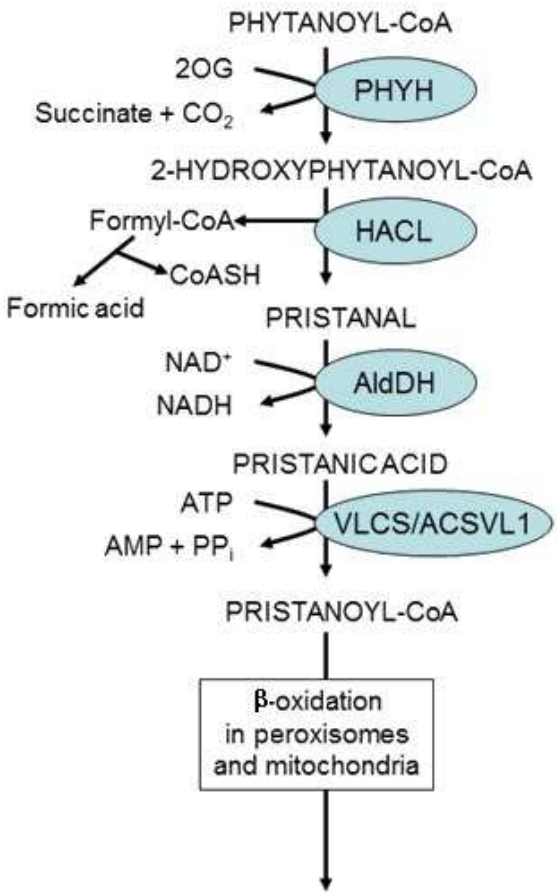

Figure 1.

Metabolic pathway showing the different steps involved in the alpha-oxidation of phytanoyl-CoA to pristanoyl-CoA as catalyzed by the enzymes: phytanoyl-CoA, 2-hydroxylase (PHYH), 2-hydroxyphytanoyl-CoA lyase (HACL), a hitherto uncharacterized aldehyde dehydrogenase (AldDH) and the enzyme pristanoyl-CoA synthetase (VLCS/ACSVL1) [Wanders et al 2011]

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