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Zellweger Spectrum Disorder

Synonym: ZSD

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Summary

Clinical characteristics

Zellweger spectrum disorder (ZSD) is a phenotypic continuum ranging from severe to mild. While individual phenotypes (e.g., Zellweger syndrome [ZS], neonatal adrenoleukodystrophy [NALD], and infantile Refsum disease [IRD]) were described in the past before the biochemical and molecular bases of this spectrum were fully determined, the term "ZSD" is now used to refer to all individuals with a defect in one of the ZSD-PEX genes regardless of phenotype.

Individuals with ZSD usually come to clinical attention in the newborn period or later in childhood. Affected newborns are hypotonic and feed poorly. They have distinctive facies, congenital malformations (neuronal migration defects associated with neonatal-onset seizures, renal cysts, and bony stippling [chondrodysplasia punctata] of the patella[e] and the long bones), and liver disease that can be severe. Infants with severe ZSD are significantly impaired and typically die during the first year of life, usually having made no developmental progress.

Individuals with intermediate/milder ZSD do not have congenital malformations, but rather progressive peroxisome dysfunction variably manifest as sensory loss (secondary to retinal dystrophy and sensorineural hearing loss), neurologic involvement (ataxia, polyneuropathy, and leukodystrophy), liver dysfunction, adrenal insufficiency, and renal oxalate stones. While hypotonia and developmental delays are typical, intellect can be normal. Some have osteopenia; almost all have ameleogenesis imperfecta in the secondary teeth.

Diagnosis/testing

The diagnosis of ZSD is established in a proband with the suggestive clinical and biochemical findings above by identification of biallelic pathogenic variants in one of the 13 known ZSD-PEX genes. One *PEX6* variant,

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p.Arg860Trp, has been associated with ZSD in the heterozygous state due to allelic expression imbalance dependent on allelic background.

Management

Treatment of manifestations: The focus is on symptomatic therapy and may include gastrostomy to provide adequate calories, hearing aids, cataract removal, glasses to correct refractive errors, supplementation of fat-soluble vitamins, and cholic acid supplementation; varices can be treated with sclerosing therapies; anti-seizure medication, early intervention services for developmental delay and intellectual disability; adrenal replacement therapy; vitamin D supplementation and consideration of bisphosphonates for osteopenia; treatment as per dentist for ameliogenesis imperfecta. Supportive treatment for renal oxalate stones has included hydration, lithotripsy, and surgical intervention. Annual influenza and respiratory syncytial virus vaccines should be provided.

Surveillance: Growth and nutrition should be assessed at each visit. Annual audiology and ophthalmologic evaluations; annual monitoring of liver function and coagulation factors, and ultrasound and/or fibroscan to evaluate liver architecture; monitor for changes in seizure activity; head MRI to evaluate for white matter changes that may explain changes in cognitive and/or motor ability; monitor developmental progress and educational needs; ACTH and cortisol levels by age one year and annually thereafter. Dental examinations every six months. Annual urine oxalate-to-creatinine ratio with consideration of renal imaging when performing liver imaging. Assessment of family needs at each visit.

Genetic counseling

ZSD is typically inherited in an autosomal recessive manner (one *PEX6* variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state). At conception, each sib of an individual with biallelic ZSD-causing pathogenic variants has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives is possible if the pathogenic variants have been identified in an affected family member. Prenatal testing for a pregnancy at increased risk is possible by DNA testing if both ZSD-related pathogenic variants have been identified in an affected family member, or by biochemical testing if the biochemical defects have been confirmed in cultured fibroblasts from an affected family member.

GeneReview Scope

Zellweger Spectrum Disorder (ZSD): Included Phenotypes
• Severe ZSD (previously called Zellweger syndrome) • Intermediate/milder ZSD (previously called neonatal adrenoleukodystrophy, infantile Refsum disease, or Heimler syndrome)

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

Zellweger spectrum disorder (ZSD) **should be suspected** in children with the following clinical and laboratory findings.

Clinical Findings

In newborns:

- Hypotonia

- Poor feeding
- Distinctive facies
- Brain malformations
- Seizures
- Renal cysts
- Hepatomegaly, cholestasis, and hepatic dysfunction
- Bony stippling (chondrodysplasia punctata) of the patella(e) and other long bones

In older infants and children:

- Developmental delays with or without hypotonia (Note: Intellect can be normal.)
- Failure to thrive
- Hearing loss
- Vision impairment
- Liver dysfunction
- Adrenal dysfunction
- Leukodystrophy
- Peripheral neuropathy and ataxia

Laboratory Findings

The screening assays for ZSD are summarized in Table 1. Note that because some individuals with ZSD do not have abnormalities of these screening assays in body fluids or cultured cells, molecular genetic testing is necessary to establish the diagnosis (see Establishing the Diagnosis). Functional testing in fibroblasts remains an ancillary tool to confirm equivocal molecular and/or biochemical results.

Table 1. Screening Assays for Zellweger Spectrum Disorder

Compound	Test	Expected Findings	Limitations of Test
C26:0 LPC [1]	Dried blood spot concentrations	↑ C26:0-LPC concentrations	Persons w/mild ZSD may not be detected.
VLCFA	Plasma concentration	↑ plasma concentrations of C26:0 & C26:1; ↑ ratios of C24/C22 & C26/C22 [2]	Non-fasting samples, hemolyzed samples, or a person on a ketogenic diet can cause false positive results.
Phytanic acid & pristanic acid [3]	Plasma concentration	↑ concentrations of phytanic acid &/or pristanic acid	Branched-chain fatty acid accumulation depends on dietary intake of phytanic acid, which is minimal in formula- & breast-fed infants. Thus, phytanic & pristanic acid levels are normal in a neonate w/ZSD.
Plasmalogens	Erythrocyte membrane concentrations	↓ amounts of C16 & C18 plasmalogens	Persons w/moderate-to-mild ZSD may have marginally↓-to-normal plasmalogen levels.
Pipecolic acid	Plasma/urine concentration	↑ concentration of pipecolic acid in both plasma & urine	Urinary excretion of pipecolic acid is high in neonatal period but diminishes w/age. [4] Thus, urine should be tested in a neonate & plasma in an older child or adult.

Table 1. continued from previous page.

Compound	Test	Expected Findings	Limitations of Test
Bile acids	Plasma/urine concentration	↑ concentrations of C27 bile acid intermediates THCA & DHCA	In most cases plasma testing is more sensitive than urine analysis.

DHCA = dihydroxycholestanoic acid; LPC = lysophosphatidylcholine; THCA = trihydroxycholestanoic acid; VLCFA = very-long-chain fatty acids

1. C26:0-LPC is measured in dried blood spots (DBS) in newborn screening programs for X-linked adrenoleukodystrophy (X-ALD) in many states in the USA [Vogel et al 2015, Moser et al 2016]. Elevated C26:0-LPC concentrations are also detected in individuals with ZSD. Clinical evaluation, molecular testing, and additional biochemical testing of newborns with elevated C26:0-LPC on DBS can help to distinguish those with peroxisomal disorders other than X-ALD.

2. Low plasma concentration of LDL and HDL can cause false negative results. In a person with low plasma concentrations of LDL and HDL without a defect in peroxisomal fatty acid metabolism, the plasma concentration of specific fatty acids (e.g., C22:0, C24:0, C26:0) are significantly lower than normal control levels. Persons with defects in peroxisomal fatty acid metabolism and very low LDL and HDL concentrations do not have significant elevations in C26:0 and C26:1, but do have modest elevations in the ratios of C24/C22 and C26/C22.

3. This analysis is usually included in VLCFA measurement.

4. Pipecolic acid measurement is an adjunct to more definitive biomarkers such as plasma VLCFA and erythrocyte plasmalogen levels. Elevations in pipecolic acid can also occur in pyridoxine-dependent seizures [Plecko et al 2000].

Establishing the Diagnosis

The diagnosis of ZSD **is established** in a proband with the suggestive clinical and biochemical findings described in Suggestive Findings by identification of biallelic pathogenic (or likely pathogenic) variants in one of the 13 PEX genes listed in Table 2.

1 One *PEX6* variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state due to allelic expression imbalance dependent on allelic background (see Molecular Genetics). (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (3) Identification of biallelic variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) in one of the 13 PEX genes listed in Table 2 does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the suggestive clinical and biochemical findings of ZSD described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a nondistinct phenotype that does not suggest a specific diagnosis are more likely to be diagnosed using genomic testing (see Option 2). Note: Single-gene testing (i.e., sequence analysis of one of the PEX genes, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended. A multigene panel and/or exome sequencing are typically used in lieu of single-gene testing.

Option 1

A multigene panel for peroxisome biogenesis disorders that includes the 13 genes listed in Table 2 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options

may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the clinical and laboratory findings in an affected individual do not lead to consideration of ZSD, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) can be the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 2. Molecular Genetic Testing Used in Zellweger Spectrum Disorder (ZSD)

Gene [1, 2]	% of ZSD Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
		Sequence analysis [5, 6]	Gene-targeted deletion/duplication analysis [7]
PEX1	60.5%	~98% [8]	~2% [8]

Table 2. continued from previous page.

Gene [1, 2]	% of ZSD Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
		Sequence analysis [5, 6]	Gene-targeted deletion/ duplication analysis [7]
PEX6	14.5%	77/77 [9, 10]	Unknown [11]
PEX12	7.6%	43/43 [9]	
PEX26	4.2%	17/17 [9]	
PEX10	3.4%	17/18 [9]	
PEX2	3.1%	19/22 [9]	
PEX5	2.0%	13/13 [9]	
PEX13	1.5%	7/7 [9]	
PEX16	1.1%	8/8 [9]	
PEX3	0.7%	3/3 [9]	
PEX19	0.6%	3/3 [9]	
PEX14	0.5%	1/2 [9]	
PEX11B	0.1%	1/1 [12]	

1. Genes are listed from most frequent to least frequent genetic cause of ZSD.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Based on complementation studies using somatic cell hybridization and/or cDNA complementation analysis in 810 individuals with biochemical confirmation of ZSD (197 at Kennedy Krieger Institute [unpublished] and 613 reported by Ebberink et al [2011])
4. See Molecular Genetics for information on variants detected in these genes.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. An estimate, based on the assumption that large deletions or promoter and deep intronic pathogenic variants would be missed; however, these types of variants do not appear to be common in ZSD.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. This estimate is based on the number of individuals identified with a *PEX1* defect, defined by having two pathogenic *PEX1* variants, one of which was a deletion detected by MLPA [Molly Sheridan, PhD; Johns Hopkins DNA Diagnostic Laboratory].
9. Based on Ebberink et al [2011]. The numerator is the number of individuals belonging to this complementation group who had two pathogenic variants identified and the denominator is the total number of individuals belonging to this complementation group who underwent sequencing of that gene.
10. One *PEX6* variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state due to allelic expression imbalance dependent on allelic background [Falkenberg et al [2017]; see Molecular Genetics.
11. No data on detection rate of gene-targeted deletion/duplication analysis are available.
12. PEX11B: single case report [Ebberink et al 2012]. Taylor et al [2017] reported five additional individuals from three families. All had congenital cataracts and other clinical features, but normal or equivocal peroxisomal biomarkers in limited testing.

Clinical Characteristics

Clinical Description

Zellweger spectrum disorder (ZSD) is defined by a continuum of three phenotypes described before the biochemical and molecular bases of these disorders had been fully determined: Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD) [Braverman et al 2016].

The ZSD phenotypic spectrum is broad; some affected individuals have mild manifestations, mainly sensory deficits and/or mild developmental delay. Recently, individuals with normal intellect have been identified [Ratbi

et al 2015, Ratbi et al 2016, Smith et al 2016] by genomic testing methods. Nonetheless, all of the peroxisome assembly disorders cause significant morbidity, frequently resulting in death in childhood.

Although the phenotypic designations listed above may be useful when evaluating undiagnosed individuals and counseling their families, one should not place too much emphasis on assigning a phenotypic label to an affected individual given that these phenotypes lie on a continuum. Thus, the terms "severe," "intermediate," and "milder" ZSD are now preferred. Because of the breadth of the phenotypic spectrum, individuals with ZSD mainly come to clinical attention in the newborn period or later in childhood. Occasionally, the subtlety of symptoms delays diagnosis until adulthood.

Newborns are hypotonic with resultant poor feeding. Neonatal seizures are frequent and caused by underlying neuronal migration defects. Liver dysfunction may be evident as neonatal jaundice and elevation in liver function tests. Distinctive craniofacial features include flat face, broad nasal bridge, large anterior fontanelle, and widely split sutures. In severely affected children, bony stippling (chondrodysplasia punctata) at the patella(e) and the long bones may be noted, as well as renal cysts.

Older children manifest retinal dystrophy, sensorineural hearing loss, developmental delay with hypotonia, and liver dysfunction. Children may first come to attention because of a failed hearing screen. Onset and severity of the hearing and visual problems vary. A few children with a clinical diagnosis of neonatal adrenoleukodystrophy had transient leopard spot pigmentary retinopathy [Lyons et al 2004]. Liver dysfunction may be first identified in children with severe bleeding episodes caused by a vitamin K-responsive coagulopathy. Older children may develop adrenal insufficiency [Berendse et al 2014] and osteopenia [Rush et al 2016].

Adults are rarely diagnosed with ZSD, but exceptions have been reported. Usually these are individuals with predominantly sensory deficits but normal neurologic development [Moser et al 1995, Raas-Rothschild et al 2002, Majewski et al 2011, Ratbi et al 2015, Ratbi et al 2016, Smith et al 2016].

Severe ZSD

Severe ZSD (previously called Zellweger syndrome [ZS]) typically presents in the neonatal period with profound hypotonia, characteristic facies, gyral malformations, seizures, inability to feed, renal cysts, hepatic dysfunction, and chondrodysplasia punctata. Infants with severe ZSD are significantly impaired and usually die during the first year of life, usually having made no developmental progress. Death is usually secondary to progressive apnea or respiratory compromise from infection.

Intermediate/Milder ZSD

Intermediate/milder ZSD (previously called neonatal adrenoleukodystrophy [NALD] and infantile Refsum disease [IRD]) may present in the newborn period, but generally comes to attention later because of developmental delays, hearing loss, and/or visual impairment. Liver dysfunction may lead to a vitamin K-responsive coagulopathy. Children have also come to attention with episodes of hemorrhage; several children have presented in the first year of life with intracranial bleeding.

The clinical course is variable: while many children are very hypotonic, many learn to walk and talk.

Intermediate/milder ZSD is a progressive disorder with hearing and vision worsening with time. Some individuals may develop progressive degeneration of CNS myelin, a leukodystrophy, which may lead to loss of previously acquired skills and ultimately death.

Children who survive the first year and who have a non-progressive course have a 77% probability of reaching school age [Poll-The et al 2004]. Some have normal intellect. They are at risk for adrenal insufficiency over time. Typically, they also have ameliogenesis imperfecta of the secondary teeth.

Other

Individuals with atypical ZSD do not show sensory losses but have ataxia and peripheral neuropathy, and may have congenital cataracts (e.g., those with *PEX2*-ZSD [Sevin et al 2011], *PEX11B*-ZSD [Ebberink et al 2012], *PEX10*-ZSD [Steinberg et al 2009], *PEX12*-ZSD [Gootjes et al 2004], and *PEX16*-ZSD [Ebberink et al 2010]).

Note that although Heimler syndrome [Ratbi et al 2015, Ratbi et al 2016, Smith et al 2016] and ataxia (see Régal et al [2010], Renaud et al [2016]) have been reported as unique phenotypes associated with PEX gene defects, the authors consider them part of the ZSD continuum. In general, screening assays of individuals described as having these milder phenotypes do not show the biochemical profile typical of ZSD (Table 1).

Neuroimaging

MRI may identify cortical gyral abnormalities and germinolytic cysts that are highly suggestive of severe ZSD. Other brain MRI findings have been identified over time in individuals with milder ZSD.

In a small number of individuals with ZSD, diffusion-weighted imaging and diffusion tensor imaging can be used to discern white matter damage not detected by standard imaging [Patay 2005]. A demyelinating leukodystrophy can occur, but it is not clear which affected individuals are at increased risk for this development, or how it progresses in the individual.

Phenotype Correlations by Gene

Biallelic pathogenic variants in the two most commonly involved genes, *PEX1* and *PEX6*, are associated with the full continuum of clinical phenotypes. This clinical variability, in general, is also found in individuals with biallelic pathogenic variants in *PEX10*, *PEX12*, and *PEX26*. Although in the past, defects in some of the less common PEX genes appeared to be associated with severe clinical phenotypes, more recently the phenotypic spectrum of defects in all PEX genes has been found to include both severely and mildly affected individuals. Overall clinical and biochemical severity appears to be most related to the genotype and not a particular PEX gene.

Genotype-Phenotype Correlations

A general relationship appears to exist among the genotype, cellular phenotype (i.e., import of peroxisomal matrix proteins), and clinical phenotype [Moser 1999]. PEX gene defects are associated with loss-of-function variants; hence, variants that abolish activity (e.g., large deletions, nonsense, frameshift variants) are most severe. In contrast, missense variants that retain some residual function have a less severe effect on peroxisome assembly; however, it should be noted that not all missense variants have residual activity.

Due to the overall rarity of ZSD the opportunities to rigorously assess genotype and phenotype are limited. The *PEX1* variants p.Ile700TyrfsTer42 and p.Gly843Asp are exceptions, as hundreds of individuals homozygous or compound heterozygous for these variants have been identified (mostly in molecular research studies or clinical laboratories and not as part of a thorough natural history assessment).

- Homozygosity for *PEX1* p.Ile700TyrfsTer42 is associated with a more severe phenotype.
- Homozygosity for *PEX1* p.Gly843Asp has to date been associated with a milder ZSD phenotype and sometimes with an intermediate phenotype [Poll-The et al 2004]. In addition, an adult with a normal neurologic examination and an ocular phenotype was reported [Majewski et al 2011].

Nomenclature

Peroxisome biogenesis disorders (PBD) can be divided into two subtypes: the Zellweger spectrum disorder (ZSD) and the rhizomelic chondrodysplasia punctata spectrum, of which rhizomelic chondrodysplasia punctata

type 1 (RCDP1) is one subtype. RCDP1 is caused by biallelic pathogenic variants in *PEX7*, the receptor that recognizes peroxisome enzymes containing peroxisomal targeting signal 2. While individuals with RCDP1 have a perturbation in matrix protein import consistent with a peroxisomal assembly defect, they have a biochemical, cellular, and clinical phenotype distinct from ZSD. (See Rhizomelic Chondrodysplasia Punctata Type 1 for an in-depth description.)

ZSD has also formerly been referred to as cerebrohepatorenal syndrome, generalized peroxisomal disorders, Zellweger syndrome, neonatal adrenoleukodystrophy, or infantile Refsum disease (also known as infantile phytanic acid oxidase deficiency). Some individuals later shown to have ZSD were initially described as having hyperpipecolatemia or Heimler syndrome. The current preferred terminology is ZSD of severe, intermediate, or milder phenotype in order to recognize the common etiology, variations, and atypical presentations now being documented in individuals with biallelic pathogenic variants in any one of the 13 ZSD-PEX genes.

Of note, although Heimler syndrome [Ratbi et al 2015, Ratbi et al 2016, Smith et al 2016] and ataxia (see Régal et al [2010], Renaud et al [2016]) have been reported as unique phenotypes associated with PEX gene defects, the authors consider them part of the ZSD continuum.

Note: Refsum disease is clinically and molecularly distinct from infantile Refsum disease.

Prevalence

ZSD occurs worldwide with varying prevalence. In the past the incidence of ZSD had been estimated at 1:50,000 [Gould et al 2001]. More recent data from the New York state newborn screening laboratory confirmed 11 individuals with ZSD in more than 1.4 million screened for X-ALD using a biochemical assay (C26:0-LPC) that also detects ZSD (see Table 1) [Hubbard et al 2006, Hubbard et al 2009]. Thus, the confirmed incidence of ZSD in this population is 1:133,000 births [JJ Orsini, M Caggana, NY State Newborn Screening Laboratory Staff, personal communication, 2020]. Any estimate relying on a biochemical assay will be an underestimate because such assays fail to detect mild ZSD not associated with a definitive biochemical phenotype.

The main diagnostic center for peroxisomal diseases in Japan reported only 31 affected individuals over a 20-year period, with an estimated birth prevalence of 1:500,000 [Shimozawa et al 2003]. This lower incidence in Japan is mainly due to the absence of the common European *PEX1* variants p.Ile700TyrfsTer42 and p.Gly843Asp.

Genetically Related (Allelic) Disorders

PEX5 pathogenic variants in the alternate long form transcript (see Table 8) that specifically affects the domain that binds to the PEX7 receptor are associated with rhizomelic chondrodysplasia punctata type 5 and not ZSD.

No phenotypes other than those discussed in this *GeneReview* have been associated with mutation of the other 12 ZSD-PEX genes (see Table 2).

Differential Diagnosis

The differential diagnosis of Zellweger spectrum disorder (ZSD) varies with age at presentation and most prominent feature of the presentation. ZSD in newborns is most often confused with other conditions that result in profound hypotonia including Down syndrome, other chromosome abnormalities, and the disorders summarized in Table 3.

Table 3. Differential Diagnosis of ZSD in a Newborn with Profound Hypotonia

Gene(s) / Genetic Mechanism	Disorder	MOI
DMPK	Congenital myotonic dystrophy type 1	AD

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI
MTM1	XL myotubular myopathy	XL
PWCR / imprinting defect	Prader-Willi syndrome	See footnote 1.
RYR1 *SELENON*	Multiminicore disease (OMIM 255320, 602771)	AR
SMN1	Spinal muscular atrophy	AR

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PWCR = Prader-Willi critical region; XL = X-linked

1. The risk to the sibs of an affected child of having PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region.

Approximately 15% of individuals with a ZSD-like clinical phenotype and increased plasma VLCFA concentration actually have a single-enzyme deficiency of peroxisomal β-oxidation (i.e., D-bifunctional enzyme deficiency or acyl-CoA oxidase deficiency) and do not have a pathogenic variant in a PEX gene. Therefore, in children with elevated plasma VLCFA but no additional biochemical evidence of ZSD, a broader peroxisomal multigene panel that includes at least *ACOX1* and *HSD17B4* in addition to the 13 PEX genes is recommended.

Other differential diagnoses of peroxisomal and non-peroxisomal disorders that do not necessarily present as profound neonatal hypotonia are summarized in Tables 4a and 4b, respectively.

Table 4a. Differential Diagnosis of ZSD – Other Peroxisomal Disorders

Gene	Disorder	MOI	Clinical Findings	Biochemical Findings
ABCD1	XL adrenoleukodystrophy [1]	XL	Affected males are almost always developmentally normal before initial presentation.	↑ plasma VLCFA concentration in males; absence of other abnormalities of peroxisomes
ACBD5	Retinal dystrophy w/leukodystrophy (OMIM 618863) [2]	AR	ZSD-like clinical phenotype	↑ plasma VLCFA concentration, mild ↓ in plasmalogens
ACOX1	Acyl-CoA oxidase deficiency (OMIM 264470) [3]	AR	Intermediate ZSD-like clinical phenotype	↑ plasma VLCFA concentration [3]
DNM1L	Lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 [4] (OMIM 614388)	AD AR	Mildly dysmorphic facial features, truncal hypotonia, absent tendon reflexes, microcephaly, optic atrophy, failure to thrive, & severe DD	Mildly ↑ plasma VLCFA & persistent lactic acidemia
HSD17B4	D-bifunctional enzyme deficiency (OMIM 261515) [2]	AR	Spectrum of severity: from severe ZSD-like clinical phenotype (often presents w/severe seizures) to milder presentations w/normal biochemistry [5]	↑ plasma VLCFA concentration, branched chain fatty acids (pristanic & phytanic acids) & ↑ bile acid intermediates (THCA/DHCA)
SCP2	Leukoencephalopathy w/dystonia & motor neuropathy (OMIM 613724) [2]	AR	ZSD-like clinical phenotype	↑ plasma VLCFA concentration

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DHCA = dihydroxycholestanoic acid; Mat = maternal; MOI = mode of inheritance; SNHL = sensorineural hearing loss; THCA = trihydroxycholestanoic acid; VLCFA = very-long-chain fatty acid; XL = X-linked; ZSD = Zellweger spectrum disorder

1. See Tran et al [2014] for an example of a *PEX6* defect mistaken for X-linked adrenoleukodystrophy.

2. Abu-Safieh et al [2013], Ferdinandusse et al [2017]

3. See Watkins et al [1995] for a comparison of acyl-CoA oxidase deficiency and ZSD.

4. Waterham et al [2007], Sheffer et al [2016], Vanstone et al [2016], Yoon et al [2016]

5. Pierce et al [2010], Lines et al [2014]

Contiguous *ABCD1*/DXS1375E deletion syndrome (CADDS). An increase in plasma VLCFA concentration consistent with a defect in peroxisomal fatty acid metabolism can also be observed in CADDS, a contiguous deletion syndrome with a critical region spanning *ABCD1* and *BCAP31* [Corzo et al 2002].

Table 4b. Differential Diagnosis of ZSD – Non-Peroxisomal Disorders

Gene(s)	Disorder / Phenotype	MOI	Clinical Findings
>100 genes [1]	Hereditary hearing loss & deafness	AD AR XL Mat	SNHL
>24 genes [2]	Leber congenital amaurosis / early-onset severe retinal dystrophy	AR (AD)	Progressive visual loss
~350 genes [3]	Mitochondrial disease	AR AD Mat	May only affect a single organ or may involve multiple organ systems; often presents w/prominent neurologic & myopathic features
>80 genes [4]	Retinitis pigmentosa	AD AR XL (Digenic)	Progressive visual loss
ADGRV1 *CDH23* *CIB2* *MYO7A* *PCDH15* *USH1C* *USH1G* *USH1H* *USH2A* *WHRN*	Usher syndrome type I & type II	AR	• Type 1: Congenital, bilateral, profound SNHL, vestibular areflexia, & RP • Type 2: Congenital, bilateral SNHL & RP
>100 genes	Hereditary leukodystrophies [5]	AD AR XL Mat	Progressive spasticity w/loss of previous skills

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MOI = mode of inheritance; RP = retinitis pigmentosa; SNHL = sensorineural hearing loss; XL = X-linked

1. See Hereditary Hearing Loss and Deafness Overview.

2. See Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview.

3. See Mitochondrial Disease Overview.

4. See Retinitis Pigmentosa Overview.

5. See Parikh et al [2015], Table 2: Major neurologic signs and symptoms in the leukodystrophies.

Management

Klouwer et al [2015] (full text) and Braverman et al [2016] (full text) have published management and treatment guidelines for Zellweger spectrum disorder (ZSD).

Evaluations Following Initial Diagnosis

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

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Zellweger Spectrum Disorder

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Feeding & nutrition assessment	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/ dysphagia &/or aspiration risk.
Hearing	Audiologic eval	Assess for hearing loss.
Eyes	Comprehensive ophthalmologic assessment	OCT exam in compliant patients has shown cystoid macular edema [Ventura et al 2016].
Hepatic	• Liver function testing (AST, ALT, total & direct bilirubin, PT, PTT, INR) • C27 bile acid intermediates (DHCA & THCA) • Ultrasound eval &/or liver fibroscan	Liver fibrosis can occur insidiously over time; portal hypertension & esophageal varices can occur; rare adults have developed hepatocellular carcinoma in the setting of fibrosis [Berendse et al 2019, Heubi & Bishop 2018].
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Endocrine	• Eval of adrenal function (ACTH & cortisol) • Consideration of ACTH stimulation test as appropriate	Adrenal insufficiency may occur during periods of stress.
	• Eval of bone density by DXA • Consider serum vitamin D level.	Pathologic fractures have occurred in persons at all ages; evaluate as clinically indicated [Rush et al 2016].
Renal	Urine oxalate /creatinine ratio, serial renal ultrasound (can be done w/liver ultrasounds)	Some patients develop urolithiasis & nephrocalcinosis assoc w/urinary oxalate load [van Woerden et al 2006].
Dental	Dental eval	Ameliogenesis imperfects, typically of secondary teeth, requires extensive dental interventions.
Genetic counseling	By genetics professionals [1]	To inform patients & families re nature, MOI, & implications of ZSD in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

DHCA = dihydroxycholestanoic acid; DXA = dual-energy x-ray absorptiometry; MOI = mode of inheritance; OCT = optical coherence tomography; THCA = trihydroxycholestanoic acid

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment focuses on symptomatic therapy.

Table 6. Treatment of Manifestations in Individuals with Zellweger Spectrum Disorder

Manifestation/ Concern	Treatment	Considerations/Other
Feeding & nutrition	• Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues. • No specific metabolic diet recommended [1]	W/many children having some degree of malabsorption, elemental formulas may be better tolerated.
Hearing	Hearing aids in children found to have hearing impairment	See also Hereditary Hearing Loss and Deafness Overview for discussion of management issues.
Vision impairment	• Cataract removal to preserve vision • Glasses to correct refractive errors	
Liver dysfunction	• Supplementation of vitamin K & other fat-soluble vitamins • Cholbam™ (cholic acid) supplementation [2] • Varices can be treated w/sclerosing therapies.	Cholic acid supplementation can worsen liver disease in individuals with preexisting fibrosis & advanced liver disease [Berendse et al 2016].
Seizures	Standard treatment w/ASM by experienced neurologist	No type of ASM is contraindicated. Seizures may be difficult to control despite use of appropriate medication.
DD/ID	Provide early-intervention services.	
Adrenal insufficiency	Adrenal replacement therapy	
Osteopenia	• Vitamin D supplementation • Consider bisphosphonate.	Benefits of bisphosphonate treatment noted in 1 case report [Rush et al 2016]
Ameliogenesis imperfecta	Treatment per dentist	Tran et al [2011], Acharya et al [2012]
Renal oxalate stones	Supportive treatment has included hydration, lithotripsy, surgical intervention.	Pyridoxine treatment did not ↓ oxalate excretion in 1 study [van Woerden et al 2006].
Vaccination	Annual influenza & respiratory syncytial virus vaccines as well as usual vaccination schedule	

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability

1. A diet low in phytanic acid has been proposed, based mainly on the weak analogy with adult Refsum disease, in which accumulation of phytanic acid is pathogenic and treatment involves restricted dietary intake of phytanic acid (including avoidance of full-fat cow's milk products and high-fat meat products from ruminants). Its effectiveness in ZSD has never been proven. All standard infant formulas are already low in phytanic acid.

2. By providing the final C24 bile acid product, the bile acid pathway undergoes feedback inhibition, thus reducing the levels of elevated C27 bile acid intermediates that are thought to be toxic to the liver. Cholic acid therapy does in fact decrease C27 bile acid intermediates (which should be measured), but its clinical effect in ZSD is not yet known.

Surveillance

Table 7. Recommended Surveillance for Individuals with Zellweger Spectrum Disorder

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Hearing	Audiology eval	Annually
Eyes	• Ophthalmologic eval • Visual field testing	

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Hepatic	• Coagulation factors & other synthetic liver functions (PT, PTT, AST, ALT, total & direct bilirubin) • Ultrasound &/or fibroscan to evaluate liver architecture	Annually; persons w/overt hepatic dysfunction require more frequent monitoring.
Neurologic	Monitor those w/seizures as clinically indicated.	At each visit
	Head MRI to evaluate for white matter changes that may explain changes in cognitive &/or motor ability	As needed
Development	Monitor developmental progress & educational needs.	At each visit
Endocrine	Assess adrenal function (ACTH & cortisol).	By age 1 yr; annually thereafter
Dental	Dental exam	Every 6 mos after dental eruption
Renal stones	• Urine oxalate-to-creatinine ratio • Consider renal imaging when performing liver imaging.	Annually
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

Evaluation of Relatives at Risk

When the proband is on the milder end of the ZSD spectrum, it is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs in order to identify as early as possible those who are affected, and thus would benefit from annual hearing and ophthalmologic evaluation and routine monitoring of coagulation factors, adrenal function, and liver function. Note that molecular genetic testing for the pathogenic variants identified in the family is warranted as the results of screening assays (Table 1) in persons at the mild end of the ZSD spectrum may be highly variable.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

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

Genetic Counseling

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

Mode of Inheritance

Zellweger spectrum disorder (ZSD) is typically inherited in an autosomal recessive manner.

Note: One *PEX6* variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state due to allelic expression imbalance dependent on allelic background (see Table 9).

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one ZSD-causing pathogenic variant based on family history).
- Once the causative pathogenic variants have been identified in the proband, molecular genetic testing of the parents is recommended to confirm that both parents are heterozygous for a ZSD-causing pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a ZSD-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- In general, greater clinical variation is observed in families in which affected sibs are on the milder end of ZSD.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- In general, affected individuals do not reproduce.
- Some individuals with milder phenotypes may reproduce; the offspring of such individuals are obligate heterozygotes (carriers of a ZSD-causing pathogenic variant).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a ZSD-causing pathogenic variant.

Carrier detection

- **Molecular genetic** carrier testing for at-risk relatives requires prior identification of the ZSD-causing pathogenic variants in the family.
- **Biochemical** testing is not accurate for carrier testing, as the biochemical markers in carriers are normal.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the ZSD-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for ZSD are possible.

Biochemical testing. Biochemical testing using CVS or amniocytes may be used for prenatal diagnosis after confirming the biochemical defects in cultured fibroblasts from an affected family member. This approach may be helpful if DNA testing in the proband yields equivocal results or if DNA testing in the proband is not possible. (Note: Only a few specialized laboratories offer biochemical prenatal testing for ZSD.)

Biochemical testing of cultured amniocytes may also be useful when abnormalities suggestive of ZSD are detected on prenatal ultrasound examination.

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

Resources

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

- **Global Foundation for Peroxisomal Disorders**
  5147 South Harvard Avenue
  Suite 181
  Tulsa OK
  Fax: 918-516-0227
  Email: contactus@thegfpd.org
  www.thegfpd.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Zellweger Syndrome Information Page
- **NCBI Genes and Disease**
  Zellweger syndrome
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  www.ulf.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Zellweger Spectrum Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PEX1	7q21.2	Peroxisomal ATPase PEX1	dbPEX, PEX1 Gene Database PEX1 database	PEX1	PEX1
PEX2	8q21.13	Peroxisome biogenesis factor 2	dbPEX, PEX2 Gene Database PEX2 database	PEX2	PEX2
PEX3	6q24.2	Peroxisomal biogenesis factor 3	dbPEX, PEX3 Gene Database PEX3 database	PEX3	PEX3
PEX5	12p13.31	Peroxisomal targeting signal 1 receptor	dbPEX, PEX5 Gene Database PEX5 database	PEX5	PEX5
PEX6	6p21.1	Peroxisomal ATPase PEX6	dbPEX, PEX6 Gene Database PEX6 database	PEX6	PEX6
PEX10	1p36.32	Peroxisome biogenesis factor 10	dbPEX, PEX10 Gene Database PEX10 database	PEX10	PEX10
PEX11B	1q21.1	Peroxisomal membrane protein 11B		PEX11B	PEX11B
PEX12	17q12	Peroxisome assembly protein 12	dbPEX, PEX12 Gene Database PEX12 database	PEX12	PEX12
PEX13	2p15	Peroxisomal membrane protein PEX13	dbPEX, PEX13 Gene Database PEX13 database	PEX13	PEX13
PEX14	1p36.22	Peroxisomal membrane protein PEX14	dbPEX, PEX14 Gene Database PEX14 database	PEX14	PEX14
PEX16	11p11.2	Peroxisomal membrane protein PEX16	dbPEX, PEX16 Gene Database PEX16 database	PEX16	PEX16
PEX19	1q23.2	Peroxisomal biogenesis factor 19	dbPEX, PEX19 Gene Database PEX19 database	PEX19	PEX19
PEX26	22q11.21	Peroxisome assembly protein 26	dbPEX, PEX26 Gene Database PEX26 database	PEX26	PEX26

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Zellweger Spectrum Disorder (View All in OMIM)

170993	PEROXISOME BIOGENESIS FACTOR 2; PEX2

Table B. continued from previous page.

202370	PEROXISOME BIOGENESIS DISORDER 2B; PBD2B
214100	PEROXISOME BIOGENESIS DISORDER 1A (ZELLWEGER); PBD1A
266510	PEROXISOME BIOGENESIS DISORDER 3B; PBD3B
600279	PEROXISOME BIOGENESIS FACTOR 19; PEX19
600414	PEROXISOME BIOGENESIS FACTOR 5; PEX5
601498	PEROXISOME BIOGENESIS FACTOR 6; PEX6
601758	PEROXISOME BIOGENESIS FACTOR 12; PEX12
601789	PEROXISOME BIOGENESIS FACTOR 13; PEX13
601791	PEROXISOME BIOGENESIS FACTOR 14; PEX14
602136	PEROXISOME BIOGENESIS FACTOR 1; PEX1
602859	PEROXISOME BIOGENESIS FACTOR 10; PEX10
603164	PEROXISOME BIOGENESIS FACTOR 3; PEX3
603360	PEROXISOME BIOGENESIS FACTOR 16; PEX16
603867	PEROXISOME BIOGENESIS FACTOR 11B; PEX11B
608666	PEROXISOME BIOGENESIS FACTOR 26; PEX26

Molecular Pathogenesis

Biallelic pathogenic variants in any one of the 13 PEX genes listed in Table 2 are known to cause Zellweger spectrum disorder (ZSD) in humans. These PEX genes encode proteins required for peroxisome biogenesis called "peroxins." Several peroxins are necessary for membrane biogenesis (PEX3, PEX16, and PEX19) and division (PEX11b), while the remaining genes associated with ZSD encode proteins comprising the peroxisomal matrix import machinery [Waterham & Ebberink 2012, Fujiki 2016].

Mechanism of disease causation. PEX gene defects associated with ZSD reported to date are predicted to be loss-of-function variants.

Table 8. Zellweger Spectrum Disorder: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
PEX5	Alternative splicing of the *PEX5* mRNA produces 2 functional protein variants. The longer variant, PEX5L, contains an additional 37 amino acids compared to the shorter PEX5S [Ebberink et al 2009 and references therein]. The reference sequence for PEX5L (X84899 or NM_001131025.1) [2] should be used for sequence analysis.
PEX6	Common variant in the 3-UTR (c.*442_445delTAAA) [3]

1. Genes from Table 1 in alphabetic order
2. Sequences of coding region are identical.
3. See Table 9.

Table 9. Zellweger Spectrum Disorder: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change (Alias [2])	Predicted Protein Change	Comment [Reference]
PEX1	NM_000466.2 NP_000457.1	c.2097dupT	p.Ile700TyrfsTer42	Most common *PEX1* variants; ~80% of persons w/a *PEX1* pathogenic variant have at least 1 of these common alleles. (See Prevalence & Genotype-Phenotype Correlations.) [3]
		c.2528G>A	p.Gly843Asp	

Table 9. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change (Alias [2])	Predicted Protein Change	Comment [Reference]
PEX6	NM_000287.3 NP_000278.3	c.2578C>T	p.Arg860Trp	Assoc w/ZSD in the heterozygous state, acting in an apparent dominant fashion due to allelic expression imbalance assoc w/common variant NM_000287.3:c.*442_445delTAAA in the 3' UTR that disrupts 1 of 2 polyadenylation sites. Persons who have c.*442_445delTAAA on both chromosomes are unaffected; but those who have c.2578C>T (p.Arg860Trp) on the c.*442_445delTAAA background but lack c.*442_445delTAAA on the opposite chromosome have a 2- to 3-fold ↑ in abnormal PEX6 (compared to controls) & biochemical & clinical features consistent w/ZSD [Falkenberg et al 2017].
PEX10	NM_002617.3 NP_002608.1	c.814_815delCT (PEX10Δ814/815)	p.Leu272ValfsTer66	Common allele in the Japanese population, where it appears to have arisen once on an ancestral haplotype [Shimozawa et al 2003]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes from Table 1 in alphabetic order
2. Variant designation that does not conform to current naming conventions
3. It has been proposed that the two common alleles reside on specific haplotypes and arose as founder variants [Collins & Gould 1999], suggesting that these sites are not hot spots for recurrent pathogenic variants.

Chapter Notes

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* Hugo W Moser, MD was Professor of Neurology and Pediatrics at Johns Hopkins University School of Medicine and former Director of the Kennedy Krieger Institute in Baltimore. He was a world-renowned expert in the field of neurogenetics. He was best known for his leadership role in understanding, diagnosing, and treating adrenoleukodystrophy (ALD). Dr Moser died of cancer on January 20, 2007 at age 82. He is greatly missed by his family, friends, colleagues, and patients.

Revision History

- 29 October 2020 (sw) Comprehensive update posted live
- 21 December 2017 (sjs) Revision: *PEX6* pathogenic variant added
- 16 November 2017 (bp) Comprehensive update posted live
- 10 May 2012 (cd) Revision: to clarify that prenatal testing using biochemical methods is possible
- 18 January 2011 (me) Comprehensive update posted live
- 26 April 2006 (me) Comprehensive update posted live
- 1 October 2004 (sjs) Revision
- 12 December 2003 (me) Review posted live
- 1 August 2003 (sjs) Original submission

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