Metachromatic Leukodystrophy (MLD)

Other names: Arylsulfatase A deficiency

What is MLD?

MLD 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.

MLD is characterized by the accumulation of fatty substances called sulfatides. This fatty deposition on neurons results in destruction of the protective covering, or myelin sheath, surrounding the neurons of the central and peripheral nervous system.

What are the symptoms of MLD?

The symptoms observed at the time of presentation differ between types:

1. **Late-infantile onset**
   (onset before 30 months of age)
   Affected individuals present with muscle weakness (hypotonia), developmental delay or loss of skills with frequent falls and unclear or slurred speech (dysarthria).

2. **Juvenile Onset**
   (onset between 30 months and 16 years of age)
   Affected individuals present with a decline in performance or behavior at school, or difficulties with walking and other motor functions.

3. **Adult Onset**
   (onset any time after 16 years of age, mostly between the 4th and 5th decade of life)
   Affected individuals present with neurological symptoms such as psychosis, emotional liability along with loss of coordination. The disease course varies with periods of decline interspersed with periods of stability.

As the disease progresses, all individuals have similar manifestations irrespective of the age of diagnosis. These symptoms include:

- Loss of cognitive skills.
- Loss of fine motor skills.
- Spasticity.
- Seizures.
- Compromised vision and hearing.
- Generalized unawareness to the surroundings.

What causes MLD?

MLD is caused by changes in the *ARSA* or *PSAP* gene.

- ***ARSA* gene** This gene is responsible for production of arylsulfatase A enzyme. This enzyme is responsible for the breakdown of cellular byproducts.
- ***PSAP* gene:** This gene is responsible for the production of proteins such as Saposin B. These proteins assist with the digestion of various fats in the human body.

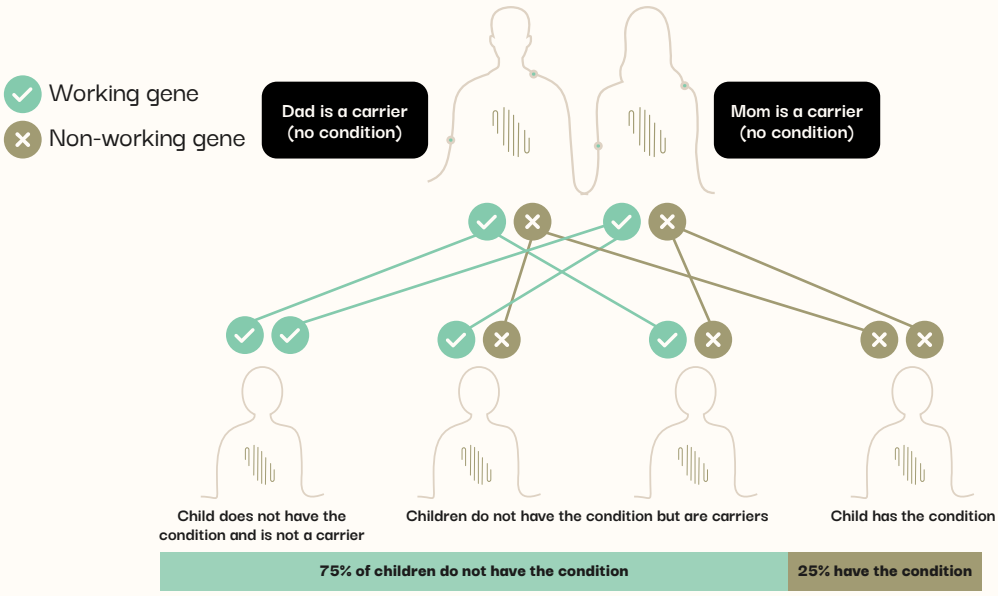
Changes in these genes result in impaired breakdown of sulfatides.

How is MLD diagnosed?

- MRI brain suggestive of leukodystrophy.
- Identification of elevated ARSA enzymes in the blood.
- Elevated levels of sulfatides in the urine.
- The diagnosis is established when changes in either *ARSA* or *PSAP* gene are identified.

How is MLD inherited?

MLD is inherited in an autosomal recessive pattern. This is where both copies of the relevant gene (*ARSA* or *PSAP*) 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 MLD be treated?

There is no cure for MLD, but treatment is available to manage symptoms and improve the quality of life for individuals affected by the disease. Hematopoietic stem cell therapy (HSCT) may be helpful if given at a very early stage in juvenile-onset disease.

Support and resources:

- **Bethany's Hope Foundation** bethanyshope.org
- **The Calliope Joy Foundation** thecalliopejoyfoundation.org
- **Cure MLD** curemld.com
- **Evanosky Foundation** evanoskyfoundation.org
- **MLD Foundation** mldfoundation.org/index.php
- **Orchard Therapeutics** orchard-tx.com/focus/#MLD
- **United Leukodystrophy Foundation: MLD Video** youtube.com/watch?v=jYXixo1E_u0
- **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=MLD&term=&cntry=&state=&city=&dist=