Chapter 5
Peroxisomal Disorders

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Abstract Peroxisomal disorders (PD) are genetic disorders caused by peroxisome dysfunction and are classified into two groups: genetic defects in peroxisome-localized proteins and genetic defects in peroxisomal biogenesis. The dawn of PD research came with the detailed analysis of the Zellweger syndrome, the prototype of PD. Even recently, new PD are still being identified by whole-exome sequencing analysis, which means that the concept of PD has been expanding. Furthermore, the role of peroxisome in cancer and age-related diseases has also been studied. In contrast, PD pathophysiology and treatment are not clarified yet completely and even in adrenoleukodystrophy, which is the most common PD, the prognosis of phenotype and disease in pre-symptomatic patients is a difficult task.

In this chapter, various types of PD based on patient clinical data will be described, which will be useful to researchers and clinicians. I hope that this chapter will be a valuable aid to many researchers and clinicians in a conjoint effort to overcome this intractable disease.

Keywords Peroxisome · β-oxidation · VLCFA · Plasmalogens · Phytanic acid · Zellweger syndrome · Adrenoleukodystrophy · Whole-exome sequencing

5.1 Introduction

Peroxisomes are single-membrane lined organelles present in all eukaryotic cells. They have many metabolic functions in humans, such as β-oxidation of saturated very long-chain fatty acids (VLCFA), unsaturated fatty acids, and bile acids; α-oxidation of phytanic acid; plasmalogen synthesis; hydrogen peroxide degradation; and glyoxylic acid detoxification (see Chap. 4).

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Peroxisomal disorders (PD) are a group of inherited metabolic diseases with genetically defective peroxisomal functions. Zellweger syndrome (ZS), a prototype of PD with generally impaired peroxisomal function, has greatly contributed to the discovery of other PD as well as to the understanding of their pathophysiology.

ZS was first reported as a 'familial syndrome of multiple congenital defects' (Bowen et al. 1964). A peroxisomal defect in the liver of ZS patients was reported (Goldfischer et al. 1973) however, at that time, the peroxisomal function had not been clarified, so not much attention was given to this finding. Later, the β-oxidation system was found not only in the mitochondria but also in the peroxisomes (Lazarow and De Duve 1976), and since then, research on the peroxisomal metabolic function in humans and in the pathology of ZS was accelerated. For some time, the genetic etiology of ZS was unknown, however, we succeeded in identifying the first gene responsible for ZS, the peroxisome assembly factor 1 (PAF1, called PEX2 later) (Shimozawa et al. 1992). Since then, 12 PEX genes responsible for ZS have been identified to date (Shimozawa et al. 2004). There are more than 30 kinds of PD caused by genes involved in faulty peroxisomal biogenesis and metabolic pathways. Furthermore, the concept of PD is still expanding by advances in basic research regarding peroxisomal function, progress of mass spectrometry for peroxisomal metabolite measurements in the patients, and emergence of the next generation sequencer (NGS).

PD are caused by mutations in genes that can be classified into two major groups (Table 5.1); including: (a) genes involved in the import of peroxisomal membrane and matrix proteins, as well as in peroxisomal proliferation and fission (Peroxisome biogenesis disorders: PBD) and (b) genes encoding enzymes that are located in the peroxisomes, where they exert their function (Single enzyme deficiencies: SED).

In this chapter, PBD, SED, and adrenoleukodystrophy (ALD)-the most frequent PD, and finally the role of peroxisomes in cancer and age-related diseases are described.

5.2 Peroxisome Biogenesis Disorders (PBD)

Peroxisomal matrix proteins can be imported into peroxisomes by the various PEX proteins via the peroxisome-targeting sequences, PTS1 and PTS2, after their synthesis on free ribosomes. PTS1 proteins bind to their receptor, a short isoform of PEX5 (PEX5S) in the cytosol, and PTS2 proteins bind to their receptors, PEX7 and the long isoform of PEX5 (PEX5L); these complexes are transferred to the peroxisome and are docked on PEX13 and 14, and only matrix proteins are imported into peroxisomes by PEX2, 10, and 12. On the other hand, the receptors are recycled in the cytosol by PEX1, 6 and 26, and recently the involvement of also TRIM37 in the recycle has been reported (see Sect. 5.2.3.2). In addition, the peroxisomal membrane proteins are recognized by PEX19 in the cytosol followed by docking on PEX3 whereas PEX16 is required for peroxisome membrane biogenesis and could play a role in the early stages of peroxisome assembly (Fig. 5.1) (Shimozawa 2011).

Table 5.1 Classification of Peroxisomal diseases (PD) (*Disease-causable genes*)

A. Peroxisome biogenesis disorders (PBD)
Zellweger spectrum disorders (ZSD) (*PEX 1,2,3,5,6,10,12,13,14,16,19,26*)
Zellweger syndrome (ZS)
Neonatal adrenoleukodystrophy (NALD)
Infantile Refsum disease (IRD)
Rhizomelic chondrodysplasia punctata (RCDP) type 1 (*PEX 7*)
type 5 (*PEX 5-long isoform*)
Broad phenotypes of PEX gene defects (*PEX1,2,3,6,7,10,12,16*)
Mulibrey nanism (*TRIM37*)
PEX11β deficiency (*PEX11β*)
Encephalopathy due to defective mitochondrial and peroxisomal fission 1 (EMPF1) (*DNM1L*)
Charcot-Marie-Tooth disease Type 4A (*GDAP1*)
B. Single enzyme deficiencies (SED)
Impaired β-oxidation of fatty acids
Adrenoleukodystrophy (ALD) (*ABCD1*)
Acyl-CoA oxidase 1 (ACOX1) deficiency (*ACOX1*)
D-bifunctional protein (DBP) deficiency (*HSD17B4*)
Sterol carrier protein X (SCPX) deficiency (*SCP2*)
2-Methylacyl-CoA racemase (AMACR) deficiency (*AMACR*)
Acyl-CoA-binding domain-containing protein 5 (ACBD5) deficiency (*ACBD5*)
Impaired bile acids synthesis
Acyl-CoA oxidase 2 (ACOX2) deficiency (*ACOX2*)
Peroxisomal membrane protein, 70KD (PMP70) deficiency (*ABCD3*)
Bile acid-CoA: amino acid N-acyltransferase (BAAT) deficiency (*BAAT*)
Impaired α-oxidation of fatty acids
Refsum disease (phytanoyl-CoA hydroxylase deficiency) (*PHYH*)
Impaired ether-phospholipid biosynthesis
RCDP type 2 (dihydroxyacetone phosphate acyltransferase deficiency) (*GNPAT*)
RCDP type 3 (alkyl-dihydroxyacetone phosphate synthase deficiency) (*AGPS*)
RCDP type 4 (fatty acyl-CoA reductase 1 deficiency) (*FAR1*)
Impaired hydrogen peroxide metabolism
Acatalasemia, Hypocatalasemia (catalase deficiency) (*CAT*)
Impaired glyoxylate metabolism
Hyperoxaluria type 1 (alanine: glyoxylate aminotransferase deficiency) (*AGXT*)
Glycolate oxidase 1 (GOX1) deficiency (*HAO1*)

As generalized peroxisomal metabolic abnormalities occur similarly in patients with *PEX* gene defects, patients with different *PEX* gene defects tend to show common clinical phenotypes. Indeed, most patients with mutations in *PEX1, 2, 5, 6, 10, 12, 13, 14*, or *26* involved in both PTS1 and PTS2 protein import tend to manifest common clinical features of Zellweger spectrum disorders (ZSD) including ZS, neonatal adrenoleukodystrophy (NALD) and infantile Refsum diseases (IRD), and their severity depend on the mutational severity and residual function of these PEX

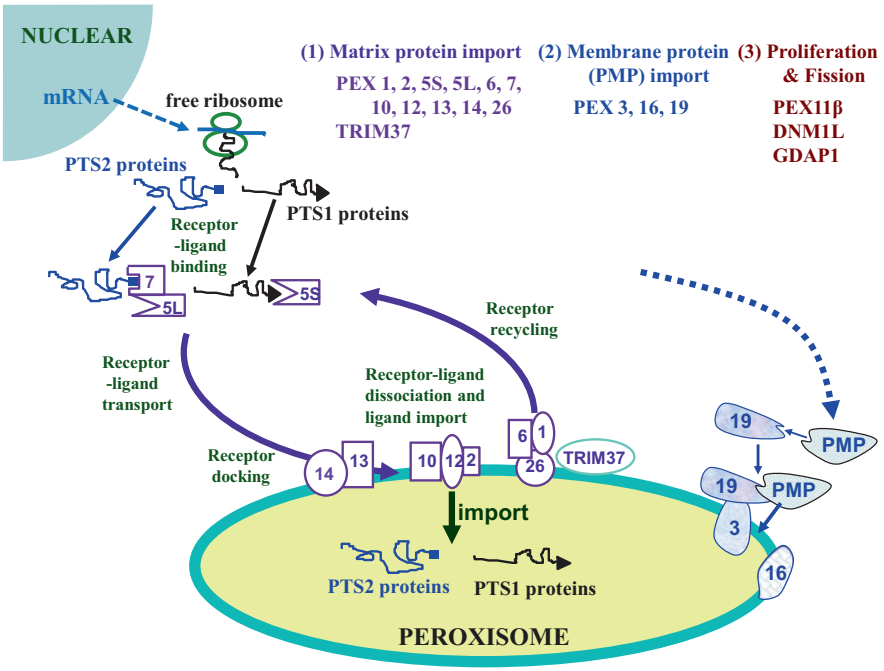

Fig. 5.1 Peroxisomal protein import and peroxisome biogenesis disorders

proteins. Most patients with defected PEX3, 16, and 19 involved in peroxisomal membrane protein import or synthesis tend to manifest phenotypes similar to the most severe ZS. On the other hand, most patients with mutated *PEX7* and *PEX5L*, which are involved only in PTS2 protein import, manifest a clinical type of rhizomelic chondrodysplasia punctate (RCDP).

With the recent expansion of whole-exome sequencing (WES), the abnormalities of these *PEX* genes have been identified in undiagnosed atypical patients, especially those with inherited neurological disorders, leading to the establishment of broad clinical phenotypes derived from *PEX* gene defects.

5.2.1 Zellweger Spectrum Disorders

ZSD are divided into different phenotypes according to clinical severity, ZS is the most severe phenotype, and NALD and IRD are milder variants, however, there is no clear distinction among these three phenotypes.

ZS is characterized by facial dysmorphism such as enlarged anterior fontanelles, high forehead, hypertelorism, broad nasal bridge, epicanthal folds, micrognathia, and malformed ears (Fig. 5.2a). Furthermore, severe hypotonia at birth (Fig. 5.2b, c), absent or weak sucking, hepatomegaly (Fig. 5.2c) with prolonged

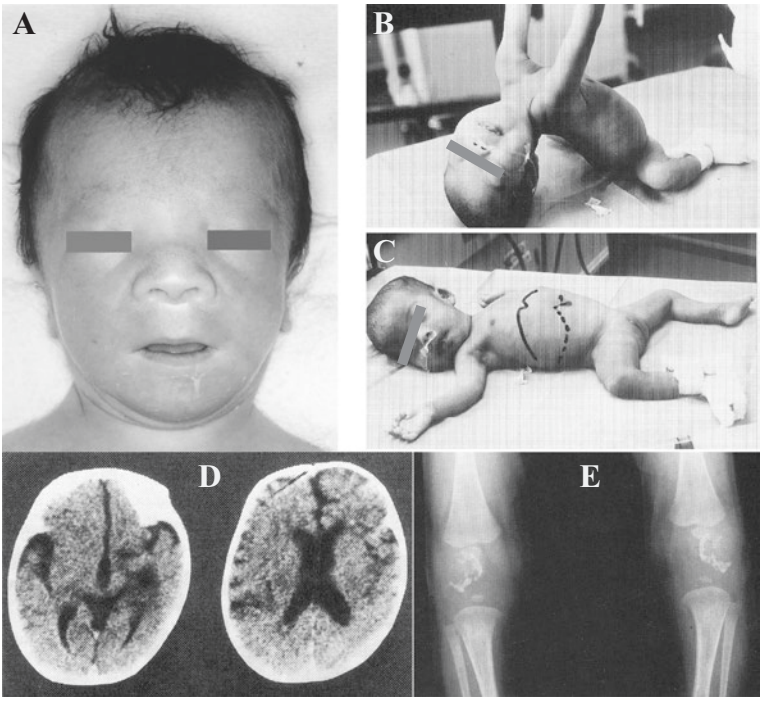

Fig. 5.2 Clinical features of Zellweger syndrome at neonatal age. (**a**) Facial features. Enlarged anterior fontanelles, high forehead, broad nasal bridge, and low-set ears. (**b**) Traction response. Severe hypotonia was seen. (**c**) Supine position. Severe hypotonia and hepatomegaly. (**d**) Brain CT. Enlarged lateral ventricles are seen. (**e**) X-ray photo of knee joints. Abnormal calcific stippling

jaundice and liver dysfunctions, renal cortical microcysts, ventricular enlargement in the brain (Fig. 5.2d), abnormal calcific stippling of multiple joints (Fig. 5.2e), cataracts and pigmentary retinopathy in the ophthalmic finding also appear. ZS patients typically show no developmental progress and die in early infancy.

In contrast, NALD patients have a less severe clinical phenotype than ZS, usually survive until the late infantile period, and exhibit mild facial dysmorphism (Fig. 5.3a) and no chondrodysplasia. Developmental regression and intractable seizures occur during the clinical course of NALD, and demyelination and progressive cortical atrophy in the brain become remarkable with age (Fig. 5.3b) as the survival time of patients is longer than that of ZS patients.

IRD, the mildest phenotype among the various ZSD, is very different from ZS. IRD patients manifest minimum facial dysmorphism, hearing impairment, retinal degeneration, and psychomotor retardation. Many patients with IRD develop up to walking alone (Fig. 5.4a) and acquiring meaningful words, therefore, IRD diagnosis in early childhood is difficult. In brain MRI findings, white matter degeneration appears first (Fig. 5.4b), and cerebral and spinocerebellar atrophies gradually become evident with increasing age (Fig. 5.4c, d); therefore, early diagnosis and

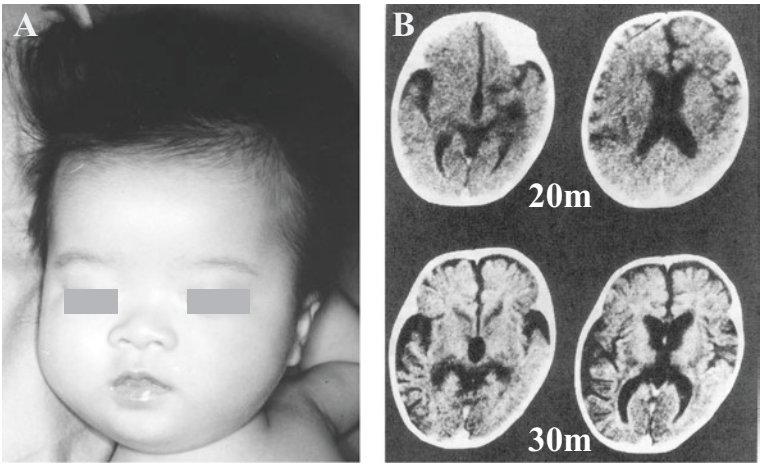

Fig. 5.3 Clinical features of neonatal adrenoleukodystrophy. (**a**) Facial features at neonatal. Mild or subtle facial dysmorphism. (**b**) Brain CT at the age of 20 months (upper row) and 30 months (lower row). Progressive cortical atrophy

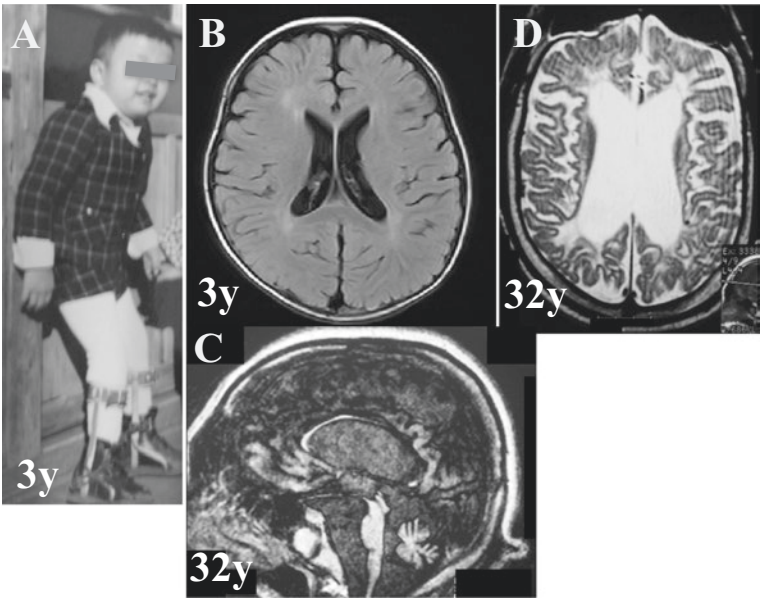

Fig. 5.4 Clinical features of infantile Refsum disease. (**a**) Standing alone at the age of 3 years. (**b**) Fluid-attenuated inversion recovery (FLAIR) image of brain MRI at the age of 3 years. High signal regions slightly in white matter of around the lateral ventricles (Matsunami et al. 2016). (**c**, **d**) Brain T2 weighted MRI at the age of 32 years. Severe atrophy of cerebellum and brain stem (**c**) and cortical atrophy and severe enlarged lateral ventricles (**d**) (Matsui et al. 2013)

subsequent treatment are important for a better prognosis. Many patients survive beyond the second decade of their life.

ZSD patients show generalized peroxisomal metabolic disturbances, such as accumulation of VLCFA, phytanic and pristanic acids, and intermediate metabolites of bile acids of di-/trihydroxycholestanoic acid (D/THCA) in the blood, as well as decreased levels of plasmalogens and docosahexaenoic acid (DHA), however, it should be noted that some biochemical parameters do not appear abnormal, especially in the mild phenotypes (see Table 7.1).

In ZSD therapy, although curative treatment is difficult, early liver transplantation may improve prognosis of patients with a mild ZSD phenotype. We performed a liver transplantation from a heterozygous parent to a 3-year-old patient diagnosed with IRD at 1 year of age, and observed that the increased VLCFA and phytanic acid concentrations in the patient's serum were improved (Matsunami et al. 2016), and no obvious symptoms worsening was noticed during the first 3 years after transplantation. Furthermore, Demaret et al. also speculated that liver transplantation performed before the onset of severe sensorineural defects in mild ZSD enables partial metabolic remission and improves long-term clinical outcome (Demaret et al. 2018). Dietary treatment with decreased phytanic acid intake may be effective for mild ZSD patients with elevated phytanic acid levels (Sá et al. 2016). Further treatment options for ZSD refer to the overview by Braverman et al. (2016). Recently, the Food and Drug Administration (FDA) in the U.S. has approved cholic acid for adjunctive treatment of ZSD patients with symptoms of liver disease, steatorrhea, or complications from decreased absorption of fat-soluble vitamins (https://www.fda.gov/Drugs/InformationOnDrugs/ucm446282.htm).

5.2.2 Rhizomelic Chondrodysplasia Punctate Type 1 and 5

Patients with rhizomelic chondrodysplasia punctate (RCDP) type 1 and type 5 caused by PEX7 and PEX5L defects respectively, exhibit limited peroxisomal metabolic abnormalities, including a deficiency in plasmalogen synthesis and

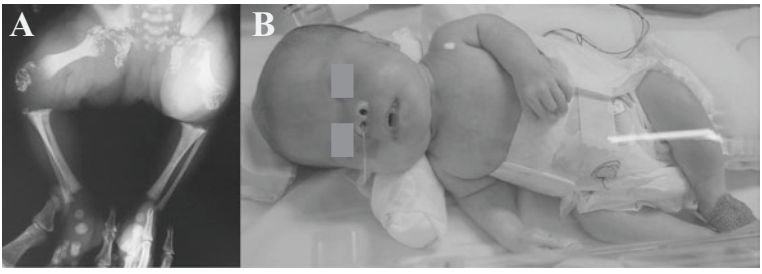

Fig. 5.5 Clinical features of rhizomelic chondrodysplasia punctata type 1 at neonatal. (**a**) X-ray photograph of knee joints. Abnormal calcific stippling. (**b**) Whole picture. The proximal extremity truncated short stature

α-oxidation of phytanic acid. Defective PEX7 and PEX5L are involved only in PTS2 protein import (Fig. 5.1) and result in the common clinical phenotype of RCDP. RCDP type 1 has been classified as a skeletal dysplasia characterized by the presence of calcific stippling in multiple joints (Fig. 5.5a); the patients show a disproportionally short stature with symmetric shortening of the proximal extremities, typical craniofacial dysmorphism resembling that of ZS (Fig. 5.5b), ichthyosis, cataract, failure to thrive, and severe mental retardation. Patients with RCDP type 1 show biochemical alterations, such as accumulation of phytanic acid and decrease in plasmalogens, whereas their pristanic acid and VLCFA levels are normal (see Table 7.1). Patients with a defect in *PEX7* display various clinical phenotypes, including severe typical RCDP and milder bone lesions with moderately decreased plasmalogen levels. Many patients die in the first 2 years of life, but some survive beyond the second decade of life. Furthermore, there are patients with a *PEX7* defect manifesting similar phenotypes to those with Refsum disease, who do not display bone lesions and their plasmalogen levels remain normal (see Sect. 5.2.3.1).

RCDP type 5 caused by a mutation in *PEX5L* was recently identified by WES and biochemical verification (Barøy et al. 2015). *PEX5* encodes two distinct isoforms, PEX5L and PEX5S, and previous patients with a *PEX5* defect manifested ZSD only, mainly owing to deficient import of PTS1 and PTS2 proteins. However, patients with *PEX5* mutations located in *PEX5L* specific exon 9, loose only PEX5L, a co-receptor of PTS2-proteins with PEX7, resulted in intact PEX5S, a receptor of PTS1-proteins (Fig. 5.1). The clinical and biochemical features of RCDP type 5 patients have similar manifestations to mild *PEX7* defect patients who manifest less pronounced skeletal abnormalities, milder growth delay and intellectual disability, and fewer biochemical disturbances.

5.2.3 Broad Phenotypes of Known PEX *Gene Defects and Newly Identified Disease-Causing Genes*

5.2.3.1 Broad Phenotypes of *PEX* Gene Defects

The phenotypic spectrum of *PEX7* mutations appears broad, including not only the severe phenotype of RCDP, but also relatively mild phenotypes. Some patients with the mild phenotypes display clinical symptoms similar to those of patients with Refsum disease, which are characterized by increased phytanic acid caused by a single enzyme deficiency [Phytanoyl-CoA hydroxylase (PHYH) deficiency (see Sect. 5.3.3)]. The biochemical abnormalities in Refsum patients due to *PEX7* defect show only increase in phytanic acid whereas the plasmalogen levels remain normal (Braverman et al. 2002; van den Brink et al. 2003).

There have been also reported extensive phenotypic heterogeneity among patients with mutation of several PEX genes which cause the ZSD. Indeed, there was a report in 2002 on patients with compound heterozygous mutations of PEX6 manifesting as Usher syndrome characterized by sensory hearing loss and retinitis pigmentosa

(Raas-Rothschild et al. 2002). Furthermore, since 2010, gene mutations in *PEX10* (Régal et al. 2010), *PEX16* (Ebberink et al. 2010), *PEX2* (Sevin et al. 2011), and *PEX6* (Tran et al. 2014) have been detected in undiagnosed patients with cerebellar ataxia and progressive leukodystrophy by combined biochemical analysis and Sanger sequencing, following detection of mild peroxisomal metabolite abnormalities in the patients. Among these cases, there was a 51-year-old man who presented with childhood onset and slowly progressive disease, caused by a mutated *PEX2*, with symptoms of ataxia, areflexia, nystagmus and strabismus (Mignarri et al. 2012).

After NGS became widely available, further disease-causing *PEX* mutations have been reported, mainly in patients with neurodegenerative diseases who had mutations in genes, such as *PEX1* (Ventura et al. 2016), *PEX3* (Bjørgo et al. 2017), *PEX10* (Renaud et al. 2016; Blomqvist et al. 2017; Yamashita et al. 2017), *PEX12* (Schabhüttl et al. 2014), and *PEX16* (Ohba et al. 2013; Bacino et al. 2015; Kumar et al. 2016), and in patients with Heimler syndrome who had mutations in *PEX1* and *PEX6* (Ratbi et al. 2015; Smith et al. 2016) (in detail, see Sect. 7.3).

Interestingly, it was reported that the allelic expression imbalance (AEI) induces mutant *PEX6* allele to cause ZSD, and the AEI of *PEX6* was correlated with heterozygosity of a frequent variant in the 3′ untranslated region (UTR) of the mutant allele (Falkenberg et al. 2017). The patients that carry this mutation presented multiple symptoms similar to the symptoms of patients with a mild phenotype of ZSD, characterized by neurological abnormalities, such as profound hypotonia, gait abnormalities, developmental delay, neuropathy, visual impairment, sensorineural hearing loss, and white matter abnormalities detected through brain MRI. The biochemical findings showed elevated VLCFA levels in the serum of patients and impaired peroxisomal biogenesis in their fibroblasts.

5.2.3.2 Mulibrey Nanism (TRIM37 Deficiency)

TRIM37, which was identified as a disease-causing gene of muscle–liver–brain–eye (Mulibrey) nanism, encodes a peroxisomal RING-B-box-coiled-coil protein; therefore, Mulibrey nanism is characterized by severe growth retardation of prenatal-onset, characteristic dysmorphic features, pericardial constriction, and hepatomegaly and was classified as a PD. TRIM37 was localized in the peroxisomes; however, peroxisomes of fibroblasts from the patients appeared normal by immunocytochemical methods, using both the peroxisomal matrix and membrane protein markers, suggesting normal peroxisomal biogenesis (Kallijärvi et al. 2002). Subsequent studies have revealed that TRIM37-mediated ubiquitination stabilizes PEX5 and promotes peroxisomal matrix protein import, which means that inactivation of TRIM37 leads to reduced PEX5 accumulation by inducing proteasomal degradation and compromising PEX5 functions in cargo binding and PTS protein import (Fig. 5.1); thereby Mulibrey nanism has been classified as a new PBD (Wang et al. 2017).

5.2.4 Dysfunction of Peroxisomal Proliferation and Fission

5.2.4.1 PEX11β Deficiency

A homozygous nonsense mutation of *PEX11β* involved in peroxisomal growth and division, was found in a 26-year-old male patient with congenital cataract, mild intellectual disability, progressive hearing loss, sensory nerve involvement, gastrointestinal problems, recurrent migraine-like episodes, and Chiari I malformation on MRI. Biochemical parameters of peroxisomal metabolites were normal, including VLCFA, phytanic and pristanic acids, bile acid intermediates and plasmalogens, whereas patient's fibroblasts did not contain PEX11β protein and exhibited a low number of enlarged and elongated peroxisomes (Ebberink et al. 2012) (see Table 7.1).

5.2.4.2 Encephalopathy Due to Defective Mitochondrial and Peroxisomal Fission 1 (EMPF1) (DNM1L Deficiency)

Waterham et al. reported a case of a newborn girl with microcephaly, abnormal brain development, optic atrophy and hypoplasia caused by heterozygous dominant negative mutations in dynamin 1-like (*DNM1L*) gene involved in the fission of both mitochondria and peroxisomes. The patient's biochemical profile showed persistent lactic acidemia and mildly elevated VLCFA. Peroxisomes in patient's fibroblasts were less in number, varied in size and were regularly arranged in rows (Waterham et al. 2007) (see Table 7.1). These patients developed epileptic encephalopathy with intractable seizures, followed by neurologic decline and died during childhood. Additionally, in several families with autosomal dominant optic-atrophy 5, heterozygous mutations in *DNM1L* have been identified (Gerber et al. 2017). Furthermore, Yoon et al. reported that in patients with autosomal recessive encephalopathy due to defective mitochondrial and peroxisomal fission resulting in early infantile death, complex heterozygous truncating mutations in *DNM1L* were identified (Yoon et al. 2016).

5.2.4.3 Charcot-Marie-Tooth Disease Type 4A (GDAP1 Deficiency)

Distinct mutations in the ganglioside-induced differentiation-associated protein 1 (*GDAP1*) gene, expressing a tail-anchored mitochondrial protein that induces mitochondrial fragmentation, were found in patients with Charcot-Marie-Tooth disease type 4A (Cuesta et al. 2002). The patients showed demyelinating peripheral neuropathy characterized by distal motor and sensory impairment resulting in gait difficulties and foot deformities. It was reported that GDAP1 was imported to peroxisomes by the import receptor Pex19, and regulated peroxisomal fission (Huber et al. 2013).

5.3 Single Enzyme Deficiencies (SED)

Single enzyme deficiencies (SED) exhibit clinical phenotypes caused by individual metabolic disturbances. Here, we describe the metabolic dysfunction in each PD, including β-oxidation of fatty acids, bile acids synthesis, α-oxidation of fatty acids, plasmalogen biosynthesis, hydrogen peroxide metabolism and glyoxylate metabolism (Table 5.1). Broad phenotypes and newly identified PD have also been reported in SED through WES.

5.3.1 Impaired β-Oxidation of Fatty Acids

5.3.1.1 Adrenoleukodystrophy (ALD)

ABCD1 was identified as the gene responsible for adrenoleukodystrophy (ALD) and encoding a peroxisomal membrane protein that may transport VLCFA-CoA through the peroxisomal membrane. Defect in this protein results in accumulation of VLCFA, however, various phenotypes of ALD are not correlated to genotypes and VLCFA values. The mechanism underlying the onset of cerebral ALD remains unknown. ALD is described in more detail later (see Sect. 5.4).

5.3.1.2 Acyl-CoA Oxidase 1 (ACOX1) Deficiency

ACOX1 catalyzes the initial step in peroxisomal fatty acid β-oxidation. Patients with ACOX1 deficiency have decreased muscle tone since the neonatal period, convulsions since infancy, hearing and vision disturbances, but absence of prominent facial dysmorphism (Fig. 5.6a). These symptoms gradually regress, whereas patients survive until childhood. The clinical findings resemble those of the mild ZSD phenotypes. In brain MRI, abnormal findings in cerebellar and cerebral white matter progress with age (Fig. 5.6b, c). As this enzyme oxidizes only the saturated fatty acids, VLCFA accumulation is the only biochemical abnormality that occurs. Peroxisomes appear larger than usual in the immunocytochemical analysis (Funato et al. 2006). Furthermore, adult patients with ACOX1 deficiency characterized by cerebellum and brain stem atrophy have been reported (Ferdinandusse et al. 2010). In therapy, although there is no curative treatment, a sibling comparison study on the effects of hematopoietic stem cell transplantation (HSCT) has been reported (Wang et al. 2014).

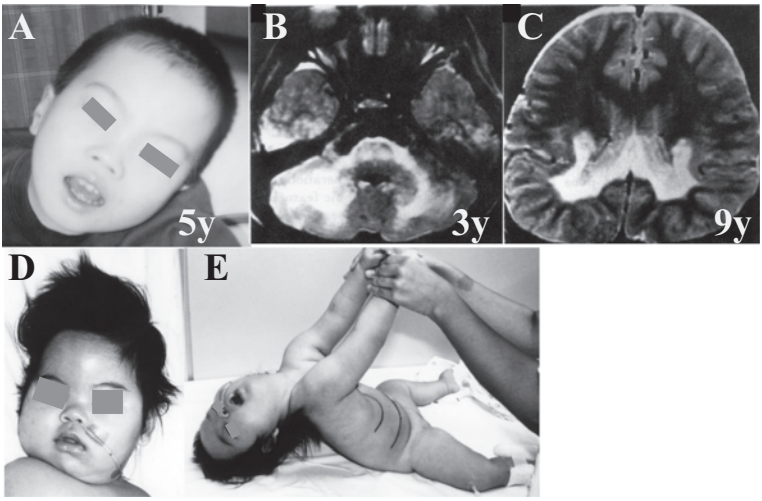

Fig. 5.6 Clinical features of acyl-CoA oxidase 1 (ACOX1) and D-bifunctional protein (DBP) deficiencies. (**a**) Facial feature of ACOX1 deficiency at the age of 5 years. (**b**) Brain T2 weighted MRI of ACOX1 deficiency at the age of 3 years. High signal regions in cerebellar white matter, peduncle and pons. (**c**) Brain T2 weighted MRI of ACOX1 deficiency at the age of 9 years. High signal regions in white matter around the occipital horn of lateral ventricles, subcortical white matter, and splenium of corpus callosum. (**d**) Facial features of patient with DBP deficiency. High forehead and broad nasal bridge. (**e**) Traction response of patient with DBP deficiency at neonatal. Severe hypotonia was seen

5.3.1.3 D-Bifunctional Protein (DBP) Deficiency

HSD17B4 encodes DBP which catalyzes the second and third steps of peroxisomal fatty acid β-oxidation. In addition to straight-chain fatty acids, bile acids and branched fatty acids are oxidized by this enzyme, therefore, the biochemical findings show accumulation of VLCFA, D/THCA, phytanic, and pristanic acids. Patients with DBP deficiency are in a more severe condition than those with ACOX1 deficiency and are characterized by facial dysmorphism (Fig. 5.6d), hypotonia from the neonatal period (Fig. 5.6e), poor feeding, hepatomegaly, convulsions since the neonatal period, and die within 2 years of life. These clinical findings seem to resemble those of the severe phenotypes of ZS patients (Fig. 5.2a, b). Peroxisomes in DBP deficient patients also present a larger shape than usual, similar to that of peroxisomes in ACOX1 deficient patients (Funato et al. 2006). In DBP deficiency, as well, broad phenotypes, including the Perrault syndrome, which is characterized by ovarian malformation, hearing loss, and cerebellar ataxia (Pierce et al. 2010), and sensorineural hearing loss, progressive cerebellar ataxia and subclinical retinitis pigmentosa (McMillan et al. 2012) have been reported.

5.3.1.4 Sterol Carrier Protein X (SCPx) Deficiency

The SCPx enzyme encoded by *SCP2* exerts thiolase activity in the last step of peroxisomal β-oxidation and oxidizes branched-chain fatty acids. Patients with SCPx deficiency have elevated levels of pristanic and phytanic acids, and D/THCA whereas normal VLCFA levels, and clinical manifestations of leukoencephalopathy with dystonia and motor neuropathy (Ferdinandusse et al. 2006).

5.3.1.5 2-Methylacyl-CoA Racemase (AMACR) Deficiency

AMACR is a peroxisomal enzyme that catalyzes the conversion of 2R-pristanoyl-CoA and 25R-D/THCA to their (S)-stereoisomers. Consequently, the enzymatic defect causes accumulation of plasma pristanic acid and D/THCA in patients with various clinical symptoms, such as adult-onset sensorimotor neuropathy (Ferdinandusse et al. 2000). Furthermore, a homozygous mutation in the *AMACR* was identified in an infant with defect in bile acid synthesis and increased levels of THCA (Setchell et al. 2003).

5.3.1.6 Acyl-CoA-Binding Domain-Containing Protein 5 (ACBD5) Deficiency

ACBD5 is a peroxisomal membrane protein with a cytosolic acyl-CoA binding domain. A variant of *ACBD5* in three siblings characterized by cone-rod dystrophy, developmental delay, spastic paraparesis, and white matter disease was identified by autozygome analysis followed by exome sequencing (Abu-Safieh et al. 2013). Next, Ferdinandusse et al. identified another patient with a homozygous deleterious indel mutation in *ACBD5* presenting progressive leukodystrophy, syndromic cleft palate, ataxia, retinal dystrophy, and accumulation of VLCFA due to impaired peroxisomal β-oxidation (Ferdinandusse et al. 2017).

5.3.2 Impaired Bile Acids Synthesis

5.3.2.1 Acyl-CoA Oxidase 2 (ACOX2) Deficiency

ACOX2 is a peroxisomal branched-chain acyl-CoA oxidase participating in bile acid synthesis. A patient with *ACOX2* deficiency identified by WES presented intermittently elevated transaminase levels, liver fibrosis, mild ataxia, and cognitive impairment (Vilarinho et al. 2016). The patient showed increased D/THCA levels in plasma and urine, whereas no increase in branched-chain fatty acids, phytanic acid, and pristanic acid was noticed.

5.3.2.2 Peroxisomal Membrane Protein, 70KD (PMP70) (ABCD3) Deficiency

ABCD3 encodes a PMP70 involved in the transport of branched-chain fatty acids and C27 bile acids into the peroxisomes. A patient with a homozygous 1758-bp deletion in *ABCD3* had accumulation of D/THCA, and increased C26/C22 and C24/C22 ratios owing to low levels of C22:0 whereas normal phytanic and pristanic acids in the plasma levels (see Table 7.1). On the contrary, measurement of peroxisomal beta-oxidation activities in fibroblasts from the patient revealed decreased beta-oxidation of pristanic acid, whereas that of C26:0 was normal. Peroxisomes in PMP70 deficient patients present a larger shape than usual and fewer in number. The patient manifested hepatosplenomegaly with severe liver dysfunction, but normal developmental milestones (Ferdinandusse et al. 2015).

5.3.2.3 Bile Acid-CoA: Amino Acid N-Acyltransferase (BAAT) Deficiency

BAAT transfers bile acid moiety from the acyl-CoA thioester to either glycine or taurine. Hence, bile acids conjugated glycine or taurine are decreased in the body fluids of patients deficient in BAAT. Patients' phenotype shows familial hypercholanemia characterized by elevated bile acid serum concentrations, itching, and fat malabsorption (Carlton et al. 2003).

5.3.3 Impaired α-Oxidation of Fatty Acids

5.3.3.1 Phytanoyl-CoA Hydroxylase (PHYH) Deficiency (Refsum Disease)

Refsum disease is characterized by an increase in phytanic acid due to deficiency of PHYH, localized in the peroxisomes. Phytanic acid is converted to pristanic acid by α-oxidation and then is subjected to β oxidation; therefore, pristanic acid levels in the patients are not increased. Many patients with Refsum disease have been reported in UK and Northern Europe and develop symptoms, such as retinitis pigmentosa, polyneuropathy (atrophy of lower limb muscles, muscle weakness, sensory paralysis), and cerebellar ataxia at the age of 1–50 years. Treatment is based on a diet that severely restricts dairy products rich in phytanic acid, and also meat and fats derived from cows, sheep, goats, etc.

5.3.4 Impaired Plasmalogen Biosynthesis

(a) Dihydroxyacetone phosphate acyltransferase (GNPAT) deficiency (RCDP type 2)
(b) Alkyl-dihydroxyacetone phosphate synthase (AGPS) deficiency (RCDP type 3)

The first and second steps of plasmalogen biosynthesis are performed in peroxisomes by GNPAT (PTS1 protein) and AGPS (PTS2 protein), respectively. Clinical findings in both deficiencies revealed an RCDP phenotype, including rhizomelic shortening of upper extremities, typical facial appearance, cataract, dwarfism, and severe mental retardation. Biochemically, both types of patients only show decreased levels of plasmalogens, whereas plasma phytanic acid levels are normal.

(c) Fatty acyl-CoA reductase 1 (FAR1) deficiency (RCDP type 4)

Mutations of *FAR1* involved in plasmalogen biosynthesis in peroxisomes were identified by WES in two families affected by severe intellectual disability, early-onset epilepsy, microcephaly, congenital cataracts, growth retardation and spasticity (Buchert et al. 2014). This disease was later named as RCDP type 4, although showing no typical RCDP phenotype.

5.3.5 Impaired Hydrogen Peroxide Metabolism

5.3.5.1 Catalase Deficiency (Acatalasemia, Hypocatalasemia)

Acatalasemia (Takahara disease) a metabolic disorder characterized by a total or near total loss of catalase activity in erythrocytes was first discovered by Takahara in patients with progressive oral gangrene (Takahara and Miyamoto 1948). Patients with hypocatalasemia have heterozygous mutations of the *catalase* gene and manifest half-normal levels of catalase activity and no obvious clinical symptoms, however, studies on Hungarian patients with hypocatalasemia showed increased occurrence of type 2 diabetes (see Sect. 5.5.2).

5.3.6 Impaired Glyoxylate Metabolism

5.3.6.1 Hyperoxaluria Type 1 (Alanine: Glyoxylate Aminotransferase Deficiency)

Primary hyperoxaluria type 1 (PH1) is a glyoxylate metabolism disorder caused by a deficiency of alanine: glyoxylate aminotransferase (AGT) present in liver peroxisomes. Glyoxylic acid is a precursor of oxalic acid, and due to the deficiency in AGT, an enzyme converting glyoxylate to glycine, a large amount of oxalic acid is

produced, and insoluble calcium oxalate is deposited on the whole body organs, including the kidney. After successive renal colic and hematuria, typical symptoms of urinary calculus, the disease progressed to nephrocalcinosis and renal failure, and most of the cases resulted in end-stage renal failure. In mild cases, administration of vitamin B6, a coenzyme of AGT, can be effective. Early liver transplantation for replacement of the AGT enzyme is considered an effective curative treatment. Kidney transplantation may be necessary in cases of renal failure, when recovery is not expected.

5.3.6.2 Glycolate Oxidase 1 (GOX1) Deficiency

The hydroxy-acid oxidase 1 (*HAO1*) gene encodes glycolate oxidase 1 (GOX1), which catalyzes the oxidation of glycolate to glyoxylate in the peroxisomes of hepatocytes. Frishberg et al. reported a patient with a homozygous splicing site mutation in *HAO1* who manifested a persistent and markedly increased urinary glycolate excretion; normal excretion of oxalate, citrate and glycerate; and no obvious renal symptoms. This observation suggested that substrate reduction might be targeted for the development of novel approaches for the treatment of PH1 (Frishberg et al. 2014).

5.4 Adrenoleukodystrophy (ALD)

Adrenoleukodystrophy (ALD) is the most common PD characterized by demyelination of the cerebral white matter and adrenal dysfunction. ALD is an X-linked inherited disease attributed to mutations in the *ABCD1* gene, and its product, ALDP/ABCD1, a peroxisomal membrane protein. ALDP possesses an ATP-binding cassette region at the C-terminus involved in the import of saturated VLCFA into the peroxisomes, leading to β-oxidation of the saturated VLCFA. Therefore, a dysfunction of ALDP/ABCD1 results in the accumulation of saturated VLCFA in the tissues and plasma. Various clinical phenotypes exist in ALD, such as the childhood cerebral ALD (CCALD), adolescent cerebral ALD (AdolCALD), adult cerebral ALD (ACALD), adrenomyeloneuropathy (AMN), olivo-ponto-cerebellar type of ALD (OPCALD) and Addison only with no genotype-phenotype correlation. Even female carriers of the mutated gene present occasionally mild spinal symptoms with age. The prognosis of cerebral ALD is generally very poor and many patients risk becoming bedridden within a few years if they remain without effective treatment. Hematopoietic stem cell transplantation (HSCT) is currently the only curative approach, which can prevent the progression of brain deterioration; however, HSCT is only effective for patients in the early stages of cerebral ALD (Peters et al. 2004). Therefore, not only is early diagnosis just after disease onset critical, but presymptomatic diagnosis is also essential in order to prevent the progression of cerebral ALD.

5.4.1 Epidemiology and Phenotypes

In the United States, one ALD patient in 21,000 newborn boys and one ALD carrier in 14,000 newborn girls have been reported (Bezman et al. 2001). Furthermore, in New York, over 700,000 newborns were screened; 45 babies (22 boys and 23 girls) were identified as having ALD, suggesting that the birth-incidence of ALD could be 1:15,000 (https://adrenoleukodystrophy.info/clinical-diagnosis/newborn-screening). At least 4.1% of individuals with ALD have de novo mutations (Wang et al. 2011); therefore, the mothers of male probands may not be carriers. There are various phenotypes, shown below, which do not correlate with genotypes; however, the incidence of each phenotype varies from country to country, probably due to different genetic backgrounds.

5.4.1.1 Childhood Cerebral ALD (CCALD)

CCALD is the most common phenotype and is characterized by the progressive deterioration of the intellectual, psychic, visual, and gait characteristics at the age of onset between 3 and 10 years. The prognosis of CCALD is generally very poor and many patients become bedridden within a few years.

5.4.1.2 Adolescent Cerebral ALD (AdolCALD)

AdolCALD has symptoms similar to CCALD at the age of onset between 11 and 21 years but tends to progress more slowly.

5.4.1.3 Adrenomyeloneuropathy (AMN)

AMN is a noninflammatory distal axonopathy which develops after puberty with gait disturbance, rectal bladder dysfunction, and impotence. AMN progresses slowly, however, it may develop to cerebral ALD.

5.4.1.4 Adult Cerebral ALD (ACALD)

ACALD develops after adulthood and presents personality changes, intellectual deterioration and psychiatric symptoms, therefore, sometimes is misdiagnosed as psychosis or dementia. Clinical progression varies and can lead to bedridden patients after a few years.

5.4.1.5 Olivo-Ponto-Cerebellar Type of ALD (OPCALD)

Cerebellar ataxia is the main symptom of patients with OPCALD, with most of them being diagnosed in Japan. Some patients with OPCALD may develop cerebral ALD.

5.4.1.6 Addison Only

Addison disease develops between the age of 2 years and adulthood with symptoms of adrenal insufficiency, such as unexplained vomiting, weight loss, and pigmentation. The youngest patient showing abnormal adrenal function was reported to be 7 months old. There was no significant difference in the VLCFA values of the plasma among patients with adrenal insufficiency (Huffnagel et al. 2019). It should be noted that most patients with an "Addison only" phenotype may progress to AMN and/or cerebral ALD and most male patients with ALD have adrenal insufficiency regardless of their phenotype.

5.4.1.7 Symptomatic Female

Some female carriers have symptoms like those of AMN patients including gait disorder, sensory disturbance, and fecal incontinence. Symptoms rarely appear before the age of 20, and the incidence increases with age. In details, 18% of women under 40 and 88% of women over 60 years of age present light neurological signs (Engelen et al. 2014). In female carriers, the adrenal dysfunction is rare and cerebral ALD is even rarer.

5.4.2 Diagnostic Methods

(a) Very long chain fatty acids (VLCFA)
Male patients show increased saturated VLCFA plasma levels such as C26:0, C25:0, C24:0. There is no correlation between the rate of accumulation of VLCFA and clinical severity. Fifteen percent to 20% of female carriers have normal VLCFA levels, although increased VLCFA levels are observed in the majority (Kemp et al. 2001). Therefore, *ABCD1* mutation analysis should be performed in all suspected female carriers even with normal VLCFA levels.

(b) Brain MRI
In cerebral ALD, CT and T2 weighted MRI imaging show a low density and a high signal region, respectively, coinciding with the site of demyelination in the cerebral white matter (Fig. 5.7a). The distribution of demyelination is common in the white matter of the occipital lobe, around the lateral ventricle in the white matter of the parietal lobe, and in the splenium of the corpus callosum; however,

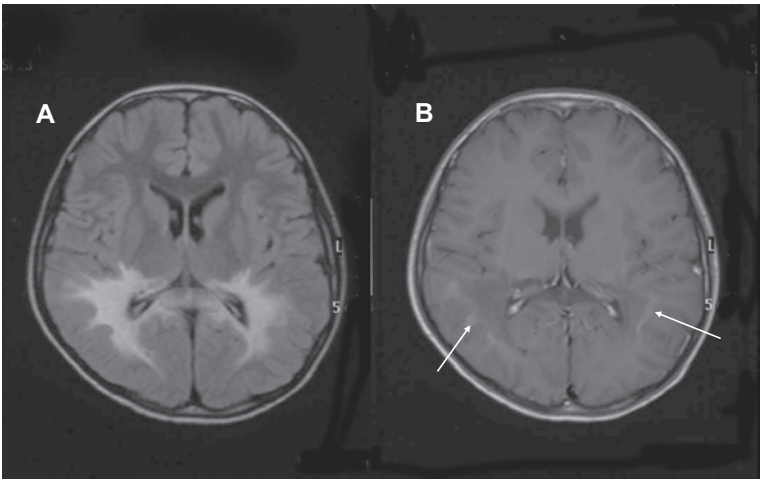

Fig. 5.7 Brain MRI of adolescent cerebral ALD at the age of 13 years. (**a**) FLAIR image of brain MRI. High signal regions in white matter of occipital lobe with subcortical region. (**b**) Gadolinium enhancement. Contrast effect is recognized at the sites with active phase of neuroinflammation

in some cases, it initiates from the white matter of the frontal lobe. At sites with active neuroinflammation, the contrast effect is recognized by gadolinium (Gd) enhancement (Fig. 5.7b). In AMN and OPCALD, abnormal T2 weighted MRI findings are mainly observed in the pyramidal tract, cerebellum, and spinocerebellar tract.

(c) Adrenal function test
The lifetime risk of adrenal insufficiency in male patients with ALD is nearly 80% (Huffnagel et al. 2019). Even without adrenal insufficiency symptoms, elevated plasma ACTH levels or low response to rapid ACTH loading test are observed. Adrenal insufficiency affects the prognosis of ALD patients, and a recent study on the natural history of adrenal insufficiency in ALD recommends adrenal testing every 4–6 months for patients aged ≤10 years, annual testing for those aged 11–40 years, and testing on demand for those aged >40 years (Huffnagel et al. 2019).

(d) *ABCD1* mutation analysis
The mutations in the *ABCD1* are diverse, as more than 750 different mutations have been identified (https://adrenoleukodystrophy.info/mutations-and-variants-in-abcd1). There is no genotype-phenotype correlation, even in female carriers. As 15–20% of female carriers display normal VLCFA levels (Kemp et al. 2001), *ABCD1* mutation analysis is recommended for female carrier detection.

(e) Pathological findings
In autopsy of patients with cerebral ALD, demyelination of the white matter, gliosis, and infiltration of the inflammatory cells around the blood vessel are recognized in the cerebral lesion.

(f) Neurophysiological and psychological findings (see Chap. 12)

5.4.3 Differential Diagnosis

5.4.3.1 Diseases to Be Differentiated in ALD of Boys

Attention deficit hyperactivity disorder (ADHD), learning disability, psychosomatic disorder, strabismus, blurred vision, hearing loss, Addison's disease, brain tumor, subacute sclerosing panencephalitis (SSPE), and other leukodystrophies.

5.4.3.2 Diseases to Be Differentiated in ALD of Adults

Familial spastic paraplegia, multiple sclerosis, psychosis, dementia, spinocerebellar degeneration, Addison's disease, brain tumor, malignant lymphoma, and other leukodystrophies.

5.4.4 Treatment

(a) Steroid replacement therapy
Adrenal insufficiency significantly affects prognosis; therefore, it is necessary to evaluate the adrenal function of all male patients, including asymptomatic and post HSCT patients. Corticosteroid replacement therapy should be initiated when necessary, however it should not affect the cerebral and spinal cord lesions.

(b) Lorenzo's oil
Lorenzo's oil, a blend of 4:1 mixture of glycerol trioleate and glycerol trierucate reduces VLCFA in plasma, whereas it does not affect the natural course of the disease after the onset of cerebral symptoms. It has also been tried in the treatment of presymptomatic or AMN patients; however, its efficiency was not defined.

(c) HSCT
HSCT is the only curative approach, that when performed early can prevent the progression of brain involvement in CCALD and AdolCALD. Raymond et al. recently reported that prognosis of early HSCT was clearly improved when survival was assessed without the major functional disabilities considered as a relevant treatment goal, rather than solely assessing overall survival as an indicator of treatment success (Raymond et al. 2018). Because of that, it is essential to suspect ALD as soon as possible and to obtain a prompt diagnosis. Kato et al. reported that allogeneic HSCT with reduced intensity conditioning for ALD patients was safely performed without major transplant-related complications even in symptomatic patients (Kato et al. 2018). Furthermore, the effectiveness of transplantation has been reported even in ACALD, through a retrospective analysis of the feasibility, toxicity, and long-term neurological outcome of 14 adult males treated with allogeneic HSCT in four European centers (Kühl et al. 2017).

There was a report that 3 out of 5 cases developed myelopathy in a long-term follow-up study of patients transplanted at an early stage. It is suggested that although the inhibitory effect on the progression of inflammation in the cerebral type is recognized in HSCT, the effect of inhibiting the onset of AMN may not be recognized (van Geel et al. 2015).

(d) AMN and symptomatic female
For myelopathy in AMN and symptomatic females, there has been no effective therapy available yet, therefore, physical therapy and antispasmodic drugs are the main treatments. Studies using *Abcd1* knockout mice have revealed that oxidative stress may be involved in axonal degeneration of AMN, hence, the examinations on antioxidant drugs are ongoing (López-Erauskin et al. 2011).

(e) HSC gene therapy
ALD patients at the early stages of the cerebral-type of disease were administered Lenti-D gene therapy, where autologous $CD34^+$ cells transduced with Lenti-D lentiviral vector were injected in patients as a phase II-III safety and efficacy study (Eichler et al. 2017). Based on results, the FDA in the US has granted the Breakthrough Therapy designation to Lenti-D™ for treating patients with the cerebral type of ALD on May 23, 2018.

(f) Further therapeutic strategies for ALD (see Chap. 8)

5.4.5 Presymptomatic Diagnosis and Newborn Screening

5.4.5.1 Presymptomatic Diagnosis

Patients after cerebral ALD onset have limitations in HSCT effect; hence, in order to improve prognosis, it is important to identify patients before the onset of disease, by familial analysis of the probands. This is also important for improving the prognosis of adrenal insufficiency. Furthermore, as the onset of symptoms cannot be predicted, it is necessary to present a system of long-term follow-up (Engelen et al. 2012) (in detail, see Sect. 7.4.2 and Fig. 7.3).

5.4.5.2 Newborn Screening (NBS)

In New York, neonatal screening for ALD was initiated on December 30, 2013. During the first 3 years, over 700,000 newborns were screened in New York and 45 babies with ALD, including 22 boys and 23 girls, were identified (https://adrenoleukodystrophy.info/clinical-diagnosis/newborn-screening). Later, testing was conducted in many states in the United States. In an effort to arrive to a steady effect on overcoming ALD, it is essential to establish a precise diagnostic system even for female ALD patients and other PD, a genetic counseling system and a long-term follow up system for patients found by NBS.

5.4.6 Pathophysiology

5.4.6.1 Elucidated Facts and Unresolved Issues

Dysfunction of ALDP/ABCD1 due to mutated *ABCD1* in ALD patients, which is a peroxisomal membrane transporter causes impaired β-oxidation of saturated VLCFA resulting in the accumulation of VLCFA in the tissues and plasma. Therefore, diagnosis of ALD can be confirmed by elevated saturated VLCFA in plasma and detection of *ABCD1* mutations, however there is no correlation between genotypes and various phenotypes. Cerebral ALD is an inflammatory demyelinating disease, whereas AMN is a non-inflammatory distal axonopathy, and some AMN patients can develop cerebral ALD. We cannot predict phenotypes and prognosis in presymptomatic patients, therefore, it is now difficult to perform HSCT before cerebral ALD onset. *Abcd1* knockout mice exhibited only minor neurologic symptoms without inflammatory demyelination (Pujol et al. 2002), whereas there was a recent report that chimpanzee naturally developed cerebral ALD (Curiel et al. 2017). Furthermore, the function of ALDP/ABCD1 as a transporter in the peroxisomal membrane and the pathophysiology caused by accumulated VLCFA are not completely understood.

5.4.6.2 Task to Be Solved

The most important task should be the development of a phenotype prediction diagnosis method for medical intervention before the onset of the disease. For that purpose, the search for modifier factors causing cerebral ALD onset is essential and can lead to the development of a cerebral-type onset in a mice model. This model can help to elucidate the mechanism of onset of inflammatory demyelination as well as the therapeutic mechanism of HSCT, leading to new treatments and optimal transplantation methods for patients with cerebral ALD. It is also important to clarify the underlying biochemical and molecular pathology of ALDP/ABCD1, including synthesis and β-oxidation of VLCFA, for the discovery of new approaches for successful preventive treatment.

5.4.7 Current and Future Prospective

Currently, early diagnosis is the most important factor in conquering ALD; hence, it is important to spread information regarding the first symptoms of ALD widely and provide a prompt diagnostic system to detect VLCFA levels and *ABCD1* mutations. We have developed a prompt ALD diagnostic system that provides results on VLCFA values and *ABCD1* mutations within a few days (see Sect. 7.4.1). In addition, presymptomatic diagnosis and neonatal screening combined with genetic

counseling and a long-term follow-up system may have to be adopted as a national strategy. Furthermore, in an effort to improve the prognosis of patients diagnosed before disease onset, it is important to develop a phenotype prediction method, as well as further therapeutic approaches.

5.5 Role of Peroxisome in Cancer and Age-Related Diseases

Research on the pathology of patients with PD, including the prototype of ZS, has greatly contributed to the elucidation of the physiological functions of peroxisomes in humans. Furthermore, the spread of WES in recent years has led to the discovery of further variants of known genetic diseases and also newly identified PD (see Sect. 7.3); hence, the concept of PD has been expanding.

On the other hand, in age-related diseases, such as diabetes, cancer and neurodegenerative disorders, the association with peroxisomal function has been suggested long ago, through disease models and genetic, epidemiological, and biochemical research. For example, there have been reports on the induction of liver cancer in rodents by peroxisome proliferators, increased occurrence of type 2 diabetes in Hungarian patients with hypocatalasemia, reduced plasmalogen levels in postmortem brain tissues of patients with Alzheimer's disease *etc*. Furthermore, recent studies suggest that peroxisomal function may be altered with aging and could contribute to these age-related diseases (Cipolla and Lodhi 2017).

It is well known that mitochondrial dysfunction may be involved in the onset and progression of age-related diseases *via* reactive oxygen species (ROS). Peroxisomes produce ROS during the process of fatty acid oxidation, and also contain catalase, an enzyme that reduces ROS (see Sect. 4.5). Peroxisomal functions are performed in cooperation with the function of other organelles, including mitochondria (see Sect. 4.6), thus it can be difficult to evaluate the exact role of peroxisomes independently.

In a report of age-related changes in peroxisomes of human cells, aging compromised PTS1 protein import, affecting the critical anti-oxidant enzyme catalase, which led to an increased load of ROS, further reduction of peroxisomal protein import, and exacerbation of aging effects (Legakis et al. 2002). Furthermore, the analysis of peroxisome dynamics in mammalian cells also suggested heterogeneity in peroxisomal import ability with age (Huybrechts et al. 2009). In this section, we pay particular attention to the relationship between age-related diseases and PD.

5.5.1 Role of Peroxisomes in Neurodegenerative Diseases

PD patients themselves exhibit neurologic symptoms, such as white matter degeneration, cerebellar ataxia, and developmental regression, as described above (see Sects. 5.2–5.4). Peroxisomes are involved in the biosynthesis of plasmalogens that

are rich in myelin sheaths (Wanders and Poll-The 2017); therefore, patients with ZSD and RCDP manifest decreased levels of plasmalogens in plasma and tissues (see Table 7.1), which may be related to myelination deficits in these patients (Bams-Mengerink et al. 2006). Moreover, a mouse model of RCDP type 2 (*Gnpat*$^{-/-}$), which completely lacked plasmalogens, showed defects in myelination in the cerebellum (Teigler et al. 2009). On the other hand, although no impaired plasmalogen synthesis was seen in ALD (see Sect. 5.4), not only increased VLCFA levels, but also reduced plasmalogen levels and increased ROS levels were observed in the white matter of the brains of cerebral ALD patients (Khan et al. 2008).

In Alzheimer's disease (AD), Han et al. reported a dramatic decrease in plasmalogen contents in white matter at a very early stage, which indicated that plasmalogen defects may play an important role in AD pathogenesis and suggested that altered plasmalogen contents may contribute to neurodegeneration, synapse loss, and synaptic dysfunction in AD (Han et al. 2001). Recently, it was reported that oral administration of scallop-derived purified plasmalogens may improve cognitive functions of mild AD (Fujino et al. 2017).

In Parkinson's disease, reduced levels of plasmalogen were reported in lipid rafts isolated from the cortical gray matter of patients (Fabelo et al. 2011). Furthermore, Zellweger model mice (*Pex2*$^{-/-}$, *Pex5*$^{-/-}$ and *Pex13*$^{-/-}$) exhibited increased α-synuclein phosphorylation, oligomerization, and inclusion body formation (Yakunin et al. 2010). These findings are seen in the pathology of patients with Parkinson's disease. Later, Wang et al., using a *pex3* yeast mutant, reported that a defect in peroxisomal biogenesis prevents the binding of alpha-synuclein to lipid droplets in lipid-loaded yeast (Wang et al. 2013). These *PEX* are disease-causing gene for PBD (see Fig. 5.1).

5.5.2 Role of Peroxisomes in Diabetes

In a study on Hungarian patients with acatalasemia, the frequency of occurrence of type 2 diabetes is high in patients with hypocatalasemia who are heterozygous for a mutation in the catalase gene, which detoxifies cells from hydrogen peroxide (Nagy et al. 2015). Increased levels of ROS are a key factor involved in the pathogenesis of type 2 diabetes, and oxidative stress is thought to promote pancreatic β-cell dysfunction and contribute to type 2 diabetes. On the contrary, recent studies have shown that β-cells have the capacity to detoxify hydrogen peroxide through a thioredoxin reductase-dependent mechanism and are not as sensitive to oxidative damage as was previously thought (Stancill et al. 2019).

5.5.3 *Role of Peroxisomes in Cancer*

There are many reports on peroxisomal function in cancer. Some of them show decreased peroxisomal function in many tumors, whereas others show the requirement of peroxisomal function for efficient tumor growth. These contradictory findings might be a result of tumor heterogeneity (Islinger et al. 2018). Recent studies revealed that the overexpression of a tumor suppressor, phospholipase A/acyltransferase (PLA/AT)-3, inhibited the binding of PEX19 to peroxisomal membrane proteins, resulting in the specific disappearance of peroxisomes and decrease in levels of plasmalogen. PLA/AT-3 inhibited the binding of PEX19 to various peroxisomal membrane proteins, such as PEX3 and PEX11β (see Fig. 5.1), which suggested that PLA/AT-3 may be involved in a novel regulatory mechanism of peroxisomal biogenesis (Uyama et al. 2015). Moreover, Asare et al. found that the imbalance in epidermal differentiation resulting from PEX11β deficiency and peroxisome mislocalization in mitosis was caused by the inability of basal stem cells to orient their spindle perpendicularly to the underlying basement membrane (Asare et al. 2017). Further studies on the metabolic function, proliferation, and division of peroxisomes in cells might elucidate their role in cancer development and proliferation by clarifying the dynamics of organelles in cell growth and differentiation.

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Ethics Statement The diagnostic studies of PD are approved by the Ethical Committee of the Graduate School of Medicine, Gifu University.

Conflict of Interest The author declares no conflict of interest.

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