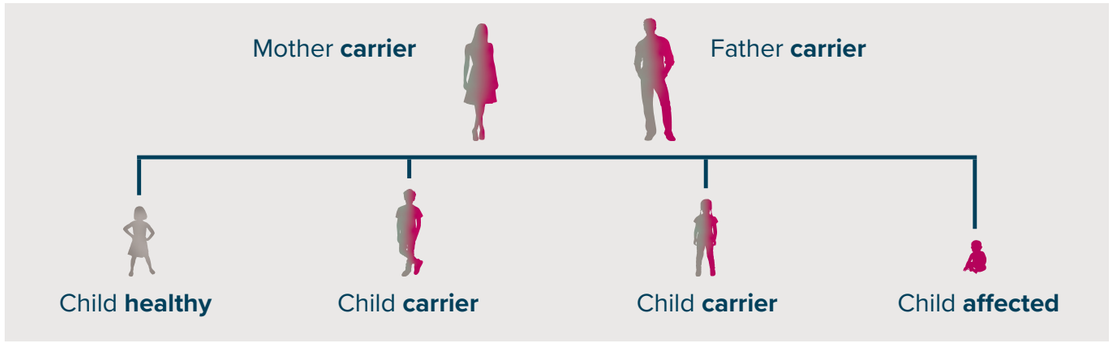
Every day counts – identify MLD patients earlier

Expediting diagnosis – 5 things to do

- Educate referral network to overcome “wait and see” mentality in the first line
- Symptomatic patients: expedited referral to an expert centre is critical
- Confirming MLD diagnosis early is essential for improved prognosis
- **Screen siblings of affected patients urgently to identify pre-symptomatic affected patients**
- Counselling on family planning for affected families



Differential diagnosis: neurodevelopmental delay

Other neurodegenerative diseases can mimic MLD[7]

- Elevated sulfatides or sulfatide accumulation
  - Multiple sulfatase deficiency (onset at 1–4 years, MLD-like clinical picture/Mucopolysaccharidosis-like features, very low ARSA enzyme activity)
  - Saposin B deficiency (variable onset: MLD-like clinical picture, ARSA enzyme activity in normal range)
- Progressive degenerative disorders that manifest after a period of normal development
  - Krabbe disease, x-linked adrenoleukodystrophy, Pelizeus-Merzbacher disease, Alexander disease, Fucosidosis, Canavan disease, Gangliosidosis, Mucopolysaccharidoses
- Other genetic disorders where neuromotor delays may be a presenting feature
  - Angelman syndrome, Becker muscular dystrophy, Fragile X syndrome, Mitochondrial myopathies, Spinal muscular atrophy

References:

1. Kreysing J et al. Am. J. Hum. Genet 53:339–346, 1993. **2.** Rosenberg JB et al. J Neurosci Res 2016;94(11):1169–79. **3.** Zsolt et al. Acta Medica Marisiensis 2015;61(3):233–235. **4.** Patil S, Maegawa GHB. Drug Des Devel Ther 2013;7:729–745. **5.** Ferreira CR, Gahl WA. Transl Sci Rare Dis 2017;2(1–2):1–71. **6.** Gieselmann V, Krägeloh-Mann I. Neuropediatrics 2010;41(1):1–6. **7.** Lamichhane A, Rocha Cabrero F. Metachromatic Leukodystrophy. StatPearls Publishing; 2020 Available from: https://www.ncbi.nlm.nih.gov/books/NBK560744 Accessed Feb 2021 **8.** Parikh et al. Molecular Genetics and Metabolism, 2015:501–515

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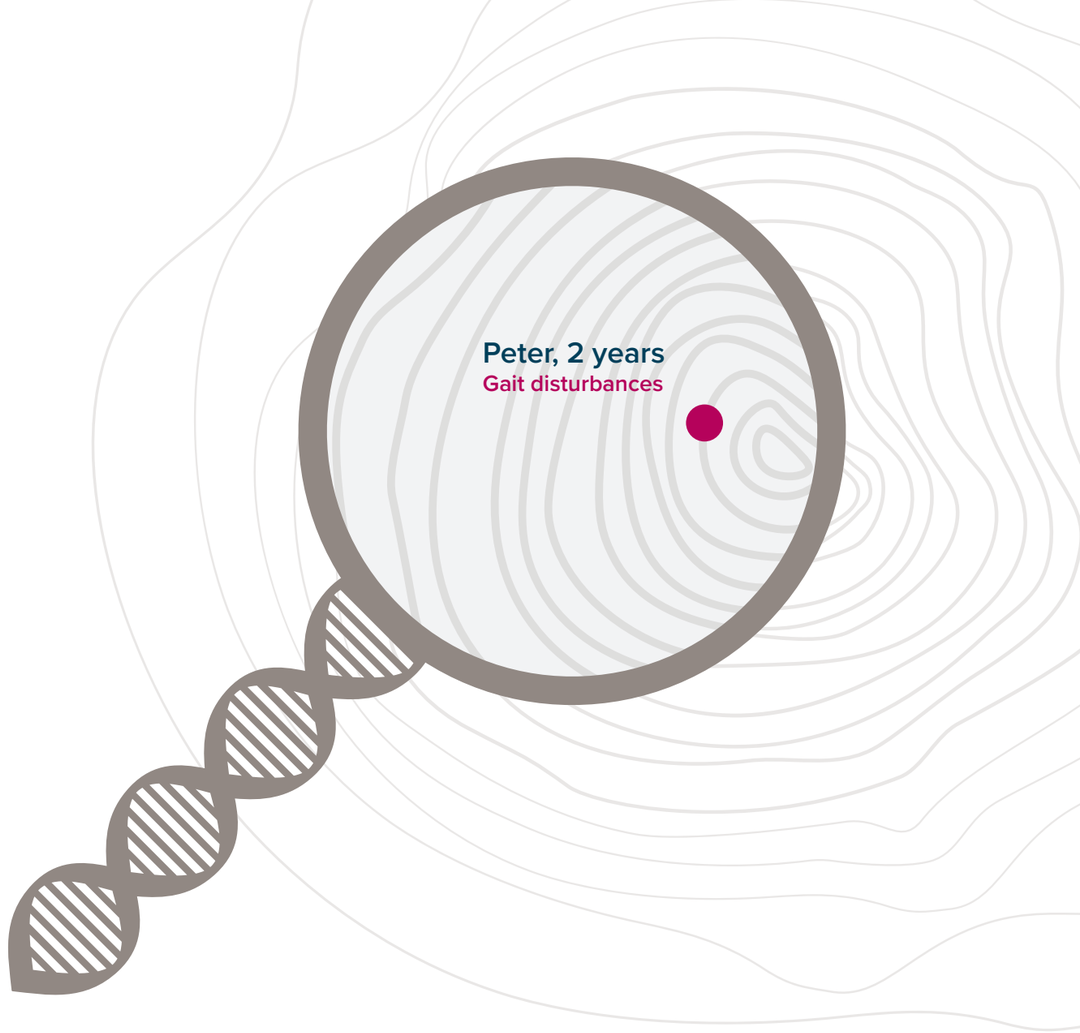


How to identify and diagnose MLD patients earlier and faster

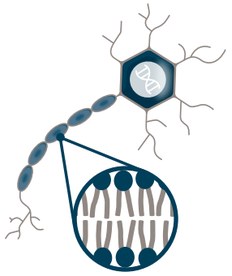
Metachromatic Leukodystrophy (MLD) is a rare, fatal, inherited neurometabolic disease causing progressive demyelination and neurodegeneration.

IE-NoP-2200031 July 2022

Orchard therapeutics™

MLD causes progressive demyelination and neurodegeneration

PHYSIOLOGIC

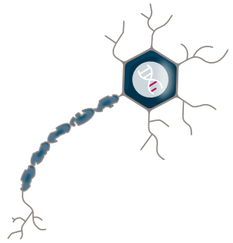


Sulfatides are a major component of the myelin membrane [1]

The **ARSA enzyme** usually breaks down sulfatides in the lysosome [2,3]

PATHOLOGIC

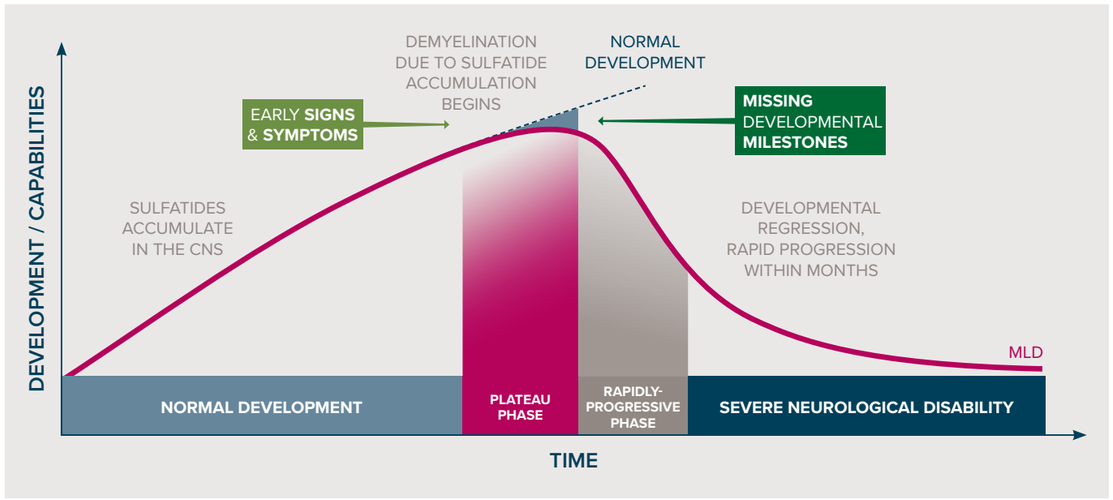
Mutations in the **ARSA gene** causes deficiency of the ARSA enzyme reducing sulfatide breakdown



Intra-lysosomal **sulfatides accumulation** leads to demyelination and neurodegeneration [1-4]

- Autosomal-recessive genetic disease caused by a deficiency of arylsulfatase A (ARSA) enzyme[1-3]

Clinical course of MLD



- Symptoms, age of onset and disease course vary, patients progress to dysphagia, severe neurological disability and death[2,4-6]

Recognition of early symptoms of MLD

		LI-MLD	JU-MLD
First Signs		<30 months	30 months – 16 years
EARLY SYMPTOMS (selected)			
Motor	**Hypotonia**	✓	
	Weakness	✓	
	Frequent falls	✓	
	Gait disturbances	✓	✓
	Abnormal movement patterns	✓	✓
Overall Development	**Missing milestones**	✓	✓
	General regression	✓	✓
Cognitive	**Cognitive decline (school performance)**		✓
	Speech difficulties		✓
	Behavioural changes (education problems)		✓
Trigger		**MOTOR**	**MOTOR / COGNITIVE**
Time to diagnosis		12 months	24 months

- Early symptoms are difficult to recognise, missing developmental milestones and general regression should trigger further investigations[7]

How to diagnose symptomatic MLD?

SUGGESTIVE
Clinical Symptoms

Early motor and / or **Behavioural/ cognitive**

Clinical signs and symptoms suggesting possible MLD diagnosis.

CONFIRMATORY
Laboratory

Biochemical testing and **Genetic testing**

- ARSA enzyme activity *plus*
- 24 hour urinary sulfatides

- Specific
- Multigene (panels)

Refer to neuropaediatrician urgently and test siblings as soon as possible.

ONLY INDICATIVE
Magnetic Resonance Imaging

MRI

Patients may not have evidence on MRI early in the disease course. A normal MRI is not sufficient to rule out MLD.

- Blood ARSA levels should be used as a screening tool if milestones are missed or general regression occurs[8]