

What are Zellweger spectrum disorders?

Zellweger spectrum disorders are a group of inherited diseases that include Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease,¹ and Heimler syndrome.² Zellweger spectrum disorders vary in severity and age at onset and are characterized by progressive neurological disease, hypotonia, liver disease, and hearing and vision loss.¹ Individuals with Zellweger spectrum disorders have defects in peroxins, proteins required for peroxisome biogenesis.³ Peroxisomes are found in almost every cell of the body and are essential for normal brain and nervous system development as well as normal eye, liver, kidney, and bone functions.⁴

What are the symptoms of Zellweger spectrum disorders and what treatment is available?

Zellweger syndrome is the most severe Zellweger spectrum disorder and typically has neonatal onset, with death occurring within the first year of life.¹ Signs and symptoms of neonatal adrenoleukodystrophy and infantile Refsum disease are usually seen in late infancy or early childhood.³ Children with neonatal adrenoleukodystrophy often survive into childhood and children with infantile Refsum disease may reach adulthood.^{1,3} Heimler syndrome has distinct and milder symptoms.²

Zellweger syndrome symptoms usually include:^{1,3}

- Profound hypotonia (low muscle tone)
- Feeding problems
- Severe developmental delay
- Seizures
- Hearing and vision loss
- Distinctive facial features
- Liver and kidney disease
- Chondroplasia punctata (x-ray findings of scattered calcification at the end of the long bones and knee)

Children with neonatal adrenoleukodystrophy and infantile Refsum disease have many of the same symptoms as Zellweger syndrome with slower progression of symptoms. Symptoms may include:^{1,3}

- Variable hypotonia (low muscle tone)
- Intellectual disability
- Liver and kidney disease
- Seizures
- Hearing and vision loss
- Hemorrhage (severe bleeding episodes) including intracranial bleeds
- Regression (loss of previously acquired skills)

Individuals with Heimler syndrome do not have many of the features of other Zellweger syndrome spectrum disorders. Symptoms may include:²

- Sensorineural hearing loss
- Amelogenesis imperfecta (abnormal tooth enamel)
- Variable retinal pigmentation with progressive visual impairment
- Nail abnormalities

There is no cure for Zellweger spectrum disorders. Treatment includes periodic medical evaluation and supportive care for symptoms.¹

How are Zellweger spectrum disorders inherited?

Zellweger spectrum disorders are a group of autosomal recessive diseases caused by mutations in at least 12 different genes, including *PEX1*, *PEX2*, *PEX6*, *PEX10*, *PEX12*, and *PEX26*, which account for more than 90% of cases of Zellweger spectrum disorders.¹ An individual who has one mutation in any of the *PEX* genes is a carrier and is not expected to have related health problems. An individual who has two mutations in the same gene, one from each parent, is expected to be affected with one of the Zellweger spectrum disorders. For example, a child with two *PEX1* mutations is expected to be affected, and a child with one *PEX1* mutation and one *PEX6* mutation is a carrier.

If both members of a couple are carriers, the risk for an affected child is 25% in each pregnancy; therefore, it is especially important that the reproductive partner of a carrier be offered testing.

Who is at risk for a Zellweger spectrum disorder?

A Zellweger spectrum disorder can occur in individuals of all races and ethnicities, although some variation in frequency has been observed. Zellweger spectrum disorders are estimated to have an overall incidence of 1 in 50,000.³

Estimated carrier frequencies by causative gene^{1,3,5}

Zellweger spectrum disorder	Population	Carrier Frequency
<i>PEX1</i> -related	Worldwide	1 in 134
<i>PEX2</i> -related	Ashkenazi Jewish	1 in 123
<i>PEX6</i> -related	Worldwide	1 in 280
<i>PEX10</i> -related	Worldwide	1 in 646
<i>PEX12</i> -related	Worldwide	1 in 373
<i>PEX26</i> - related	Worldwide	1 in 646

Having a relative who is a carrier or is affected can also increase an individual’s risk of being a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

What does a positive test result mean?

If a gene mutation is identified, an individual should speak to a physician or genetics health professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

What does a negative test result mean?

A negative result reduces, but does not eliminate, the possibility that an individual carries a gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results.

Where can I get more information?

National Institute of Neurological Disorders and Stroke (NINDS): Zellweger Spectrum Information Page
<https://www.ninds.nih.gov/Disorders/All-Disorders/Zellweger-Syndrome-Information-Page>

Genetics Home Reference: <http://ghr.nlm.nih.gov/condition/zellweger-spectrum-disorder>

National Organization for Rare Disorders: <http://rarediseases.org/rare-diseases/zellweger-spectrum-disorders/>

References

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2. Ratbi I, *et al.* Heimler Syndrome Is Caused by Hypomorphic Mutations in the Peroxisome-Biogenesis Genes PEX1 and PEX6. *Am J Hum Genet.* 2015;97:535-545.
3. Zellweger spectrum. *Genetics Home Reference*. Available at <http://ghr.nlm.nih.gov/condition/zellweger-spectrum-disorder>. Accessed February 3, 2016.
4. NINDS Zellweger Syndrome Information Page. Available at <http://www.ninds.nih.gov/disorders/zellweger/zellweger.htm>. Accessed February 3, 2016.
5. Fedick A, *et al.* A deleterious mutation in the PEX2 gene causes Zellweger syndrome in individuals of Ashkenazi Jewish descent. *Clin Genet.* 2014;85:343-346.