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Adult Refsum Disease

Synonym: Classic Refsum Disease

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Summary

Clinical characteristics

Adult Refsum disease (ARD is associated with elevated plasma phytanic acid levels, late childhood-onset (or later) retinitis pigmentosa, and variable combinations of anosmia, polyneuropathy, 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 that develop later in life.

Diagnosis/testing

The diagnosis of ARD is established in a proband with suggestive clinical and biochemical findings by identification of biallelic pathogenic variants in either *PHYH* or *PEX7* on molecular genetic testing.

Management

Treatment of manifestations: Plasmapheresis or lipid apheresis to decrease phytanic acid levels is used only for acute arrhythmias or extreme weakness. Dietary restriction of phytanic acid intake helps resolve ichthyosis, sensory neuropathy, and ataxia. A high-calorie diet and avoidance of fasting prevent mobilization of phytanic acid stored in adipose tissue into the plasma. Hypercaloric parenteral infusions are required during periods of severe illness or postoperatively. Supportive treatment includes hydrating creams for ichthyosis and drugs for cardiac arrhythmias and cardiomyopathy.

Agents/circumstances to avoid: Food products containing phytanic acid, mostly from ruminants (cow, sheep, goat), some fish and walnuts; fasting and/or sudden weight loss; use of either ibuprofen or amiodarone.

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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

ARD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PHYH* or *PEX7* pathogenic variant, each sib of an affected individual has at conception 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 the *PHYH* or *PEX7* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, molecular genetic prenatal testing, and preimplantation genetic testing for ARD are possible.

Diagnosis

Adult Refsum disease (ARD), also referred to as "classic Refsum disease," is a peroxisomal disorder. In the majority of individuals, it is caused by a deficiency of the peroxisomal enzyme phytanoyl-CoA hydroxylase due to biallelic pathogenic variants in *PHYH*. In ~10% of individuals, the disorder is milder and is associated with biallelic pathogenic variants in *PEX7*.

No consensus clinical diagnostic criteria for ARD have been published.

Suggestive Findings

ARD **should be suspected** in individuals with the following clinical, laboratory, and family history findings.

Clinical findings. Late childhood-onset (or later) retinitis pigmentosa and variable combinations of the following findings (listed in descending order of frequency):

- Anosmia
- Polyneuropathy (sensory and motor)
- Hearing loss
- Ataxia
- Ichthyosis
- Short metacarpals and metatarsals present from birth
- Cardiac arrhythmias and cardiomyopathy

Note: (1) The full constellation of signs and symptoms is rarely seen in an affected individual. (2) Most features develop with age.

Laboratory findings. Elevated plasma phytanic acid level (>20x upper limit of normal) is highly suggestive of ARD. Other peroxisomal metabolites may be abnormal, with differences associated with the particular gene involved. See Table 1.

Table 1. Comparison of Peroxisomal Metabolites in Adult Refsum Disease by Gene Involved

	Adult Refsum Disease		Normal
Associated Gene	***PHYH***	***PEX7***	--
Plasma phytanic acid concentration [1]	>200 µmol/L [2]	>200 µmol/L [2]	<10 µmol/L
Plasma pristanic acid concentration	<2 µmol/L	<2 µmol/L	<3.0 µmol/L
Phytanic acid / pristanic acid ratio	↑	↑	Normal
Plasma pipecolic acid concentration	Mildly ↑ in 20%	Normal	Normal
Erythrocyte plasmalogen concentration [1]	Normal	↓ to normal	Normal

Table 1. continued from previous page.

	Adult Refsum Disease		Normal
Di- & trihydroxycholestanoic acid	Normal	Normal	Normal

Plasma very-long-chain fatty acids (VLCFA) are normal in adult Refsum disease.
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.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of ARD **is established** in a proband with suggestive clinical and biochemical findings by identification of biallelic pathogenic variants in one of the genes listed in Table 2.

Note: Identification of biallelic variants of uncertain significance (or identification of one known pathogenic variant and one variant of uncertain significance) in one of the genes listed in Table 2 does not establish or rule out the diagnosis of this disorder.

If molecular genetic testing is unavailable or the results are not diagnostic, specialized biochemical testing can be used to establish the diagnosis.

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determines which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those with a phenotype indistinguishable from many other inherited disorders with retinitis pigmentosa are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1. A retinitis pigmentosa multigene panel that includes both the *PHYH* and *PEX7* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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*. (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.

Option 2. Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 2. Molecular Genetic Testing Used in Adult Refsum Disease

Gene [1, 2]	Proportion of ARD Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
PHYH	>90% [6]	>95% [7]	Unknown [8]
PEX7	<10% [6]	>95% [7]	Unknown [8]

ARD = adult Refsum disease
1. Genes are listed in order of frequency of causation.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Waterham & Wanders, unpublished observations
7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
8. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Specialized Biochemical Testing

Measurement of phytanoyl-CoA hydroxylase enzyme activity in fibroblasts has been used in the past to confirm the diagnosis of ARD – or when the diagnosis of ARD could not be confirmed by molecular genetic testing. However, this testing is no longer available on a clinical basis.

As an alternative, cellular phytanic acid alpha-oxidation (the conversion of phytanoyl-CoA into 2-hydroxyphytanoyl-CoAl; which is expected to be deficient in ARD) can be measured. This test does not allow differentiation between ARD due to variants in *PHYH* or *PEX7*, however, and is also not clinically available.

Clinical Characteristics

Clinical Description

Clinical manifestations in adult Refsum disease (ARD) are retinitis pigmentosa, anosmia (loss of sense of smell), sensorineural hearing loss, polyneuropathy (sensory and motor), ataxia (balance issues), ichthyosis, skeletal abnormalities including shortened fingers and toes, and cardiac arrhythmias and cardiomyopathy.

To date, more than 200 individuals have been identified with biallelic pathogenic variants in *PHYH* or *PEX7*.

Table 3. Adult Refsum Disease: Frequency of Select Features

Feature [1]	% of Persons with Feature	Comment
Retinitis pigmentosa	100%	
Anosmia	87.5%	
Polyneuropathy	70%	Mixed motor & sensory neuropathy
Deafness	62.5%	Sensorineural hearing loss that may incl auditory neuropathy
Ataxia	50%	
Skeletal abnormalities	30%	
Ichthyosis	25%	

Table 3. continued from previous page.

Feature [1]	% of Persons with Feature	Comment
Cardiac arrhythmia	Unknown	
↑ CSF protein concentration	Unknown	↑ when measured

Data derived from Wierzbicki et al [2002]
1. Features are listed in decreasing order of frequency.

Onset of symptoms in ARD ranges from age seven months to after age 50 years. Most individuals report the onset of first symptoms between ages ten and 20. 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; Authors, unpublished observation]. Early-onset disease is not necessarily associated with a poor prognosis for life span.

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, retinitis pigmentosa is present, but the other features of ARD are relatively subtle.

Ophthalmologic findings. Retinitis pigmentosa (rod-cone dystrophy, pigmentary retinal degeneration, tapetoretinal degeneration) is present in all individuals with biochemical findings of ARD.

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

Typically, individuals with ARD 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 support the diagnosis in early stages (see Retinitis Pigmentosa Overview).

In general, individuals with retinitis pigmentosa due to ARD keep some visual function until late in life, albeit with severely concentrically constricted visual fields [Rüether et al 2010; Leroy 2014; Leroy, unpublished observations].

Cataracts in ARD often develop at an earlier age than age-related cataracts, similar to what is seen in patients with other forms of rod-cone dystrophy. The cataracts in ARD are of the posterior subcapsular type, in addition to the classic corticonuclear type.

Cataract surgery (see Treatment of Manifestations) may be hampered by the poor pupillary dilatation typically seen in ARD and the brittle zonular fibers, which suspend the lens within the ciliary body. Poor pupillary dilatation may be due to atrophy of the iris dilator muscle.

Anosmia (i.e., absence of the sense of smell). While 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 ARD. Studies have shown that anosmia is present in most if not all individuals with ARD [Wierzbicki et al 2002, 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 the trunk.

Almost without exception, individuals with ARD 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 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 [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 Overview).

Ataxia. Although cerebellar dysfunction is considered to be a main clinical sign of ARD, 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. Although less frequent, phalanges may also be short, leading to shortened finger nails.

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

Cardiomyopathy. Cardiac arrhythmia and heart failure resulting from cardiomyopathy are potentially severe health problems that develop later in life and are frequent causes of death in ARD.

Other laboratory findings

- **Elevated plasma concentration of pipecolic acid.** Wierzbicki et al [2002] found elevated plasma pipecolic acid levels in 20% of individuals with ARD.
- **CSF protein concentration** in individuals with ARD is considerably higher than normal. In one Arab family, CSF protein concentration was 101 mg/dL [Fertl et al 2001] (normal range in adults:15-50 mg/dL). Although this finding may be suggestive of ARD, spinal tap is not routinely performed in individuals with ARD for diagnosis or other indication.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Even in a family with identical pathogenic variants, the manifestations of ARD may vary considerably among affected individuals, comparable to those seen among affected individuals from different families. The observed phenotypic variation may be related to the dietary intake and subsequent accumulation of phytanic acid.

Nomenclature

ARD 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, ARD is also referred to as "classic Refsum disease" (CRD) or "Refsum disease." The terms ARD and CRD are preferred over the term “Refsum disease” because ARD and CRD distinguish the disorder from so-called "infantile Refsum disease" (IRD), which is a Zellweger spectrum disorder. Distinction between "infantile Refsum disease" and ARD 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 ARD is the accumulation of phytanic acid in plasma and tissues. In 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 ARD.

Prevalence

No estimates of the prevalence of ARD have been reported. The fact that most individuals described in the literature have been identified in the United Kingdom and Norway, where awareness of ARD is high, suggests that worldwide prevalence may be higher than expected. The estimated incidence is around one in 1,000,000 in the United Kingdom.

Genetically Related (Allelic) Disorders

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

PEX7. Biallelic pathogenic variants in *PEX7* are predominantly associated with rhizomelic chondrodysplasia punctata type 1 (RCDP1).

- Classic (severe) RCDP1 is characterized by proximal shortening of the humerus and to a lesser degree the femur, punctate calcifications in cartilage with epiphyseal and metaphyseal abnormalities, coronal clefts of the vertebral bodies, and cataracts. Birth weight, length, and head circumference are often at the lower range of normal; postnatal growth deficiency is profound. Intellectual disability is severe, and the majority of children develop seizures. Most affected children do not survive the first decade of life; a proportion die in the neonatal period.
- Nonclassic (mild) RCDP1 is characterized by congenital or childhood cataracts, chondrodysplasia punctata or infrequently, chondrodysplasia manifesting only as mild epiphyseal changes, variable rhizomelia, and milder intellectual disability and growth restriction than classic RCDP1.

Adult Refsum disease (ARD) can be easily distinguished from classic (severe) RCDP1. The phenotype in individuals with nonclassic (mild) RCDP1 may overlap that of ARD [van den Brink et al 2003]. In these individuals plasma phytanic acid concentration is also elevated.

Differential Diagnosis

Table 4. Genes of Interest in the Differential Diagnosis of Adult Refsum Disease

Gene(s)	Disorder	MOI	Clinical Features	Distinguishing Features / Comment
Disorders w/elevated phytanic acid				
AMACR	Alpha-methylacyl-CoA racemase (AMACR) deficiency [1] (OMIM 614307)	AR	Typically adult-onset sensory motor neuropathy ± assoc pigmentary retinopathy.[2] Other presentations are dominated by early-onset liver failure w/cholestasis, hepatomegaly, & ↑ liver enzymes.	Distinguished from ARD by screening peroxisome metabolites in plasma

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Distinguishing Features / Comment
PEX1 *PEX6* *PEX12* *PEX26* *PEX10* *PEX2* (13 genes) [3]	Zellweger spectrum disorder (ZSD)	AR	Affected persons usually present in newborn period or later in childhood. Newborns are hypotonic, feed poorly, & have distinctive facies, congenital malformations, & liver disease that can be severe. Infants w/severe ZSD are significantly impaired & typically die during 1st yr of life, usually having made no developmental progress.	Persons w/ARD have a biochemical profile distinct from ZSD & are developmentally normal before presenting in their late teens, 20s, or even later.
Disorders w/retinitis pigmentosa (RP) ± sensorineural hearing loss (SNHL)				
~90 genes [4]	RP	AD AR XL Digenic	RP refers to a group of inherited retinal disorders in which abnormalities of the photoreceptors (rods & cones) of the retina → progressive visual loss. RP is classified as nonsyndromic, or "simple" (not affecting other organs or tissues); syndromic (affecting other neurosensory systems, e.g., hearing); or systemic (affecting multiple tissues).	Because visual deterioration is almost always the 1st symptom of ARD, plasma phytanic acid concentration should be measured in any person w/RP, esp when combined w/other features suggestive of ARD (e.g., anosmia, shortened metacarpals & metatarsals, impaired hearing).
ADGRV1 *CDH23* *CIB2* *CLRN1* *HARS1* *MYO7A* *PCDH15* *USH1C* *USH1G* *USH2A* *WHRN*	Usher syndrome (USH) type I, type II, & type III (OMIM 276902, 614504)	AR	USH1: Congenital bilateral profound SNHL, vestibular areflexia, & adolescent-onset RP USH2: Congenital bilateral SNHL (mild-moderate in low frequencies & severe-profound in higher frequencies); intact or variable vestibular responses; & RP USH3: Postingual progressive SNHL, late-onset RP, & variable impairment of vestibular function	ARD can be distinguished by screening peroxisome metabolites (phytanic acid) in plasma.
ALMS1	Alström syndrome	AR	Severe cone-rod dystrophy (typically early-onset), obesity, progressive SNHL, cardiomyopathy, insulin resistance/type 2 diabetes mellitus, nonalcoholic fatty liver disease, & chronic progressive kidney disease	ARD is assoc w/rod-cone dystrophy (not cone-rod dystrophy). ARD can also be distinguished by screening peroxisome metabolites (phytanic acid) in plasma.
BBS1 *BBS2* *BBS4* *BBS10* *BBS12* *MKKS* (~26 genes) [5]	Bardet-Biedl syndrome	AR	Cone-rod or rod-cone dystrophy, obesity & related complications, postaxial polydactyly, cognitive impairment, hypogonadotropic hypogonadism &/or genitourinary malformations, & renal malformations &/or renal parenchymal disease	RP in BBS is generally more severe than that seen in ARD. ARD can also be distinguished by screening peroxisome metabolites (phytanic acid) in plasma.

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Distinguishing Features / Comment
mtDNA (single large-scale deletion)	Kearns-Sayre syndrome (KSS) (See Mitochondrial DNA Deletion Syndromes.)	Mat	Defined by triad of onset before age 20 yrs, pigmentary retinopathy, & PEO. Addl features: cerebellar ataxia, impaired intellect, SNHL, ptosis, oropharyngeal & esophageal dysfunction, exercise intolerance, muscle weakness, cardiac conduction block, & endocrinopathy.	The RP in ARD is characterized by intraretinal pigment migration rather than the hyperpigmentation at the level of the retinal pigment epithelium as seen in KSS. ARD can also be distinguished by screening peroxisome metabolites (phytanic acid) in plasma.
Disorder w/ataxia (see also Hereditary Ataxia Overview)				
FXN	Friedreich ataxia	AR	Slowly progressive ataxia w/mean onset at age 10-15 yrs (usually before age 25 yrs). Typically assoc w/ dysarthria, muscle weakness, spasticity in lower limbs, scoliosis, bladder dysfunction, absent lower-limb reflexes, & loss of position & vibration sense. Hearing loss is uncommon.	ARD is frequently assoc w/ progressive SNHL. ARD can also be distinguished by screening peroxisome metabolites (phytanic acid) in plasma.
Disorder w/ichthyosis				
ALDH3A2	Sjögren-Larsson syndrome (OMIM 270200)	AR	Congenital ichthyosis & onset of ataxia in early childhood	ARD can be distinguished by screening peroxisome metabolites (phytanic acid) in plasma.

AD = autosomal dominant; AR = autosomal recessive; ARD = adult Refsum disease; CSF = cerebrospinal fluid; MOI = mode of inheritance; PEO = progressive external ophthalmoplegia; RP = retinitis pigmentosa; SNHL = sensorineural hearing loss; VLCFA = very-long-chain fatty acids; XL = X-linked

1. The enzyme 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).

2. Ferdinandusse et al [2000]

3. >90% of ZSD is attributed to pathogenic variants in the listed genes. ZSD is also associated with pathogenic variants in *PEX11β*, *PEX13*, *PEX14*, *PEX16*, *PEX19*, *PEX3*, and *PEX5*.

4. OMIM PS268000

5. ~65% of BBS is attributed to pathogenic variants in the listed genes. See Bardet-Biedl syndrome for additional associated genes.

Management

No clinical practice guidelines for adult Refsum disease (ARD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ARD, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Adult Refsum Disease

System/Concern	Evaluation	Comment
Retinitis pigmentosa (RP)	Ophthalmologic eval incl extensive history taking on night blindness & restricted visual fields; as well as: • Visual field testing • Electroretinography • Autofluorescence imaging • Spectral domain optical coherence tomography	Although the degree to which the retina is affected by RP varies, there is no essential difference between what is seen in classic RP & the retinal phenotype assoc w/ARD.
Anosmia	University of Pennsylvania Smell Identification Test (described by Gibberd et al [2004]) or any other standardized test	
Polyneuropathy	Complete neurologic eval incl electrophysiologic testing	
Ataxia		
Deafness	Pure tone audiometry & possibly otoacoustic emission testing & BAER testing if hearing difficulties are not identified on pure tone audiometry	
Skeletal abnormalities	Clinical & radiographic eval of hands & feet for metacarpal & metatarsal anomaly	
Cardiomyopathy	Complete eval directed by cardiologist	
Genetic counseling	By genetics professionals [1]	To inform patients & families re nature, MOI, & implications of ARD in order to facilitate medical & personal decision making

ARD = adult Refsum disease; BAER = brain stem auditory evoked response; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management by multidisciplinary specialists including ophthalmologist, neurologist, cardiologist, ENT specialist or audiologist, dietician, dermatologist, and clinical geneticist is recommended.

Table 6. Treatment of Manifestations in Individuals with Adult Refsum Disease

Manifestation/ Concern	Treatment	Considerations/Other
↑ phytanic acid level	Acute care: plasmapheresis or lipid apheresis	• Can be used if acute arrhythmias or extreme weakness because phytanic acid is transported on lipoproteins • Plasma phytanic acid concentrations can be ↓ by 50%-70%, typically to ~100-300 µmol/L.
	Postoperative care requires parenteral nutrition w/solutions that do not contain phytanic acid, e.g., Intralipid® available in 10%, 20%, & 30% concentrations & all based on soybean oil & egg yolk phospholipid.	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
	Chronic care: dietary restriction of phytanic acid intake • A low-phytanic acid diet can be given orally or by nasogastric tube. • If oral intake is restricted, appropriate parenteral nutrition & fluid therapies are needed to maintain plasma glucose concentrations & prevent ketosis. • A high-calorie diet is necessary to avoid mobilization of stored lipids (incl phytanic acid) into the plasma.	• Plasma phytanic acid concentrations can be ↓ by 50%-70%, typically to ~100-300 µmol/L. • ↓ in plasma phytanic acid concentration successfully resolves symptoms of ichthyosis, sensory neuropathy, & ataxia (in approx that order). • Despite strict dietary treatment, RP appears to be very slowly progressive [BP Leroy, unpublished observations]. • It is unknown if treatment affects progression of anosmia & deafness.
RP (rod-cone dystrophy)	• Strict diet may slow evolution. • Low vision aids are useful where & when required.	Visual rehab by specialist center preferable
Cataracts	• Iris hooks may be required during cataract surgery to allow sufficient pupillary enlargement (pupils do not dilate well if at all in ARD). • An anterior chamber lens w/iris fixation may be needed because the brittleness of the zonular fibers holding the lens capsule may prevent positioning of an intraocular lens in the capsular bag after cataract removal. • However, capsular tension rings may provide further stability to zonular fibers & capsule during cataract surgery.	
Ichthyosis	Hydrating creams	
Cardio-myopathy	• Regular care by cardiologist for cardiac arrhythmias & cardiomyopathy in order to treat signs & symptoms properly w/ antiarrhythmic & cardiogenic supportive drugs • Once cardiomyopathy has become difficult to treat, cardiac transplantation can be life saving. 2 persons w/ARD have had successful heart transplant [BP Leroy 2007 & 2015, personal observations].	During & after heart transplantation surgery: hypercaloric parenteral infusions &/or diet is paramount.

RP = retinitis pigmentosa

Surveillance

Table 7. Recommended Surveillance for Individuals with Adult Refsum Disease

System/Concern	Evaluation	Frequency
↑ phytanic acid levels	Plasma phytanic acid level	Every 3-6 mos; more frequently during illnesses or ↑ stress that may → a catabolic state

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Ophthalmologic concerns	Ophthalmic exam to: • Identify vision loss from cataracts • Quantify extent of visual loss from RP (rod-cone dystrophy) w/visual fields & electroretinography where & when suitable	Annually
Cardiomyopathy	Cardiac eval to identify cardiomyopathy & concomitant arrhythmias	

RP = retinitis pigmentosa

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 including almonds, coconut, peanuts, and walnuts were tested; except for walnuts, which contain phytanic acid and phytol, and thus should be avoided, all were negative for phytanic acid and phytol [Brown et al 1993].
- **Fasting and/or sudden weight loss,** because stored lipids, including phytanic acid, are mobilized into the plasma. Care should be taken during periods of illness or in the pre- and postoperative phase when undergoing surgical procedures, including prior discussions with the surgeon and anesthetist. If intravenous infusions are required, lipid emulsions in 10%, 20%, or 30% concentrations may be used.
- **Ibuprofen,** because it may interfere with the metabolism of phytanic acid
- **Amiodarone** because of the risk that it may cause hyperthyroidism, which 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 ARD 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 ARD.

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. However, Dubot et al [2019] reported no clinical events during pregnancies for an affected mother and her consanguineous, heterozygous husband, despite increasing phytanic acid levels during the last trimester of pregnancy.

Unaffected children born to mothers with ARD do not have ARD-related health concerns [Dubot et al 2019, Stepien et al 2016]. However, to prevent infant ingestion of high levels of phytanic acid, breastfeeding is not advised. More importantly, avoiding breastfeeding reduces the risk of a catabolic state in the affected mother after pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Adult Refsum disease (ARD) 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., presumed to be carriers of one *PHYH* or *PEX7* pathogenic variant based on family history).
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *PHYH* or *PEX7* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PHYH* or *PEX7* pathogenic variant, each sib of an affected individual has at conception 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.
- Manifestations of ARD may vary considerably between sibs with identical pathogenic variants. These phenotypic differences are comparable to those among affected individuals from different families.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an individual with ARD has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *PHYH* or a *PEX7*.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PHYH* or *PEX7* 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 and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *PHYH* or *PEX7* pathogenic variants have been identified in an affected family member, molecular genetic prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for ARD are possible.

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

Resources

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

- **Global DARE Foundation**
  P.O.Box 865
  Windham ME 04062
  Email: info@GlobalDAREFoundation.org
  www.defeatadultrefsumeverywhere.org
- **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

- **FIRST - Foundation for Ichthyosis and Related Skin Types**
  Phone: 215-997-9400; 800-545-3286
  Email: info@firstskinfoundation.org
  www.firstskinfoundation.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  ulf.org
- **Global DARE Foundation's Registry at CoRDS**
  Phone: 877-658-9192
  Email: cords@sanfordhealth.org
  www.defeatadultrefsumeverywhere.org/refsum-patient-registry

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. Adult 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 Adult 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 Pathogenesis

Pathogenic variants in *PHYH* and *PEX7* are known to cause adult Refsum disease (ARD) by interfering with the alpha-oxidation (breakdown) 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).

ARD is caused by deficits in the first step in this process by one of two causes:

- Deficient enzyme phytanoyl-CoA hydroxylase (encoded by *PHYH*), which is required for the hydroxylation of phytanoyl-CoA to 2-hydroxyphytanoyl-CoA
- Deficient PTS2 receptor (encoded by *PEX7*), which is required to target the PTS2 signal on phytanoyl-CoA hydroxylase to the peroxisome where the alpha-oxidation occurs.

As a consequence of the phytanoyl-CoA hydroxylase deficiency, phytanic acid cannot be degraded and will accumulate in body tissues to toxic levels.

Mechanism of disease causation. ARD occurs via a loss-of-function mechanism.

Chapter Notes

Revision History

- 30 September 2021 (ha) Comprehensive update posted live
- 11 June 2015 (me) Comprehensive update posted live
- 22 April 2010 (me) Comprehensive update posted live
- 20 March 2006 (me) Review posted live
- 30 March 2004 (rw) Original submission

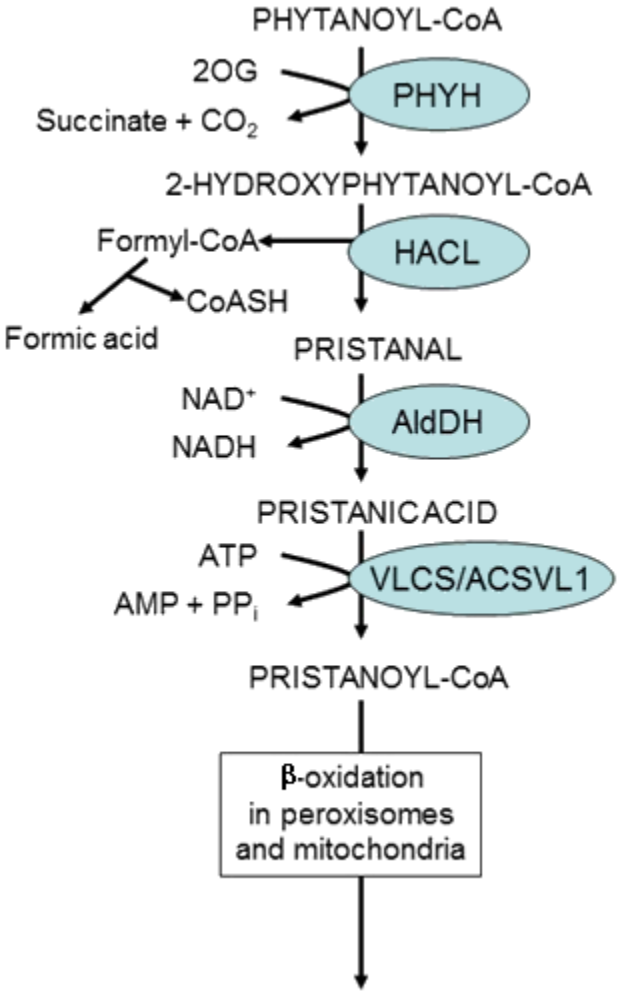

Figure 1. Metabolic pathway showing the different steps involved in the alpha-oxidation of phytanoyl-CoA to pristanoyl-CoA as catalyzed by the enzymes: phytanoyl-CoA, 2-hydroxylase (PHYH), 2-hydroxyphytanoyl-CoA lyase (HACL), a hitherto uncharacterized aldehyde dehydrogenase (AldDH) and the enzyme pristanoyl-CoA synthetase (VLCS/ACSVL1) [Wanders et al 2011]. Adult Refsum disease is caused by a deficiency of phytanoyl-CoA, 2-hydroxylase (PHYH) or by an inability of PHYH to be directed to the peroxisome due to a deficiency of the PTS2 receptor encoded by *PEX7* (not shown in figure).

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