

MINI-REVIEW

Refsum's disease: a peroxisomal disorder affecting phytanic acid α -oxidation

Anthony S. Wierzbicki,^{*,†} Matthew D. Lloyd,^{‡,§} Christopher J. Schofield,[‡] Michael D. Feher[†] and F. Brian Gibberd[†]

^{*}Department of Chemical Pathology, St. Thomas' Hospital, London, UK

[†]Refsum Disease Clinic, Chelsea & Westminster Hospital, London, UK

[‡]The Dyson Perrins Laboratory & Oxford Centre for Molecular Sciences, Oxford, UK

[§]The Department of Pharmacy and Pharmacology, The University of Bath, Bath, UK

Abstract

Refsum's disease (hereditary motor sensory neuropathy type IV, hereditary ataxia polyneuritis) is an autosomal recessive disorder the clinical features of which include retinitis pigmentosa, blindness, anosmia, deafness, sensory neuropathy, ataxia and accumulation of phytanic acid in plasma- and lipid-containing tissues. The transport and biochemical pathways of phytanic acid metabolism have recently been defined with the cloning of two key enzymes, phytanoyl-CoA 2-hydroxylase (PAHX) and 2-hydroxyphytanoyl-CoA lyase, together with the confirmation of their localization in peroxisomes. PAHX, an iron(II) and 2-oxoglutarate-dependent oxygenase is located on chromosome 10p13. Mutant forms of PAHX have been shown to be responsible for some, but not all, cases of Refsum's disease. Certain cases have been

shown to be atypical mild variants of rhizomelic chondrodysplasia punctata type 1a. Other atypical cases with low-plasma phytanic acid may be caused by α -methylacyl-CoA racemase deficiency. A sterol-carrier protein-2 (SCP-2) knockout mouse model shares a similar clinical phenotype to Refsum's disease, but no mutations in SCP-2 have been described to-date in man. This review describes the clinical, biochemical and metabolic features of Refsum's disease and shows how the biochemistry of the α -oxidation pathway may be linked to the regulation of metabolic pathways controlled by isoprenoid lipids, involving calcineurin or the peroxisomal proliferator activating α -receptor.

Keywords: oxygenase, peroxisomes, phytanic acid, Refsum's disease, review.

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Peroxisomes are cellular organelles involved in biosynthetic and degradative functions (Titorenko and Rachubinski 2001) which, like mitochondria, may have originated from ancient commensal bacteria. Anabolic functions of peroxisomes include the biosynthesis of cholesterol and plasmalogens for cell and neuronal membranes (Moser 1987; Singh 1997; Wanders 2000; Parsons *et al.* 2001). Their degradative functions include the metabolism of unsaturated and aromatic fatty acids including bile acids. Peroxisomes also contain an analogous fatty acid β -oxidation pathway to that found in mitochondria and also specific enzymes for the α -oxidation of 3-methyl branched fatty acids including phytanic acid (Moser 2000; Moser 1999; Wanders 2000; Parsons *et al.* 2001).

Refsum's disease – a disorder of fatty acid α -oxidation

The symptoms of adult Refsum's disease (ARD; OMIM 266510; on-line Mendelian inheritance in man, [http://](http://www.ncbi.nlm.nih.gov)

www.ncbi.nlm.nih.gov), also called hereditary ataxia polyneuritis and hereditary sensory motor neuropathy type IV, were first described in 1945 (Refsum 1945; Wanders *et al.* 2001). He described a constellation of signs comprising

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Address correspondence and reprint requests to Dr A. S. Wierzbicki, Department of Chemical Pathology, St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK.

E-mail: Anthony.Wierzbicki@kcl.ac.uk

Abbreviations used: ARD, adult Refsum's disease; CoA, coenzyme A; HAOXs, hydroxy acid oxidases; 2HPCL, 2-hydroxyphytanoyl-CoA lyase; IRD, infantile Refsum's disease; LCFA-CoA, long-chain fatty acyl-coenzyme A; PAHX, phytanoyl-CoA 2-hydroxylase; PPAR, peroxisome proliferator activating receptor; PTS, peroxisomal targeting signal; RCDP, rhizomelic chondrodysplasia punctata; SCP-2, sterol-carrier protein-2; TPP, thiamine pyrophosphate; VLCFA-CoA, very-long-chain fatty acyl-coenzyme A.

retinitis pigmentosa, anosmia, deafness, ataxia and polyneuropathy allied with raised levels of CSF protein. The biochemical defect was identified in 1963 by Kenke and Kahlke, who noticed the presence of excess phytanic acid in the plasma of affected patients (Kenke and Kahlke 1963). Phytanic acid cannot be degraded by β -oxidation because of the presence of a 3-methyl group; instead it undergoes one round of α -oxidation that shortens phytanic acid by one carbon atom to give pristanic acid. Steinberg *et al.* postulated that ARD results from a deficiency in the enzyme responsible for α -oxidation of phytanic acid (Steinberg *et al.* 1967).

The pathophysiology of ARD remained obscure, although cell complementation analyses assigned it to complementation group 14 of the peroxisomal diseases (Moser *et al.* 1995). This proposal was disputed as the enzyme activity in rats was apparently localized to mitochondria. Recent work has completely revised the major pathway involved in the metabolism of phytanic acid, and has confirmed its subcellular localization as peroxisomal and has identified the mutated gene responsible for some cases of ARD (Mannaerts *et al.* 2000; Verhoeven and Jakobs 2001).

Clinical signs and symptoms

In contrast to Zellweger's syndrome (OMIM 214100), neonatal adrenoleukodystrophy (OMIM 202370), infantile Refsum's disease (IRD; OMIM 266500) and rhizomelic chondrodysplasia (RCDP; OMIM 601757) (Singh 1997), ARD usually presents in late childhood with progressive deterioration of night vision, the occurrence of progressive retinitis pigmentosa and anosmia. After 10–15 years, deafness, ataxia, polyneuropathy (sometimes termed hereditary sensory motor neuropathy type IV), ichthyosis and cardiac arrhythmias can occur (Fig. 1) (Gibberd and Wierzbicki 2000). Short metacarpals or metatarsals are also found in

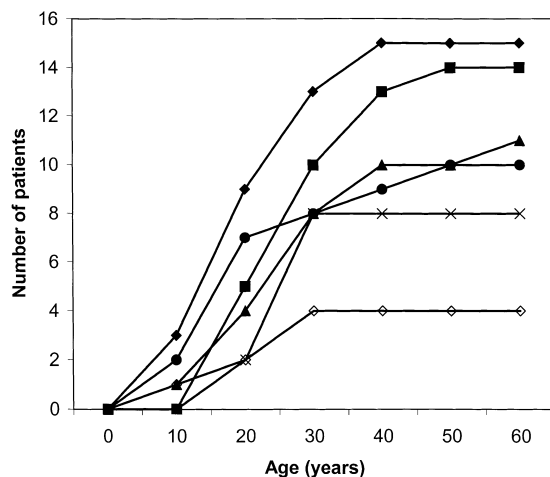


Fig. 1 Cumulative incidence of clinical features on presentation of 15 patients with Refsum's disease. ◆, retinitis pigmentosa; ■, anosmia; ▲, neuropathy; ●, deafness; ×, ataxia; ◇, ichthyosis.

around 30% of patients (Plant *et al.* 1990). Rare findings include psychiatric disturbance and proteinuria (Pabico *et al.* 1981). Premature death can occur either from cardiac arrhythmias caused by an acute release of a labile phytanic pool from the liver following infection or rarely as a result of stress-induced catecholamine release during plasmapheresis (Wanders *et al.* 2001).

The pathognomic finding of ARD on serum analysis is a highly raised phytanic acid level ($> 200 \mu\text{mol/L}$; normal $< 30 \mu\text{mol/L}$), in contrast to other peroxisomal disorders where levels are usually lower and other metabolic abnormalities are also present (Gibberd and Wierzbicki 2000; Wanders *et al.* 2001). Unlike in RCDP or the peroxisomal biogenesis disorders, no intellectual defects are seen, bone abnormalities are mild (if at all present) and there is no defect in plasmalogen synthesis. In IRD, which is a mild clinical variant of the peroxisomal biogenesis disorder encompassing Zellweger's disease as its most severe form, numerous subtle peroxisomal defects are present and the condition presents from birth (Wanders 2000). The age at which symptoms first present in ARD can be variable, with cases described with an onset at age 2 years whilst others do not present until age 40–50 (Gibberd and Wierzbicki 2000). In addition the classical presentation with phytanic acidemia may not be exclusive, as one family with offspring affected with a 'Refsum-like' syndrome has been described in which other subjects had signs of leukodystrophy, intellectual impairment and the co-occurrence of pipecolic acidemia (OMIM 600964) (Tranchant *et al.* 1993). The disease is treated symptomatically by the restriction of phytanic acid intake in the diet or by its elimination by plasmapheresis or lipid apheresis (Gibberd *et al.* 1979; Moser *et al.* 1980; Gutsche *et al.* 1996). These regimes reduce plasma phytanic acid levels by 50–70% to values typically around 100–300 $\mu\text{mol/L}$. Treatment successfully resolves symptoms of ichthyosis, sensory neuropathy and ataxia in approximately that order. However, it has uncertain effects on the progression of the retinitis pigmentosa, anosmia or deafness (Gibberd and Wierzbicki 2000; Wanders *et al.* 2001).

Clinical enzymology

Phytanic acid (3*R*,5*R*,7*R*,11*R*,15-tetramethylhexadecanoic acid) (1a; Fig. 2) is an isoprenoid lipid derived from the phytol side-chain of chlorophylls by bacterial degradation in ruminants, invertebrates or pelagic fish. High levels of phytanic acid in mutton were described in New Zealand in 1959 but the clinical significance of this was not appreciated at the time. The average human daily dietary intake of phytanic acid in Western societies is 50–100 mg, of which around 50% is absorbed and metabolized (Dhopeswarkar 1980; Coppack *et al.* 1988; Brown *et al.* 1993).

Phytanic acid is transported in plasma allied to very-low-density lipoprotein (VLDL) and later in low-density

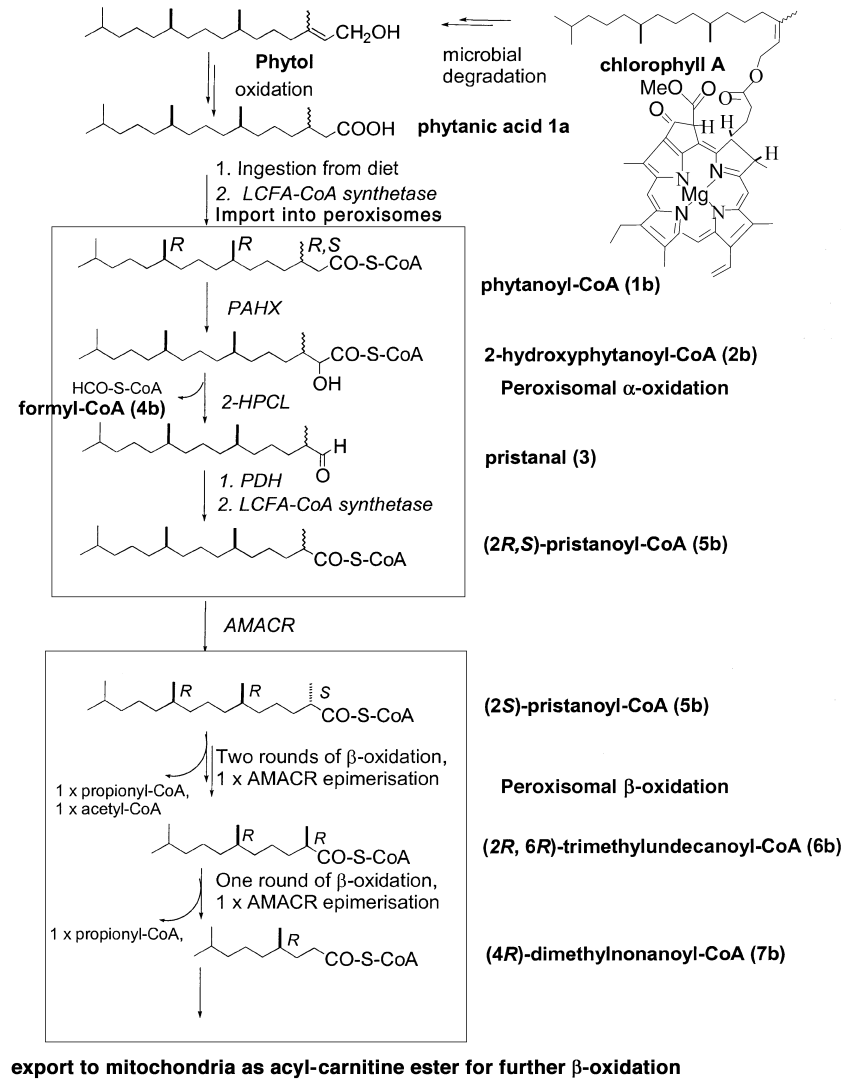


Fig. 2 The degradation of phytanic and pristanic acids within peroxisomes by the α - and β -oxidation pathways. LCFA-CoA synthetase, long-chain fatty acyl-CoA synthetase; PAHX, phytanoyl-CoA 2-hydroxylase; 2HPCL, 2-hydroxyphytanoyl-CoA lyase; PDH, pristanal dehydrogenase; AMACR, α -methylacyl-CoA racemase.

lipoprotein (LDL) (Wierzbicki *et al.* 1999), with its elimination from tissue stores occurring by mechanisms associated with reverse cholesterol transport (high-density lipoprotein; HDL). It also condenses to form triglycerides, but apparently only occupies the 1 or 3 positions because of steric constraints (Wanders *et al.* 2001). Phytanoyl-glycerides are also resistant to plasma lipases, which limits their metabolism in plasma. Phytanic acid is preferentially taken up by the liver and may account for up to 50% of the free fatty acid pool in hepatocytes. This pool is labile and can be acutely mobilized by stress, infection or starvation resulting in rapid phytanic acid release (Britton *et al.* 1989). Plasma phytanic levels are <10% of the levels found in adipose tissue and neurones, which accumulate phytanic acid because of its hydrophobicity and the longer half-life for elimination. The elimination half-life of total body phytanic acid is usually 1–2 years (Wanders *et al.* 2001).

Most fatty acids are metabolized by the β -oxidation pathways in peroxisomes and mitochondria. Phytanic acid

cannot be metabolized by this route because of the presence of a β -methyl group. Instead, phytanic acid (1a) is metabolized either by α -oxidation to pristanic acid (5a) or by ω -oxidation from the other end of the molecule. Using radiolabelled [¹⁴C]phytanic acid as a substrate, an enzyme activity responsible for the α -oxidation of phytanic acid (1a) in cell lysates was described in 1967 (Steinberg *et al.* 1967; Herndon *et al.* 1969). This activity was eventually localized within peroxisomes and after 30 years the pathway responsible for α -oxidation has been clarified (Verhoeven *et al.* 1998).

Patients with ARD are unable to detoxify phytanic acid (1a) by α -oxidation, and so the ω -oxidation pathway is the only metabolic pathway available for phytanic acid degradation. This pathway produces 3-methyladipic acid as the final metabolite, which is excreted in the urine (Wanders *et al.* 2001). Activity of the ω -oxidation pathway is approximately doubled in ARD patients compared with normal levels (Wierzbicki, unpublished data).

Metabolism of phytanic acid

Most metabolism of phytanic acid seems to occur in the liver and kidney, although skin fibroblasts are used for clinical diagnostic purposes (Wanders *et al.* 2001). Phytanic acid from plasma enters the peroxisome in association with the sterol carrier protein-2 (SCP2) and is metabolized by a four-step initial α -oxidation pathway (Fig. 2). Unusually, it appears this pathway can equally well metabolize two stereoisomers of its substrate, i.e. both the (3*R*)- and (3*S*)-epimers of phytanic acid. Initially, phytanic acid (1a) is thioesterified with coenzyme A (CoA) to give phytanoyl-CoA (1b), which is then hydroxylated to give 2-hydroxy-phytanoyl-CoA (2b). One carbon atom is then removed from the latter in a lyase reaction to give epimeric pristanal (3) and formyl-CoA (4b). Pristanal (3) is then oxidized to pristanic acid (5a). Pristanic acid is then thioesterified using CoA to give the epimeric (2*R,S*) mixture. The action of a α -methylacyl-CoA 'racemase' converts the (2*R*)- epimer to the (2*S*)- epimer. Further degradation of (2*S*)-pristanic acid by the stereospecific β -oxidation pathway then occurs, with the release of propionyl and acetyl-CoA units (Ferdinandusse *et al.* 2000). Further β -oxidation reactions (including epimerization) are required to generate the dimethylundecanoic (6), dimethylnonanoic (7) and methyl-heptanoic acid derivatives, which are finally exported for mitochondrial β -oxidation (Ferdinandusse *et al.* 1999).

The enzyme responsible for esterification of phytanic acid with CoA has not been unequivocally identified. Candidates, based on cell extract studies, include a non-specific long chain fatty acyl (LCFA)-CoA synthetase (Watkins *et al.* 1996) and a specific enzyme, which has not been cloned (Pahan *et al.* 1993). Completion of the pathway requires thioesterification of pristanic acid by LCFA-CoA synthetase, the product of the α -oxidation pathway, before β -oxidation can take place.

The second (hydroxylation) step is catalysed by phytanoyl-CoA 2-hydroxylase (PAHX; Jansen *et al.* 1997; Mihalik *et al.* 1997). In many regards this enzyme appears to be a typical member of the family of non-haem, iron(II) and 2-oxoglutarate-dependent oxygenases (Mihalik *et al.* 1995; Prescott and Lloyd 2000; Kershaw *et al.* 2001; Mukherji *et al.* 2001a), and it contains the 2-*His*-1-carboxylate (HXD) iron(II)-binding motif (amino acids 175–177) typical of these oxygenases (Hegg 1997). The enzyme exists in two active forms, a pro-protein containing the PTS-2 signal, and a mature (peroxisomal) protein in which this signal is removed. The enzyme can apparently utilize both epimers of phytanoyl-CoA as substrates (Kershaw *et al.* 2001; Mukherji *et al.* 2001a). In addition to its role in the α -oxidation pathway, recent results indicate that PAHX might play other roles in the cell, including cell signalling and blood coagulation (Chambraud *et al.* 1999; Chen *et al.* 2001). These putative roles are unconnected with its role in the α -oxidation pathway.

The third (cleavage) step is performed by 2-hydroxyphytanoyl-CoA lyase (2HPCL) (Foulon *et al.* 1999). The reaction requires thiamine pyrophosphate (TPP) as a cofactor, and presumably its mechanism proceeds via the addition of TPP to the thioester followed by the rupture of the C-1, C-2 bond of (2b). The products of the reaction are formyl-CoA (4b), which is subsequently converted to formate (4a) (Croes *et al.* 1996), and pristanal (3) (Verhoeven *et al.* 1997). Formate (4a) may be further metabolized via one-carbon pathways outside the peroxisome. Other hydroxylated CoA derivatives can also be utilized as substrates by this enzyme (Foulon *et al.* 1999; Jansen *et al.* 2001). However, high-level expression of 2-hydroxy acid oxidases (HAOXs) in the liver, of which HAOX-2 shows the highest ability to metabolize 2-hydroxy-palmitate, suggests that these enzymes may have a role in metabolism of 2-hydroxy-phytanoyl-CoA through a 2-keto derivative (Jones *et al.* 2000). The substrate specificity of these enzymes with 2-hydroxy-phytanoyl-CoA has not been investigated.

The fourth (oxidation) step from pristanal (3) to pristanic acid (5a) has been shown to be a NAD⁺-dependent reaction in liver peroxisomal extracts, although little is known about the enzyme (Jansen *et al.* 2001). It has been suggested that the dehydrogenase responsible is identical to the deficient enzyme in Sjögren–Larsson syndrome (OMIM 270200) (Verhoeven *et al.* 1997; Sillen *et al.* 1998) although other data does not support this identification (Jansen *et al.* 2001).

Molecular genetics

Two groups identified the gene for PAHX simultaneously in 1997. One group employed molecular cloning using the N-terminal sequence information from the purified native enzyme (Jansen *et al.* 1997). The other identified PAHX via a homologous cloning strategy for enzymes with a PST-2 recognition site similar to that found in 3-ketoacyl-CoA thiolase (Mihalik *et al.* 1997). The human PAHX gene has been localized to chromosome 10p13 in the region between D10S196 and D10S547 by three groups (Nadal *et al.* 1995; Mihalik *et al.* 1997; Wierzbicki *et al.* 2000a). The PAHX gene includes nine exons and codes for a 338 amino acid protein including the 30 amino acid 'signal' domain, which is cleaved on entry into the peroxisome (Jansen *et al.* 2000).

Like all PTS-2-containing proteins, PAHX is transported into peroxisomes by the protein transporter peroxin 7 (Pex 7). Deficiency in this transporter is responsible for type-1 RCDP (Purdue *et al.* 1999). The peroxisomal transport process is complex, and it is interesting to note that PAHX is a ligand for the tacrolimus-binding protein FKBP52, given the occurrence of renal disease in some patients with ARD. This rotamase or peptidyl-prolyl isomerase corresponds to the mouse lupus nephritis antigen LN1. These findings imply that PAHX may have a role in

cytosolic calcineurin-dependent cell signalling pathways, and also may be processed by FKBP52 on entry to the peroxisome (Chambraud *et al.* 1999).

PAHX is an iron(II) and 2-oxoglutarate-dependent oxygenase with little overall sequence similarity to other human oxygenases including prolyl hydroxylase, lysyl hydroxylase, γ -butyrobetaine or N,N',N'' -trimethyl-lysine hydroxylase (Prescott and Lloyd 2000). Numerous mutations in the PAHX have now been described in ARD patients, many of which affect 2-oxoglutarate conversion. Some of the mutations affecting 2-oxoglutarate binding can be rescued *in vitro* by the use of alternative 2-oxoacids as 2-oxoglutarate analogues (Table 1), and this has led to insight into their molecular effects (Mukherji *et al.* 2001a,b). Other mutations probably disrupt the 8-chain β -barrel core of the enzyme (Mukherji *et al.* 2001a).

Despite the new data on PAHX mutations and their consequences, some biochemical aspects of ARD variants remain to be elucidated. Phenotypic variants exist for ARD including one family with concurrent pipecolic academia, which has been found to colocalize to the chromosome 10p13 PAHX locus by heterozygosity mapping (Tranchant *et al.* 1993; Nadal *et al.* 1995). Another atypical ARD family has been identified with pipecolic acidemia and an abnormal catalase distribution, which was associated with a frame-shift mutation in PAHX (Baumgartner *et al.* 2000). This suggests

that PAHX may have a role in the peroxisomal metabolism of lysine metabolites, and it is notable that pipecolic acid oxidase deficiency is a feature of Zellweger's disease. As many as 20% of patients with Refsum's disease may exhibit mildly elevated levels of pipecolic acid (Wierzbicki, unpublished data), and this may be associated with defects in 2-oxoglutarate utilization by PAHX.

Genetic mapping studies of a cohort of 17 patients with ARD has shown that only 45% of cases with classical ARD map to chromosome 10 (Wierzbicki *et al.* 2000a). Recent work has localized the locus for the second form of ARD to chromosome 6q22–24 (Wierzbicki *et al.* 2000b). Biochemical studies of fibroblasts from patients with ARD, but lacking mutations in PAHX, have established that these patients have subtle deficiencies of PTS-2-dependent enzyme functions (plasmalogen synthesis) consistent with it being a mild variant of RCDP (van den Brink *et al.* 2001). A report has previously described a patient with ARD whose complementation group was similar to that found for patients with RCDP (Moser *et al.* 1995). This indicates that Refsum's 'disease' is actually a syndrome with mutations to more than one gene responsible for producing the clinical phenotypes. The recent description of the 'Refsum-like' α -methylacyl-CoA racemase (AMACR) deficiency (OMIM 604489), the symptoms of which include adult onset retinitis pigmentosa and sensory neuropathy with a minor elevation in phytanic

Table 1 Proposed structure-function relationship of mutations to PAHX causing Refsum's disease

Report	Type	Number of patients	Mutation		Functional effect
			Genomic	Protein	
Baumgartner <i>et al.</i> (2000)	Frameshift	1	376delGG	E127R D127X	loss of enzyme
Nadal <i>et al.</i> (1995)	?	1	?	?	loss of enzyme
Jansen <i>et al.</i> (2000)	Point	2	C85T	P29S	mislocalization to cytosol?
	Point	2	C517T	P173S	β -2 strand core disruption
	Frameshift	1	C526A	Q176X	loss of enzyme
	Point	6	A530G	D177G	loss of iron binding
	Point	2	T577C	W193R	β -3 strand core disruption
	Point	1	G589C	E197Q	β -3 strand core disruption
	Point	1	A595T	I199F	β -3 strand core disruption
	Point	2	G610A	G204S	β -4 strand core disruption, uncoupling
	Point	1	C658T	H220Y	?
	Point	6	G734A	R245Q	β -5 strand core disruption
	Point	3	T770C	F257S	β -6 strand core disruption
	Point	1	A805C	N269H	uncoupling
	Jansen <i>et al.</i> (2000)	Point	7	C823T	R275W
Chahal <i>et al.</i> (1998)					
Mihalik <i>et al.</i> (1997)	Point	3	G824A	R275Q	loss of 2-oxoglutarate binding
Jansen <i>et al.</i> (2000)	Splice	8	IVS2–2 A G	Δ Y46-R82	β -1 strand core disruption

Mutations in phytanoyl-CoA 2-hydroxylase (PAHX) giving rise to adult Refsum's disease. PAHX is a member of the 2-oxoglutarate- and non-haem ferrous-dependent oxygenase family. The effects of mutation are based on primary sequence alignments, secondary structure predictions and known motifs from the crystal structures of other oxygenases (modified from Mukherji *et al.* 2001a). X = frameshift mutations leading to truncated PAHX. Uncoupling indicates that 2-oxoglutarate conversion does not always lead to phytanoyl-CoA oxidation.

acid levels but gross pristanic acidemia, also favours this hypothesis (Ferdinandusse *et al.* 2000).

No PAHX-deficient animal model has been produced to date. However, a clinical phenotype broadly similar to human ARD can be generated in mice by the deletion of the SCP-2 gene (Seedorf *et al.* 2000). These mice develop ataxia when fed diets rich in phytanic acid and are prone to die *in utero* of cardiac arrhythmias. However, they seem to lack the ocular features of ARD, which would be expected if the pathway was inducible by phytanic acid (Zomer *et al.* 2000a). Their biochemical phenotype includes elevations in both phytanic and pristanic acid and possibly subtle defects in steroid hormone synthesis (Ellinghaus *et al.* 1999). In man, the SCP-2 gene is located on chromosome 2 and mapping has excluded this region as a candidate area for ARD (Wierzbicki AS, unpublished data).

Unanswered questions

The exact mechanism of the toxicity of phytanic acid to neuronal, cardiac and bone tissue remains obscure. Some studies have indicated that it is directly toxic to ciliary ganglion cells and induces calcium-driven apoptosis in Purkinje cells (Powers *et al.* 1999). Structural homology between phytanic acid and vitamin A (11-*cis*-retinol), vitamin E (α -tocopherol), geranyl-pyrophosphate (GPP) and farnesyl pyrophosphate (FPP) has been noted (Wanders *et al.* 2001), but little work has been completed to investigate whether they are metabolized via the α -oxidation pathway. Phytanic acid may also have a role in the regulation of isoprenoid metabolism and protein prenylation, if it does compete for receptor binding with other isoprenoids of similar structure. Reduction of intracellular levels of the isoprenoids FPP and GPP is a key non-lipid lowering action of cholesterol-lowering drugs: the statins (HMG-CoA reductase inhibitors), which are used to treat atherosclerosis (Torra *et al.* 2001). The effects of phytanic acid on isoprenoid levels has not been investigated though cholesterol, and phytanic acid transport and metabolism are closely linked.

Whether the neurological and ophthalmological symptoms of ARD are directly caused by the toxic effects of the phytanic acid itself, or by the dysfunction of calcineurin or isoprenoid-controlled metabolism, remains to be determined. LCFA-CoA synthetase is promiscuous with regard to substrates and non-heme oxygenases are often able to oxidize alternative substrates. Thus, the possibility exists that the α -oxidation pathway may be involved in the degradation of many branched-chain lipids, of which phytanic acid is only one.

The identity of the other genes involved in producing the ARD phenotype is becoming clearer with the identification of a second locus for Refsum's disease (Wierzbicki *et al.* 2000b) and the identification of substantial phenotypic heterogeneity in RCDP (van den Brink *et al.* 2001). Although the

2-hydroxyphytanoyl-CoA lyase gene has been recently cloned, no mutations in it have yet been identified and there is no record of any patient with excess 2-hydroxyphytanic acid in plasma. The clinical phenotype of lyase deficiency would be predicted to share many features with RCDP and ARD.

Long-term prospects for treatment (at least some forms) of ARD are good as it is one of the few inherited disorders of metabolism with an exogenous precipitating cause, and an *in vitro* gene therapy approach has been successful in restoring enzyme activity (Chahal *et al.* 1998). Reduction of dietary phytanic acid is already successful in ameliorating some symptoms, but newer more efficacious therapies are still required to fully reverse the progression of this disease.

The wider significance of phytanic acid metabolism

Refsum's disease and associated disorders would be considered biochemical curiosities with little wider relevance to human disease if it were not for the fact that phytanic acid seems to play a key role in the regulation of peroxisomal number and activity. PPARs are involved in the regulation of lipid and glucose metabolism, obesity, inflammation, atherosclerosis and carcinogenesis, whereas peroxisomal enzyme deficiencies are clearly associated with neurological disease (Torra *et al.* 2001). Phytanic acid in rodents is a ligand for the PPAR- α receptor (Ellinghaus *et al.* 1999; Gelman *et al.* 1999), which is the target for the fibrate groups of drugs (Staels *et al.* 1998). However, differences in sterol metabolism between humans and mice suggest that the intracellular role of phytanic acid may differ substantially between rodents and man. In rodents, phytanic acid regulates nuclear retinoid-X receptors (RXR) (Kitareewan *et al.* 1996; Lemotte *et al.* 1996; Seedorf *et al.* 1998), PPAR- α (Ellinghaus *et al.* 1999), and the expression of liver fatty acid binding protein (Wolfrum *et al.* 1999). This suggests that phytanic acid may be the natural ligand for the 'orphan' PPAR- α receptor in rodents and that the α -oxidation pathway is the mechanism for inactivating this signal. However, in human cell lines phytanic acid regulates PAHX expression independently of its effects on PPAR- α or RXR (Zomer *et al.* 2000b). This implies that an alternative pathway exists in man to control the metabolism of isoprenoid lipids, and that other lipids may be the principal PPAR- α ligands in humans. The differences in the regulatory functions may also explain the differences in presentation between the SCP-2(-) mouse and human ARD or AMACR deficiency, and the relatively slow onset of the major clinical features in man compared with mouse. Additionally the possible non-peroxisomal roles of PAHX in regulation of tacrolimus binding-proteins and in the control of the levels of clotting factor VIII imply this enzyme may have other unidentified roles in metabolism (Chambraud *et al.* 1999; Chen *et al.* 2001).

The role of phytanic acid metabolism in common human neurodegenerative diseases remains to be determined.

However, the close relationship of peroxisomes to neurological disease and lipid metabolism to stroke, vascular dementia, and Alzheimer's disease, mean that it is likely to be significant.

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