Australian Leukodystrophy Clinical and Research Program

Peroxisomal Biogenesis Disorder – Zellweger Spectrum Disorder (PBD-ZSD)

What are peroxisomal biogenesis disorders (PBD)?

Peroxisomes are cellular organelles that assist in the release of energy currency and play a major role in the decomposition of amino acids, uric acids and fatty acids.

If there are disruptions to this process, as seen in PBD, the undigested acids accumulate in the cells and have toxic effects.

PBD-ZSD are a group of conditions that affect the function of the peroxisomes, resulting in hearing loss, impaired vision, movement disorders and multiple organ dysfunction.

The spectrum of disease ranges from severe to mild:

1. **Zellweger Syndrome (ZS)**
   ZS is usually diagnosed in infancy and is the most severe form on the PBD spectrum. It causes low muscle tone and feeding problems. Affected children make minimal developmental progress and may have seizures and liver disease.
2. **Neonatal Adrenoleukodystrophy (NALD)**
   NALD is an intermediate form of PBD characterized by seizures, movement disorder, progressive hearing and vision problems and developmental delay. Affected individuals are usually diagnosed in late infancy or early childhood.
3. **Infantile Refsum disease (IRD)**
   IRD is the mildest form. It causes similar health problems to the intermediate form (NALD) with later onset and/or milder symptoms. Life expectancy varies largely depending upon the age of onset and severity of symptoms.

What are the symptoms seen in PBD-ZSD?

Some of the most common features observed in PBD-ZSD are:

- Developmental delay
- Low muscle tone
- Feeding difficulties
- Seizures
- Progressive visual impairment
- Progressive hearing impairment
- Leukodystrophy
- Abnormal liver function
- Abnormal kidney function

What causes PBD-ZSD?

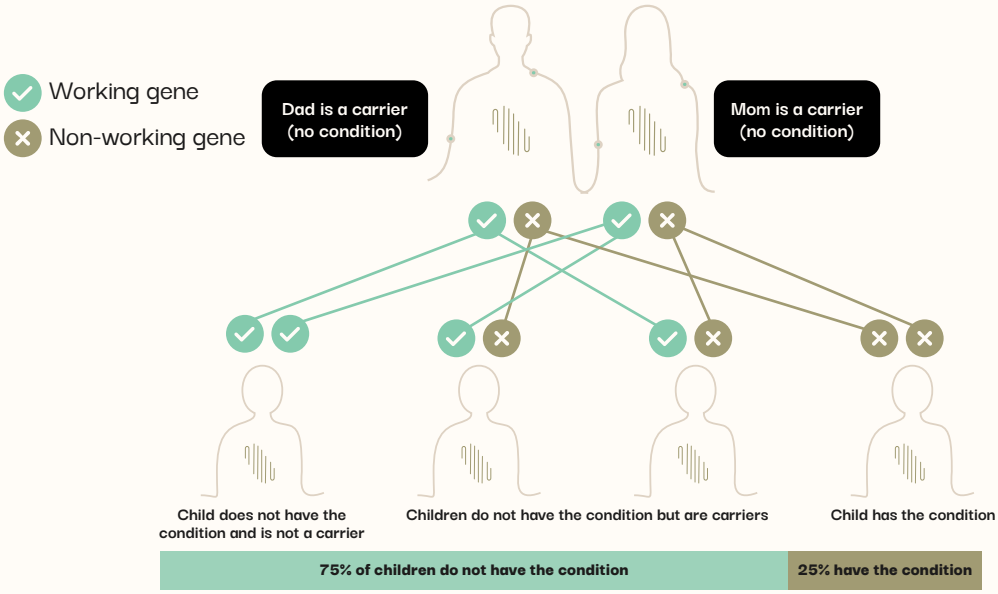
PBD-ZSD are caused by changes in any of the 13 PEX genes (*PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26*). These genes encode a group of proteins called peroxins, which are vital for the transport or biogenesis of peroxisomes. Changes in these genes result in abnormal transport or biogenesis of peroxisomes.

How are PBD-ZSD diagnosed?

- A blood test to measure levels of specific metabolites that are processed by peroxisomes.
- MRI brain showing signs of leukodystrophy (abnormal white matter).
- Detection of eye abnormalities by an ophthalmologist.
- Genetic testing: identification of disease-causing changes ("pathogenic variants") in any of the above-mentioned genes confirms the clinical diagnosis and subtype of the disorder.

How are PBD-ZSD inherited?

All subtypes of PBD-ZSD are inherited in an autosomal recessive pattern. This is where both copies of the relevant gene are altered. Each parent is a carrier and passes on one altered copy of the gene. When both parents are carriers, they have a 1 in 4 chance, in each pregnancy, of having an affected child. Siblings of the affected individual and the parents may also be carriers.



Can PBD-ZSD be treated?

There are currently no targeted treatments for PBD-ZSD. Treatment is supportive and aimed at management of symptoms by a multidisciplinary team.

Support and resources:

- **Global Foundation for Peroxisomal Disorders** thegfpd.org
- **Leukodystrophy Australia** leuko.org.au
- **Mission Massimo Foundation** missionmassimo.com
- **United Leukodystrophy Foundation** ulf.org/leukodystrophies/adrenoleukodystrophy
- **Hunter's Hope** huntershope.org/familycare/leukodystrophies/adrenoleukodystrophy

Research:

- **Australian Leukodystrophy Clinical and Research Program** leukonet.org.au
- **Clinical trials** https://clinicaltrials.gov/ct2/results?cond=peroxisomal&term=&cntry=&state=&city=&dist=