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Review article

Molecular and clinical findings and diagnostic flowchart of peroxisomal diseases

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Abstract

Peroxisomal diseases are categorized into three large groups – peroxisome biogenesis disorders (PBD), single enzyme deficiencies (SED) and contiguous gene syndrome. Thirteen complementation groups and PEX genes responsible for all subgroups of PBD, plus 10 diseases and their responsible genes in SED have been identified. We have established a diagnostic system for peroxisomal diseases in Japan, and identified 45 Japanese patients with PBD, 12 patients with beta-oxidation enzyme deficiencies and more than 100 patients with adrenoleukodystrophy (ALD). It is important for effective therapy of the cerebral form of ALD to diagnose earlier after onset, and pre-symptomatic diagnosis should also be valuable. The division of diagnostic system into several specified centers of peroxisomal diseases in the whole world should be functional for overcoming these rare inherited neurometabolic diseases.

Keywords: Peroxisomal diseases; Zellweger syndrome; Adrenoleukodystrophy; Diagnostic screening system

1. Introduction

Peroxisomes are single-membrane lined organelles present in all eukaryotic cells, which catalyze a range of essential metabolic functions, such as beta-oxidation of very long-chain fatty acids (VLCFA), branched-chain fatty acids and bile acids, phytanic acid alpha-oxidation, plasmalogen synthesis, cholesterol synthesis, glyoxylate catabolism and catalase. Inborn errors of peroxisomal metabolism, an expanding group of genetic disorders in humans, have been divided into three groups [1]. First, peroxisome biogenesis disorders (PBD) (MIM 601539) include the Zellweger spectrum, containing the Zellweger syndrome (ZS) (MIM 214100), neonatal adrenoleukodystrophy (NALD) (MIM 202370) and infantile Refsum disease (IRD) (MIM 266510), and rhizomelic chondrodysplasia punctata (RCDP) type 1 (MIM 215100). Second, single enzyme deficiencies (SED) include impaired beta-oxidation of fatty acids containing X-linked adrenoleukodystrophy (ALD) (MIM 300100), straight-chain acyl-CoA oxidase (ACOX1) deficiency (MIM 264470), D-bifunctional protein (DBP) deficiency (MIM 261515), sterol carrier protein X (SCPx) deficiency (MIM 613724) and 2-methylacyl-CoA racemase (AMACR) deficiency (MIM 604489), and impaired plasmalogen biosynthesis containing RCDP type 2 caused by dihydroxyacetone phosphate (DHAP) acyltransferase deficiency (MIM 222765) and RCDP type 3 caused by alkyl-DHAP synthase deficiency (MIM 600121). Further, SED include classical Refsum disease (MIM 266500), acatalasemia (MIM 115500), and hyperoxaluria type 1 (MIM 259900). The third major classification of peroxisomal diseases includes CADDS caused by contiguous deletion of the ALD gene (*ABCD1*) and its upstream gene, *DXS1357E* (MIM 300475) (Table 1).

We review here the clinical, biochemical and molecular findings of peroxisomal diseases, especially PBD and ALD, and introduce our screening and diagnostic

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Table 1
Peroxisomal diseases.

(A) Peroxisome biogenesis disorders (PBD)
Zellweger spectrum
Zellweger syndrome (ZS)[a] [MIM 214100]
Neonatal adrenoleukodystrophy (NALD)[a] [MIM 202370]
Infantile Refsum disease (IRD)[a] [MIM 266510]
Rhizomelic chondrodysplasia punctata (RCDP) type 1[a] [MIM 215100]
(B) Single peroxisomal enzyme deficiencies
Beta-oxidation of fatty acids
X-linked adrenoleukodystrophy (ALD)[a] [MIM 300100]
Acyl-CoA oxidase (ACOX1) deficiency[a] [MIM 264470]
D-Bifunctional protein (DBP) deficiency[a] [MIM 261515]
Sterol carrier protein X (SCPx) deficiency[a] [MIM 613724]
2-Methylacyl-CoA racemase (AMACR) deficiency[a] [MIM 604489]
Etherphospholipid biosynthesis
Dihydroxyacetone phosphate (DHAP) acyltransferase deficiency (RCDP type 2)[a] [MIM 222765]
Alkyl-DHAP synthase deficiency (RCDP type 3)[a] [MIM 600121]
Alpha-oxidation of fatty acids
Refsum disease (Phytanoyl-CoA hydroxylase deficiency)[a] [MIM 266500]
Hydrogen peroxide metabolism
Acatalasemia (Catalase deficiency) [MIM 115500]
Glyoxylate detoxification
Hyperoxaluria type 1 (Alanine glyoxylate aminotransferase deficiency) [MIM 259900]
(C) Contiguous gene syndrome
Contiguous ABCD1 DXS1357E deletion syndrome (CADDS)[a] [MIM 300475]

[a] Detectable diseases by our diagnostic screening system, using GC/MS.

system for these intractable neurometabolic diseases in Japan.

2. Molecular, biochemical and clinical findings of peroxisome biogenesis disorders

Peroxisomal proteins can be imported into the peroxisomes post-translationally by the functions of many PEX gene products, peroxins via peroxisome targeting sequences, PTS1, and PTS2 (Fig. 1). One PEX gene defect can lead to the failure of many peroxisomal protein imports and multiple peroxisomal metabolic dysfunctions, such as beta-oxidation and plasmalogen synthesis, and therefore PBD, which occur due to a mutated PEX gene, result in showing similar phenotypes, even from a different PEX gene defect.

PBD are genetically heterogeneous and have so far been classified into 13 complementation groups (CGs) which include: 12 groups in the Zellweger spectrum and 1 group in RCDP type 1 (Table 2) [2]. The PEX genes responsible for all 13 CGs so far clarified include the following: *PEX5* and *PEX7* encode the receptors for the PTS1 and PTS2 proteins which cycle between the cytosol and the peroxisome. *PEX1*, *PEX6* and *PEX26* encode the proteins which might be involved in the recycling of PTS1 and PTS2 protein receptors. *PEX2*, *PEX10* and *PEX12* encode the proteins, which might be involved in the translocation of the matrix proteins. *PEX13* and *PEX14* encode the docking factor for *PEX5* protein-mediated protein import. *PEX3*, *PEX16* and *PEX19* encode the proteins which might be involved in peroxisomal membrane-protein (PMP) biogenesis, including their import [3]. Among these PEX genes, *PEX7*, which is the receptor of PTS2 proteins, affects only the PTS2 protein function, and therefore patients with a *PEX7* gene defect; RCDP type 1 manifests different biochemical and clinical findings from those of the Zellweger spectrum, caused by the other 12 PEX gene defects except for *PEX7* (Fig. 1 and Table 2).

We have already subdivided these groups into two major categories [4]: one contains groups D, G and J with *PEX16*, *3* and *19* as the defective genes, respectively, and whose fibroblasts lack not only peroxisomal matrix-protein import but also peroxisomal membrane structures, which means these groups may be caused by a defect in peroxisomal membrane protein (PMP) synthesis. The other category includes the rest of the CGs and these are caused by defects in peroxisomal matrix-protein import and not in the biogenesis of PMPs. Hence, these fibroblasts were found to have peroxisomal remnant membrane structures (ghost peroxisomes) (Table 2).

ZS is the most severe phenotype of PBD, whose patients manifest facial dysmorphism, severe hypotonia from the neonatal period, psychomotor retardation, hepatomegaly with prolonged jaundice and liver dysfunctions, renal cortical microcysts, ventricular enlargement in the brain and abnormal calcific stippling of multiple joints. These patients usually die in early infancy. Neuropathologic lesions in ZS patients are characterized by abnormalities in neuronal migration or differentiation, defects in the formation or maintenance of central white

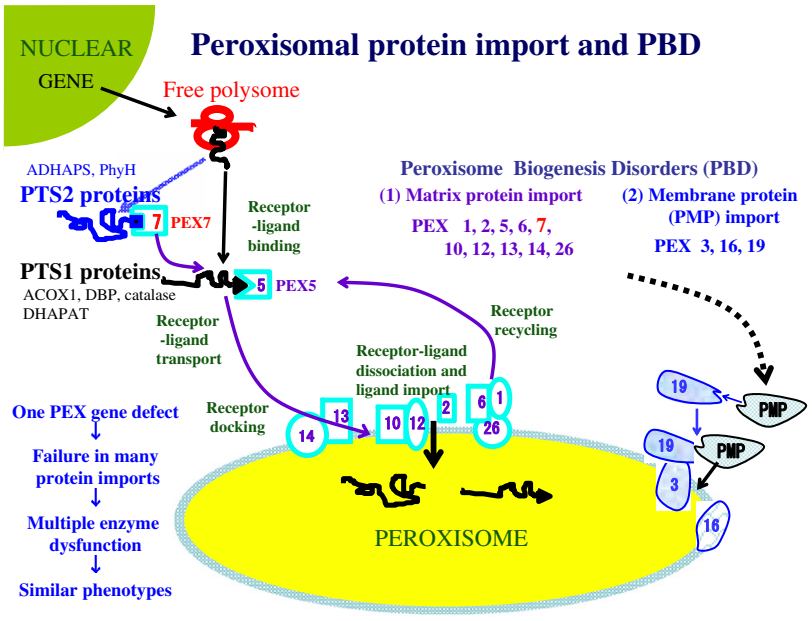

Fig. 1. Peroxisomal protein import and peroxisome biogenesis disorders. ADHAPS, alkyl-DHAP synthase; PhyH, phytanoyl-CoA hydroxylase; DHAPAT, DHAP acyltransferase.

Table 2
Complementation groups of peroxisomal biogenesis disorders.

Gifu	KKI	Phenotypes	Ghost peroxisomes	Gene	Japanese patients
A	8	ZS, NALD, IRD	+	*PEX26*	6 ZS, 1 NALD
B	7	ZS, NALD	+	*PEX10*	18 ZS
C	4	ZS, NALD	+	*PEX6*	6 ZS
D	9	ZS	−	*PEX16*	
E	1	ZS, NALD, IRD	+	*PEX1*	8 ZS, 2 NALD
F	10	ZS, IRD	+	*PEX2*	2 ZS
G	12	ZS	−	*PEX3*	
H	13	ZS, NALD	+	*PEX13*	
J	14	ZS	−	*PEX19*	
K		ZS	+	*PEX14*	1 ZS
	2	ZS, NALD, IRD	+	*PEX5*	1 ZS
	3	ZS, NALD, IRD	+	*PEX12*	
R	11	RCDP	+	*PEX7*	3 RCDP

Gifu, complementation grouping at Gifu University;
KKI, complementation grouping at Kennedy Krieger Institute;
ZS, Zellweger syndrome; NALD, neonatal adrenoleukodystrophy;
IRD, infantile Refsum disease; RCDP, rhizomelic chondrodysplasia punctata.

matter, and post-developmental neuronal degeneration. Most patients with ZS show epileptic seizures in early neonatal periods, and EEGs revealed continuous negative sharp waves and spikes at the vertex [5]. Japanese patients with ZS were also reported to have partial motor seizures, which did not culminate in generalized tonic-clonic seizures and were easily controlled by antiepileptic drugs [6].

NALD patients have less severe clinical phenotypes than ZS and usually die during the late infantile period, specifically manifesting mild facial dysmorphism and no chondrodysplasia, whereas developmental regression and intractable seizure during the clinical courses, and demyelination and progressive cortical atrophy in the brain can be seen remarkably, which may be due to longer survival than ZS patients. The first reported case of NALD developed seizures at 4 days and a hypsarrhythmic EEGs at 2 months, and the seizures continued to be severe and intractable [7]. Japanese cases with NALD were also reported to have intractable tonic seizures or epileptic spasms, and abnormal interictal EEGs consisting of high-voltage slow waves and bilateral independent multifocal spikes [6]. Epileptic seizures in NALD are usually more severe than those in ZS.

The phenotype of IRD, the mildest phenotype in PBD, is very different from that of ZS, characterized by hearing impairment, retinal degeneration and mild psychomotor retardation, and usually survives longer than the second decade of life. 7 of 23 cases of PBD with prolonged survival developed seizures [8]. These three phenotypes are distinctive forms of the Zellweger spectrum in PBD (Table 1). In the fibroblasts from patients with the Zellweger spectrum, both the C-terminal peroxisome targeting sequence, PTS1, and N-terminal peroxisome targeting sequence, PTS2, are impaired, resulting in little peroxisomal function.

Another spectrum is the RCDP type 1, caused by a defect in the *PEX7* gene encoding a receptor for matrix proteins with PTS2, therefore, those patients show only PTS2 protein dysfunction, such as plasmalogen synthesis and phytanic acid oxidation. RCDP type 1 is a fatal disease characterized by the presence of calcific stippling of multiple joints, disproportionately short stature with symmetric shortening of the proximal extremities, typical craniofacial dysmorphism, and severe mental and growth retardation. Most patients die in the first year or two of life, but some not until the second decade of life.

3. Molecular, biochemical and clinical findings of adrenoleukodystrophy

ALD is the most common peroxisomal disease, with impaired beta-oxidation of saturated VLCFA, resulting in the accumulation of VLCFA in tissues and plasma. The responsible gene for ALD, *ABCD1*, has been mapped to Xq28, and the gene product, ALDP, is a peroxisomal membrane protein with homology to the ATP-binding cassette (ABC) transporter superfamily of proteins, which can act as a transporter of VLCF acyl-CoA across the peroxisomal membrane.

There are many clinical phenotypes, such as the childhood cerebral form (CCALD) with cerebral demyelination and childhood onset, the adolescent cerebral form (AdoCALD), the adult cerebral form (ACALD), adrenomyeloneuropathy (AMN) with axonopathy of the pyramidal and somatosensory tracts and peripheral neuropathy, the olivo-ponto-cerebellar (OPC) form, and Addison only [9]. CCALD is the most common phenotype and characterized by progression of intellectual, psychic, visual and gait disturbances during school age. Patients are often misdiagnosed as having attention-deficit hyperactivity disorder (ADHD), psychologic problems, and ophthalmic or ear abnormalities at the onset of initial symptoms. Therefore, quite a number of patients are not diagnosed until further symptoms appear, such as seizures, gait disturbances and other neurologic symptoms. Nearly all the patients develop focal or generalized seizures at some stage of the illness, and a seizures was the first neurologic manifestation in 7% [9]. Brain MRI shows characteristic findings of enhanced T2 signals even at the early stage of diseases. The prognosis is generally very poor and patients were found to die within a few years, however, good general care improves the prognosis these days. The appearance of each symptom in AdoCALD occurs later than CCALD, and the progression is somewhat slower.

The ACALD characterized by slower progression of neuropsychological symptoms, is sometimes misdiagnosed as dementia or psychologic disorders, and is more common in Japan than in Western countries from the evidence of a retrospective nationwide epidemiological survey of ALD in Japan during the 1990s (Table 3) [10]. Most AMN patients manifest slowly progressive gait disturbances as the initial symptoms, and sensory and autonomic disturbances occur in some patients. The mean age of onset of AMN was 30.2 (13–51) years in Japan [10], and about half of these patients showed cerebral involvement about 10 years after onset [11]. The OPC form has been reported predominantly from Japan [12], manifesting a gait disturbance as the initial symptom, and cerebellar ataxia become evident several months to 1 year later. About half of the OPC patients also show cerebral involvement, such as intellectual and psychic problems [11]. Patients with Addison only manifest adrenal insufficiency, including unexplained vomiting and weakness or coma between childhood and adulthood.

So far, more than 500 kinds of mutations widely distributed over the *ABCD1* gene have been identified; two regions in the transmembrane domain and the ATP-binding cassette (ABC) region in ALDP contain the majority of missense mutations, which means these domains should be important for the function of ALDP (www.x-ald.nl). There is no relation between these mutations and clinical subtypes [9].

4. Carrier detection and pre-symptomatic diagnosis for early intervention in ALD

Hematopoietic stem cell transplantation (HSCT) is currently the only curative approach preventing the progression of brain involvement in the cerebral form of

Table 3
Adrenoleukodystrophy phenotype distributions in Japan (1990–1999) [10].

Phenotype	Onset (years)	Number of patients	%
Childhood cerebral	2–10	46	31.7
Adolescent cerebral	11–19	14	9.6
AMN	13–51	39	26.9
Adult cerebral	21–58	33	22.8
OPC	17–52	13	9.0
Total		145	100

AMN, adrenomyeloneuropathy; OPC, olivo-ponto-cerebellar form.

ALD, however, HSCT is only effective in patients with the early stages of cerebral symptoms [13]. Performance IQ above 80 and MRI severity score (Loes score) of less than 9 are desirable to get a good HSCT result. But in reality, many patients have various manifestations of intellectual, psychic, visual, hearing and gait disturbances at onset, which lead to misdiagnosis such as learning disorders or psychologic problems, resulting in the delay of correct diagnosis, and quite a number of patients cannot undergo HSCT. Therefore, correct and early diagnosis is essential for effective therapy of the cerebral symptoms of ALD.

Furthermore, adrenal hormone therapy is necessary to save the lives of all ALD patients who have adrenal insufficiency, therefore, pre-symptomatic diagnosis by extended familial screening from probands, including carrier detection with genetic counseling, should be valuable for early intervention, not only for patients with cerebral symptoms in order to prepare them for undergoing HSCT, but also for those with adrenocortical insufficiency necessary to replace adrenal steroids. Therefore, diagnosis of pre-symptomatic boys before 3 years of age, and long-term follow-up of subtle neuropsychological signs, brain MRI, electrophysiologic investigation, adrenal function tests, and arrangement of HSCT will be beneficial. Female carrier detection can be done by increased VLCFA in plasma and mutation analysis of the *ABCD1* gene. Elevated VLCFA confirms the diagnosis of a carrier, however, there can be an overlap of the ranges between healthy controls, therefore mutation analysis of the *ABCD1* gene is necessary for carrier detection. Newborn screening may be a potential method to discover pre-symptomatic ALD patients and female carriers widely [14], and recently, hematopoietic stem cell gene therapy was shown to arrest progression in patients with the early stages of cerebral form of ALD [15]. Further treatment strategies are expected.

5. Other peroxisomal diseases

5.1. Impairment of beta-oxidation enzyme

Patients with DBP deficiency show craniofacial dysmorphism, severe hypotonia, poor feeding, and neonatal onset and intractable seizure, and psychomotor delay, whereas those with ACOX1 deficiency show hypotonia, seizure, and psychomotor delay but no craniofacial dysmorphism. The phenotypes of both groups are similar to those of the Zellweger spectrum, and DBP is more severe than ACOX1 deficiency. 36 of 38 patients with DBP deficiency had neonatal seizures, and EEGs revealed multifocal spikes [16]. Seizures in DBP deficiency are usually more severe and intractable than those in ACOX1 deficiency. ACOX1 is only responsible for the oxidation of VLCFA resulting in an elevated VLCFA level in the serum of patients with ACOX1 deficiency, whereas DBP is involved in the oxidation of VLCFA, pristanic acids, plus di- and tri-hydroxycholestanoic acid resulting in the accumulation of VLCFA, pristanic acid, and di- and trihydroxycholestanoic acid in the plasma of patients with DBP deficiency. AMACR is responsible for the conversion of pristanoyl CoA and 27-bile acyl CoAs to their (S)-stereoisomers and consequently the accumulation of pristanic acid and bile-acid intermediates in patients with AMACR deficiency who suffer from adult-onset sensorimotor neuropathy [16]. SCPx is a peroxisomal enzyme with thiolase activity, which is required for the breakdown of branched-chain fatty acids. Such patients have leukoencephalopathy with dystonia and motor neuropathy [17].

5.2. Impairment of ether phospholipid biosynthesis

The first and second steps of ether phospholipid biosynthesis are performed in peroxisomes by DHAP acyltransferase (PTS1 protein) and alkyl-DHAP synthase (PTS2 protein). Clinical findings of both deficiencies show rhizomelic shortening of the upper extremities, typical facial appearance, cataract, dwarfism and severe mental retardation, therefore the former is named RCDP type 2 and the latter RCDP type 3. The biochemical findings are decreased plasmalogen in the serum from all types of RCDP, including type 1 due to a *PEX7* gene defect, but only type 1 shows elevated phytanic acids. Final diagnosis of RCDP types 1, 2 and 3 requires molecular analysis of the gene encoding PEX7, DHAP acyltransferase and alkyl-DHAP synthase, respectively [18].

5.3. Contiguous gene syndrome

5.3.1. Contiguous *ABCD1* and *DXS1357E* deletion syndrome (CADDS)

Three male patients manifested profound neonatal hypotonia, subsequent failure to thrive, cholestatic liver disease, and accumulation of VLCFA, which were similar to patients with the Zellweger syndrome, however, biochemical and morphological findings suggested normal peroxisomal biogenesis, except for a lack of ALDP protein. Molecular analysis revealed a deletion that extended into the promoter region of *ABCD1* and the neighboring gene, BCAP31 (*DXS1357E*) [19].

6. Diagnostic system of peroxisomal diseases in Gifu University

First, for the screening of peroxisomal diseases, we analyze VLCFA, polyunsaturated fatty acids including phytanic acid and plasmalogen in serum or plasma, using gas chromatography/mass spectrometry analysis (GC/MS) [20]. This method allows for the detection of

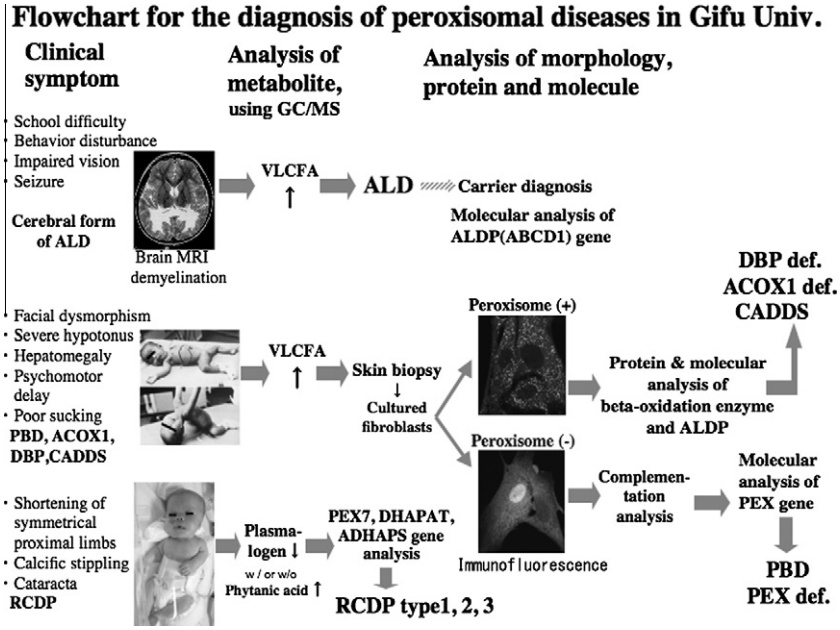

Fig. 2. Flowchart for the diagnosis of peroxisomal diseases in Gifu University.

PBD (the Zellweger spectrum and RCDP type 1), ALD, peroxisomal beta-oxidation enzyme (ACOX1, DBP, SCPx and AMACR) deficiencies, isolated enzyme deficiencies of etherphospholipid biosynthesis (RCDP type 2 and 3), Refsum disease and CADDS (Table 1). After that, we proceed with further analysis of peroxisomes for the final diagnosis by referring to Fig. 2, as follows. Patients suspected of ALD are diagnosed by increased VLCFA using GC/MS, and then we proceed to protein and molecular analysis of the *ABCD1* gene. Patients suspected of PBD/ACOX1/DBP deficiency and CADDS are screened by increased VLCFA, and then we examine the peroxisome biogenesis in the patient's fibroblasts. In the case of normal peroxisome assembly, ACOX1/DBP deficiency and CADDS are determined by protein and molecular analysis of the beta-oxidation enzyme and ALDP. In the case of abnormal peroxisome assembly, we proceed to complementation analysis among the CGs of the Zellweger spectrum by cell fusion, since there are no less than 12 different pathogenic genes in the Zellweger spectrum. If pathogenic genes are different from each other, catalase-containing particles (peroxisomes) will be found in multinuclear cells after cell fusion [4]. The final diagnosis of the Zellweger spectrum is determined by molecular analysis of the *PEX* gene. In patients suspected of RCDP, we screen peroxisomal diseases by decreased plasmalogen in the serum from the patients, using GC/MS, and the diagnosis of RCDP type 1 can be determined by increased phytanic acids and *PEX7* mutation analysis. It is possible to determine the diagnosis as RCDP type 2 and 3 by the detection of decreased plasmalogen, plus SCPx/AMACR deficiency and Refsum disease by increased phytanic acid in the serum from these patients, using GC/MS and the following molecular analysis (Fig. 2).

7. Peroxisomal diseases in Japan

We have identified 39 patients with ZS, 3 with NALD, 3 with RCDP type 1, 9 with DBP deficiency, 3 with ACOX1 deficiency, 102 patients with ALD and 1 patient with CADDS during the last 25 years in Japan (Table 4). The PBD patients were genetically subdivided into complementation groups A, B, C, E, F, K, 2 and R (Table 2). Seven patients in group A and 16 in group B had a common mutation, a homozygous missense mutation in *PEX26* and a 2-base-pair deletion in *PEX10* [21]. To determine whether these highly frequent mutations are due to a founder effect, we analyzed single nucleotide

Table 4
Japanese patients with peroxisomal diseases in Gifu University.

Peroxisomal diseases	Cases	Life span (age range)
Zellweger syndrome (ZS)	39	2–14 months
Neonatal adrenoleukodystrophy (NALD)	3	20–33 months
Rhizomelic chondrodysplasia punctata type 1	3	0 month–>5 years
Acyl-CoA oxidase (ACOX1) deficiency	3	3–11 years
D-Bifunctional protein (DBP) deficiency	9	6 months–4 years
Adrenoleukodystrophy (ALD)	102	
Contiguous gene syndrome (CADDS)	1	8 months
Total	160	

polymorphisms within *PEX26* and *PEX10* among the patients and Japanese controls. Both mutations apparently arose once on each ancestral chromosome in the Japanese population. Although we have exhaustively diagnosed the patients with PBD and beta-oxidation enzyme deficiencies, ALD patients have been diagnosed by our system and elsewhere in Japan. We have mainly diagnosed CCALD and AdoCALD patients among the ALD phenotypes. No patient with IRD, SCPx and AMACR deficiency has been found in Japan, because it is possible that information on peroxisomal diseases has not infiltrated enough into the whole of Japan.

There must be a lot of undiagnosed and untreated patients with peroxisomal diseases in the world, especially Afro-Asian countries, and therefore it is necessary to establish a diagnostic system beyond the boundary of countries, which should lead to overcoming these intractable diseases.

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