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PEX7 Mutations Cause Congenital Cataract Retinopathy and Late-Onset Ataxia and Cognitive Impairment: Report of Two Siblings and Review of the Literature

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Adult Refsum disease (ARD) is a progressive multisystem disorder that is characterized by retinitis pigmentosa, hearing and smell loss, skeletal deformities, and elevated levels of phytanic acid (PA) in tissues. Peripheral neuropathy, cardiac abnormalities, and skin ichthyosis are considered subsequent manifestations, and are often described in patients not treated with PA dietary restriction. Mutations of the gene encoding the phytanoyl-coenzyme A (CoA) hydroxylase enzyme *(PHYH)* are the major genetic cause of ARD,[1] and in a small number of cases a second gene, *PEX7*, which encodes peroxin 7 receptor protein (PEX7), has been associated with the ARD phenotype.[2]

We observed two Italian siblings who presented with late-onset progressive ataxia and cognitive decline. They comprised a 56-year-old woman and her 63-year-old brother, born from consanguineous parents, and presented with infantile bilateral cataract and retinitis pigmentosa. Except for the visual defect, both siblings exhibited normal psychomotor development. In adulthood (at age 40 years for the brother and 53 years for the sister), both patients manifested progressive behavioral and cognitive abnormalities associated with ataxic gait. At the latest examination, at ages 57 and 63 years, respectively, they presented with dementia (Mini-Mental State Examination scores of 19/30 and 13/30, respectively), motor apraxia, ophthalmoparesis, mild dysarthria, ataxic gait, mild limb dysmetria, Babinski sign, and decreased lower-limb deep-tendon reflexes. Neither of the patients had hearing loss, anosmia, or short metacarpals/metatarsals, and only the brother presented with dilated cardiomyopathy. Brain MRI revealed mild diffuse atrophy, and muscle biopsy sampling revealed normal morphology. Nerve conduction studies demonstrated a mild motor demyelinating neuropathy in the lower limbs, and somatosensory evoked potentials revealed a prolongation of the central conduction time.

Both patients also presented with increased plasma PA levels (387.5 and 188.9 μmol/L), suggesting a diagnosis of ARD. Mutational screening of *PHYH* was negative, but there was a novel homozygous mutation in *PEX7*, p.Leu12Pro, caused by a T>C transition at nucleotide 35 (c.35T>C). This missense variation involved a well-conserved residue, and has not been reported as a single-nucleotide polymorphism (SNP) in the Human Gene Mutation Database, National Center for Biotechnology Information database for SNPs (dbSNP132ver) or Exome Variant Server. *In silico* analyses predicted the mutation as probably damaging: the scores were 0.98 (PolyPhen-2-HumDiv), 0.635 (PolyPhen-2-HumVar), and 0 (Sorting Tolerant From Intolerant). The parents were not available for segregation analysis, and an asymptomatic brother was found to be heterozygous for this mutation. The patients refused a skin biopsy procedure, preventing investigations of plasmalogen synthesis.[3]

PEX7 mutations are most frequently found in infants affected by rhizomelic chondrodysplasia punctata type 1 (RCDP1), a congenital and rapidly worsening syndrome that is char-

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Table 1. Clinical, biochemical, and genetic characteristics of the patients with *PEX7* gene mutations associated with Refsum disease phenotype, including the cases described in this study and review of the literature

Fam N.	*PEX7* gene mutations	Pt N.	First symptoms	Age at onset (years)	Age at exam	Retinopathy	Cataract	Deafness	Anosmia	Neuropathy	Gait ataxia	Cognitive impairment	Epilepsy	Cardiopathy	Ichthyosis	Short fifth metacarpal	Pes cavus	Phytanic acid (μmol/L)	Reference
1	c.120 C>G c.12_18dupGTGCGGT	1	Ataxia	12	19	+	-	-	+	+	+	-	-	-	+	+	+	400	2
		2	Ataxia	20	20	+	-	-	+	+	+	-	-	-	-	-	+	1,950	
		3	Retinopathy, anosmia	24	24	+	-	-	+	-	-	-	-	-	-	-	-	372	
2	c.40 A>C c.120 C>G	4	Congenital cataract	1	25	+	+	-	-	+	+	-	-	-	-	+	-	198	2
		5	Ataxia, retinopathy	34	34	+	-	-	-	-	+	-	-	-	-	-	-	142	
3	c.345T>G IVS3-10A>G	6	Retinopathy, hearing defect, anosmia	7	64	+	-	+	+	+	+	-	-	+	+	-	-	1,200	3, 5
4	c.74C>T c.653C>T	7	Cataract	2	13	-	+	-	-	-	-	-	-	-	-	-	-	n.a	3
5	(5'UTR) c.-45C>T c.875T>A	8	Refsum disease phenotype	12	18	+	n.a	n.a	n.a	+	+	+	n.a	n.a	n.a	n.a	n.a	n.a	3
6	c.35 T>C c.35T>C	9	Congenital cataract, retinopathy	1	56	+	+	-	-	+	+	+	+	-	-	-	-	388	This study
		10	Congenital cataract, retinopathy	1	63	+	+	-	-	na	+	+	-	+	-	-	-	189	

n.a.: not available.

acterized by rhizomelia, chondrodysplasia punctata, cataract, and severe growth and mental retardation.[3] The protein encoded by *PEX7*, Pex7, is essential for peroxisomal delivery of matrix enzymes containing the peroxisomal targeting signal type 2 in the amino acid sequence, including the phytanoyl-CoA hydroxylase and the plasmalogen synthesis apparatus.[4] In both RCDP1 and ARD, patients present with elevated PA levels due to either a defect in the peroxisomal import of the metabolic enzymes or a primary loss-of-function of the phytanoyl-CoA hydroxylase enzyme.[4]

Several *PEX7* mutations have so far been described in association with the RCDP1 phenotype. Only eight patients with *PEX7* mutations and the Refsum phenotype have been reported, and in all of these cases the presentation was consistent with the ARD phenotype with a mild disease course (Table 1).[2,3,5] In the previously reported cases, the most frequent disease manifestations were retinopathy, cataract, anosmia, hearing loss, and neuropathy (Table 1). In the cases described herein, the ocular abnormalities were also the earliest signs, but neither anosmia nor deafness was observed, while in the fifth decade both siblings developed progressive signs of dementia and ataxia. It is known that the clinical severity of this disease is associated with the residual activities and reduced amounts of Pex7.[3] In particular, functional and modeling analyses have demonstrated that missense mutations associated with a severe phenotype are located in within the β sheets, probably causing a disruption of the protein structure.[3] The p.Leu12Pro mutation, unlike previous missense mutations, is not located on the WD-40 repeat motif in *PEX7*, and it can be hypothesized that a less adverse effect on protein structure—allowing correct folding and greater residual activity—can account for the mild phenotype in these two patients.

Conflicts of Interest

The authors have no financial conflicts of interest.

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