Australian Leukodystrophy Clinical and Research Program

Megalencephalic Leukoencephalopathy (MLC)

Other names: Megalencephalic leukoencephalopathy with subcortical cysts

What is MLC?

MLC 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.

MLC causes abnormal function of the white matter (leukoencephalopathy) with progressive enlargement of the brain (megalencephaly).

In individuals diagnosed with MLC:

- The protective covering, or myelin sheath, is swollen and develops numerous fluid-filled pockets (vacuoles). Over time, this results in a wasting away of the myelin (atrophy).
- Cysts may develop in the brain that grow in size and number. These cysts affect muscular function and movement.

What are symptoms associated with MLC?

MLC is divided into three subtypes: type 1, type 2A and type 2B. The severity of symptoms depends on the subtype.

Type 1 and 2a (classical MLC) have similar symptoms.

Individuals with type 2B have the ''improving type'' which is associated with improvement of motor function after the first years, and stable learning difficulty, with or without autistic features.

Symptoms for all subtypes include:

- Macrocephaly (large head)
- Muscle stiffness (spasticity)
- Loss of muscle coordination (ataxia)
- Recurrent seizures (in ~75% of affected individuals)
- Uncontrolled muscle tensing (dystonia)
- Involuntary writhing movement of limbs (athetosis)
- Difficulty in swallowing (dysphagia)
- Impaired speech (dysarthria)
- Mild to moderate learning difficulty with autistic features
- Minor head injuries might result in a deterioration of brain function.

What causes MLC?

Type 1 MLC Type 1 is caused by changes in the *MLC1* gene. This gene provides instructions for the MLC1 protein found in the junction between the glial cells (support cells for the myelin and nerves). Changes in the *MLC1* gene result in a lack of the MLC1 protein which alters the glial cell functions.

Type 2A and 2B MLC Type 2A and 2B are caused by changes in the *HEPACAM* gene. This gene provides instructions for a GlialCAM protein. Changes in *HEPACAM* results in a lack of the GlialCAM protein, affecting the regulation of the volume of the brain. The relation between the absence of MLC1 protein or the GlialCAM protein at the glial cell junction and the phenotype observed in the affected individuals is yet to be established.

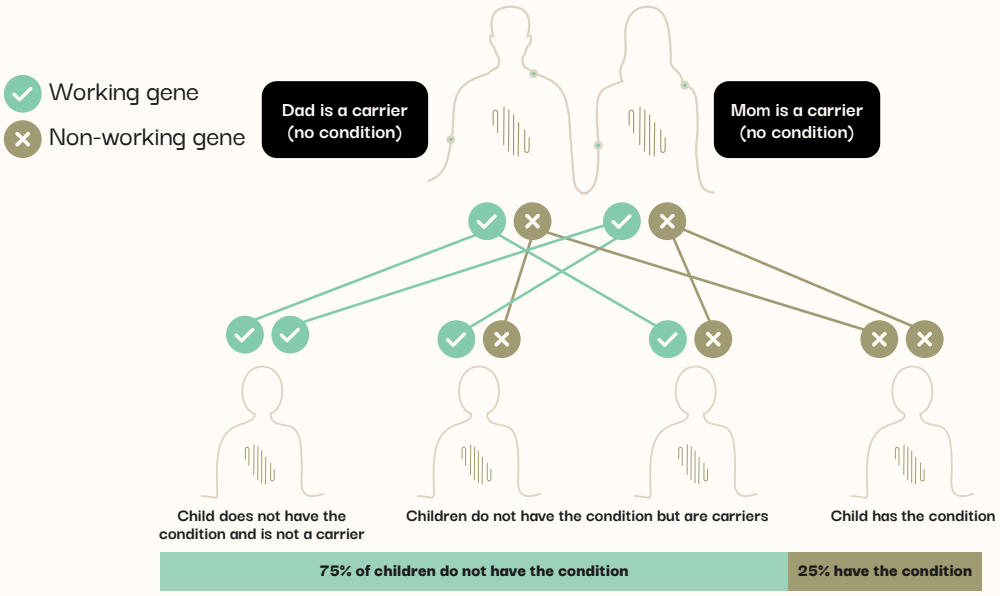
How is MLC diagnosed?

MRI brain showing classic findings such as subcortical cysts, age-dependent loss of myelination, swollen white matter and pattern specific to MLC. Following the MRI, clinical correlation is established before performing genetic testing to establish the diagnosis.

How is MLC inherited?

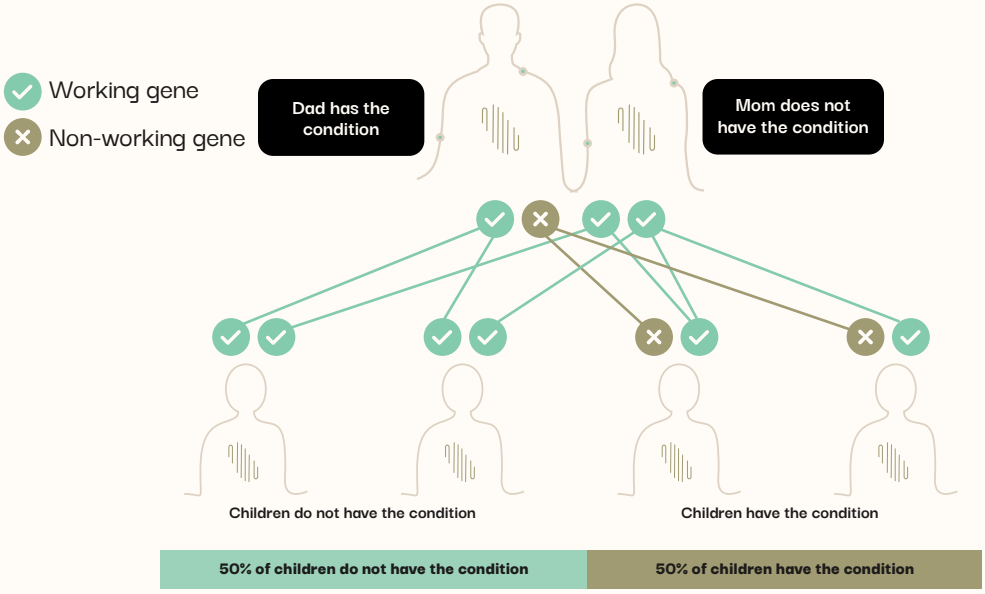
Type 1 and Type 2A

The classical forms are inherited in an autosomal recessive pattern. This is where two copies of the altered gene change (*MLC1* or *HEPACAM*) causes MLC Type 1 or Type 2A. Each parent passes on one copy of the altered gene change. This means that in each of the subsequent pregnancies the couple has a 1 in 4 chance of having an affected child. This also means that siblings of the parents can also be carriers.



Type 2B

This type is inherited in an autosomal dominant pattern or de novo where one copy of the altered gene change (*HEPACAM*) causes MLC Type 2B. Most cases are due to de novo changes that arise in the affected person due to random chance.



Can MLC be treated?

Treatment is focused on the management of the symptoms.

- Physical therapy and occupational therapy to improve the quality of life.
- Speech therapy.
- Antiepileptic drugs immediately after the onset of seizures.
- Aids to mitigate head injuries.
- Avoidance of contact supports.

Support and resources:

- **United Leukodystrophy Foundation: MLC Video** youtube.com/watch?v=ebJ7mcEDPsk
- **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** clinicaltrials.gov
- **Global Leukodystrophy Initiative** theglia.org

References:

- ulf.org/leukodystrophies/megalencephalic-leukoencephalopathy-with-subcortical-cysts-mlc
- medlineplus.gov/genetics/condition/megalencephalic-leukoencephalopathy-with-subcortical-cysts/#causes
- rarediseases.info.nih.gov/diseases/3445/megalencephalic-leukoencephalopathy-with-subcortical-cysts
- ncbi.nlm.nih.gov/books/NBK1535