



Zellweger spectrum disorder

Zellweger spectrum disorder is a group of conditions that have overlapping signs and symptoms and affect many parts of the body. This group of conditions includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease. These conditions were once thought to be distinct disorders but are now considered to be part of the same condition spectrum. Zellweger syndrome is the most severe form of the Zellweger spectrum disorder, NALD is intermediate in severity, and infantile Refsum disease is the least severe form. Because these three conditions are now considered one disorder, some researchers prefer not to use the separate condition names but to instead refer to cases as severe, intermediate, or mild.

Individuals with Zellweger syndrome, at the severe end of the spectrum, develop signs and symptoms of the condition during the newborn period. These infants experience weak muscle tone (hypotonia), feeding problems, hearing and vision loss, and seizures. These problems are caused by the breakdown of myelin, which is the covering that protects nerves and promotes the efficient transmission of nerve impulses. The part of the brain and spinal cord that contains myelin is called white matter. Destruction of myelin (demyelination) leads to loss of white matter (leukodystrophy). Children with Zellweger syndrome also develop life-threatening problems in other organs and tissues, such as the liver, heart, and kidneys. They may have skeletal abnormalities, including a large space between the bones of the skull (fontanelles) and characteristic bone spots known as chondrodysplasia punctata that can be seen on x-ray. Affected individuals have distinctive facial features, including a flattened face, broad nasal bridge, and high forehead. Children with Zellweger syndrome typically do not survive beyond the first year of life.

People with NALD or infantile Refsum disease, which are at the less-severe end of the spectrum, have more variable features than those with Zellweger syndrome and usually do not develop signs and symptoms of the disease until late infancy or early childhood. They may have many of the features of Zellweger syndrome; however, their condition typically progresses more slowly. Children with these less-severe conditions often have hypotonia, vision problems, hearing loss, liver dysfunction, developmental delay, and some degree of intellectual disability. Most people with NALD survive into childhood, and those with infantile Refsum disease may reach adulthood. In rare cases, individuals at the mildest end of the condition spectrum have developmental delay in childhood and hearing loss or vision problems beginning in adulthood and do not develop the other features of this disorder.

Frequency

Zellweger spectrum disorder is estimated to occur in 1 in 50,000 individuals.

Causes

Mutations in at least 12 genes have been found to cause Zellweger spectrum disorder. These genes provide instructions for making a group of proteins known as peroxins, which are essential for the formation and normal functioning of cell structures called peroxisomes. Peroxisomes are sac-like compartments that contain enzymes needed to break down many different substances, including fatty acids and certain toxic compounds. They are also important for the production of fats (lipids) used in digestion and in the nervous system. Peroxins assist in the formation (biogenesis) of peroxisomes by producing the membrane that separates the peroxisome from the rest of the cell and by importing enzymes into the peroxisome.

Mutations in the genes that cause Zellweger spectrum disorder prevent peroxisomes from forming normally. Diseases that disrupt the formation of peroxisomes, including Zellweger spectrum disorder, are called peroxisome biogenesis disorders. If the production of peroxisomes is altered, these structures cannot perform their usual functions. The signs and symptoms of Zellweger syndrome are due to the absence of functional peroxisomes within cells. NALD and infantile Refsum disease are caused by mutations that allow some peroxisomes to form.

Mutations in the *PEX1* gene are the most common cause of Zellweger spectrum disorder and are found in nearly 70 percent of affected individuals. The other genes associated with Zellweger spectrum disorder each account for a smaller percentage of cases of this condition.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- cerebrohepatorenal syndrome
- PBD-ZSD
- PBD, ZSS
- peroxisome biogenesis disorders, Zellweger syndrome spectrum
- Zellweger spectrum
- Zellweger syndrome spectrum
- ZSD

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
[/primer/testing/genetictesting](#)
- Genetic Testing Registry: Neonatal adrenoleucodystrophy
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3550234/>
- Genetic Testing Registry: Peroxisome biogenesis disorder 1A (Zellweger)
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4721541/>
- Genetic Testing Registry: Peroxisome biogenesis disorder 1B
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0282527/>
- Genetic Testing Registry: Peroxisome biogenesis disorders, Zellweger syndrome spectrum
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1832200/>

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22Zellweger+syndrome+spectrum%22+OR+%22Zellweger+Syndrome%22+OR+%22Zellweger+spectrum%22+OR+%22Peroxisome+Biogenesis+Disorders%22>

Other Diagnosis and Management Resources

- GeneReview: Zellweger Spectrum Disorder
<https://www.ncbi.nlm.nih.gov/books/NBK1448>
- MedlinePlus Encyclopedia: Seizures
<https://medlineplus.gov/ency/article/003200.htm>

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Hypotonia
<https://medlineplus.gov/ency/article/003298.htm>
- Encyclopedia: Myelin
<https://medlineplus.gov/ency/article/002261.htm>
- Encyclopedia: Seizures
<https://medlineplus.gov/ency/article/003200.htm>
- Health Topic: Leukodystrophies
<https://medlineplus.gov/leukodystrophies.html>

Genetic and Rare Diseases Information Center

- Peroxisome biogenesis disorder-Zellweger syndrome spectrum
<https://rarediseases.info.nih.gov/diseases/11890/peroxisome-biogenesis-disorder-zellweger-syndrome-spectrum>
- Zellweger syndrome
<https://rarediseases.info.nih.gov/diseases/7917/zellweger-syndrome>

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Infantile Refsum disease
<https://www.ninds.nih.gov/Disorders/All-Disorders/Infantile-Refsum-Disease-Information-Page>
- National Institute of Neurological Disorders and Stroke: Zellweger syndrome
<https://www.ninds.nih.gov/Disorders/All-Disorders/Zellweger-Syndrome-Information-Page>

Educational Resources

- MalaCards: peroxisome biogenesis disorder-zellweger syndrome spectrum
https://www.malacards.org/card/peroxisome_biogenesis_disorder_zellweger_syndrome_spectrum
- MalaCards: zellweger spectrum disorder
https://www.malacards.org/card/zellweger_spectrum_disorder
- Merck Manual Professional Version: Peroxisomal Disorders
<https://www.merckmanuals.com/professional/pediatrics/inherited-disorders-of-metabolism/peroxisomal-disorders>
- Orphanet: Infantile Refsum disease
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=772
- Orphanet: Neonatal adrenoleukodystrophy
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=44
- Orphanet: Peroxisome biogenesis disorder
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=79189
- Orphanet: Zellweger syndrome
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=912

Patient Support and Advocacy Resources

- European Leukodystrophy Association
<https://ela-asso.com/en/>
- Global Foundation for Peroxisomal Disorders
<https://www.thegfpd.org/>

- Hunter's Hope Foundation
<https://www.huntershope.org/>
- Metabolic Support UK
<https://www.metabolicsupportuk.org/>
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/zellweger-spectrum-disorders/>
- Resource list from the University of Kansas Medical Center: Leukodystrophy
<http://www.kumc.edu/gec/support/leukodys.html>
- United Leukodystrophy Foundation
<https://ulf.org/the-zellweger-spectrum-2/>

Clinical Information from GeneReviews

- Zellweger Spectrum Disorder
<https://www.ncbi.nlm.nih.gov/books/NBK1448>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28zellweger+spectrum%5BTIAB%5D%29+OR+%28zellweger+syndrome+spectrum%5BTIAB%5D%29+OR+%28zellweger+syndrome%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- PEROXISOME BIOGENESIS DISORDER 1A (ZELLWEGER)
<http://omim.org/entry/214100>
- PEROXISOME BIOGENESIS DISORDER 1B
<http://omim.org/entry/601539>
- PEROXISOME BIOGENESIS DISORDER 2A (ZELLWEGER)
<http://omim.org/entry/214110>
- PEROXISOME BIOGENESIS DISORDER 2B
<http://omim.org/entry/202370>
- PEROXISOME BIOGENESIS DISORDER 3A (ZELLWEGER)
<http://omim.org/entry/614859>
- PEROXISOME BIOGENESIS DISORDER 3B
<http://omim.org/entry/266510>
- PEROXISOME BIOGENESIS DISORDER 4A (ZELLWEGER)
<http://omim.org/entry/614862>
- PEROXISOME BIOGENESIS DISORDER 5A (ZELLWEGER)
<http://omim.org/entry/614866>

- PEROXISOME BIOGENESIS DISORDER 6A (ZELLWEGER)
<http://omim.org/entry/614870>
- PEROXISOME BIOGENESIS DISORDER 7A (ZELLWEGER)
<http://omim.org/entry/614872>
- PEROXISOME BIOGENESIS DISORDER 8A (ZELLWEGER)
<http://omim.org/entry/614876>
- PEROXISOME BIOGENESIS DISORDER 10A (ZELLWEGER)
<http://omim.org/entry/614882>
- PEROXISOME BIOGENESIS DISORDER 11A (ZELLWEGER)
<http://omim.org/entry/614883>
- PEROXISOME BIOGENESIS DISORDER 12A (ZELLWEGER)
<http://omim.org/entry/614886>
- PEROXISOME BIOGENESIS DISORDER 13A (ZELLWEGER)
<http://omim.org/entry/614887>
- PEROXISOME BIOGENESIS DISORDER 14B
<http://omim.org/entry/614920>

Medical Genetics Database from MedGen

- Peroxisome biogenesis disorders, Zellweger syndrome spectrum
<https://www.ncbi.nlm.nih.gov/medgen/330407>

Sources for This Summary

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