Pelizaeus-Merzbacher Disease (PMD)

What is PMD?

PMD is a type of leukodystrophy.

Leukodystrophies are a group of genetic conditions that mainly affect the white matter of the brain and spinal cord. The white matter is the wiring network of the brain that connects different brain regions and links the brain to the spinal cord and rest of the body.

PMD is characterized by a lack of development of myelin. Myelin provides support for the wiring networks and enables transmission of signals between the nerves in the brain and spine and the rest of the body. This lack of development of myelin is called 'hypomyelination'.

PMD is divided into **classic and connatal types**, depending upon of age of onset and severity of the symptoms.

What are the symptoms of PMD?

The symptoms observed in affected individuals varies between types:

1. Classical Type:

Symptoms start showing typically by 2 months of age. Affected children make slow developmental progress then lose skills from late childhood to early adulthood.

Symptoms include:

- Low muscle tone with failure to develop head control.
- Involuntary movements of the eyes (nystagmus).
- Slow speech (dysarthria).
- Delay in motor and cognitive development
- Abnormal muscle movements (choreoathetosis).
- Abnormal tightness of lower limbs (spasticity).
- Tremors of head (titubation).

2. Connatal Type:

A more severe form of the disease presenting at birth. This type of PMD progresses more rapidly and is usually fatal during childhood.

Symptoms include:

- Nystagmus.
- High pitched breathing due to obstructed airway.
- Failure to attain psychomotor milestones.
- Severe tightness of limbs (spasticity).
- Restricted movement due to joint deformities (contractures).

What causes PMD?

PMD is caused by changes in the *PLP1* gene. This gene provides instructions for two proteins: proteolipid protein 1 and DM20. These proteins are essential for making myelin. Changes in the *PLP1* gene result in hypomyelination, nerve fiber impairment and nervous system dysfunction.

How is PMD diagnosed?

- MRI brain showing a lack of myelination.
- A diagnosis is established after the identification of a disease-causing change in the *PLP1* gene.

How is PMD inherited?

The *PLP1* gene is located on the X chromosome. The X chromosome is a sex chromosome and the number of these differ between males and females: males have one X chromosome and females have two. Because of this, a disease-causing change on an X chromosome affects males and females differently. PMD usually only affects males. The *PLP1* mutation might occur for the first time in an affected male or may be inherited from a female 'carrier'. This type of inheritance is called 'X-linked recessive' and is shown in the cartoon below. Depending on the mutation type, female carriers may develop mild symptoms of the disease in adulthood.

Figure A.

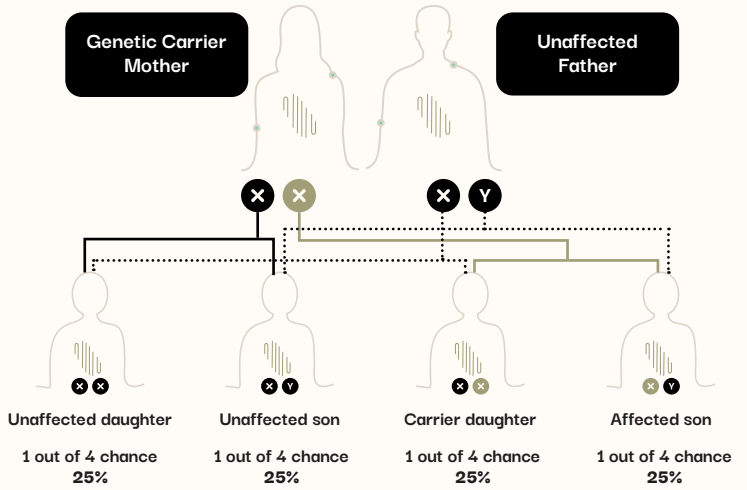

Figure B.

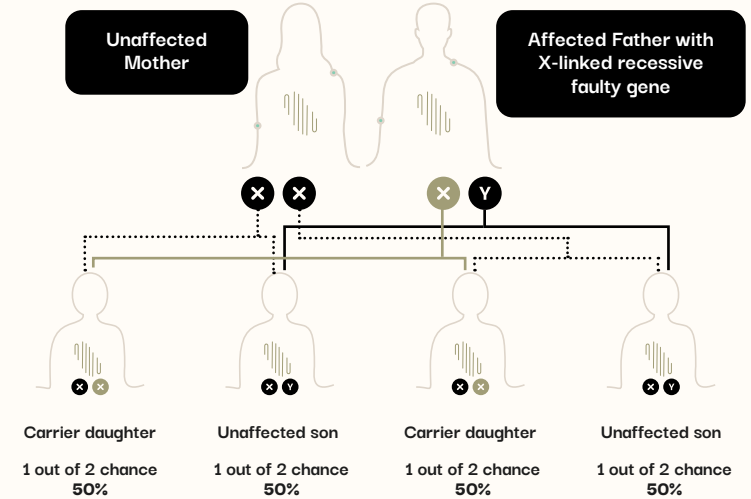

Figure A. A carrier mother's chance of transmitting the variant.
Figure B. An affected male's chance of transmitting the variant.
Source: genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-9-x-linked-recessive-inheritance

Can PMD be treated?

There is no cure for PMD, but treatment is available to manage symptoms and improve the quality of life for individuals affected by the disease.

This may include:

- Physical therapy and occupational therapy to improve the quality of life.
- Speech therapy to support feeding and communication.
- Antiepileptic drugs to treat seizures.
- Feeding support via a gastrostomy tube.
- Surgery to treat scoliosis.

Support and resources:

- **The M.O.R.G.A.N. Project** themorganproject.org
- **PMD Foundation** pmdfoundation.org
- **United Leukodystrophy Foundation: PMD Video** youtube.com/watch?v=z4-Mn9SgbzI
- **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=PMD&term=&cntry=&state=&city=&dist=