What is ALD?

ALD 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.

ALD is a condition that can affect the nervous system and / or the adrenal glands. When the brain is involved, it is known as cerebral ALD. Approximately 65% of patients with ALD have cerebral ALD. In Cerebral Adrenoleukodystrophy (cALD) the myelin that insulates the nerves in the brain and the spinal cord is susceptible to deterioration. This is called demyelination and reduces the nerves' ability to carry information to and from different brain regions.

Individuals who are affected by ALD may also experience damage to the outer layer of the adrenal glands (the adrenal cortex). This causes a shortage of particular hormones, which is called adrenocortical insufficiency.

What are the symptoms of ALD?

1. Childhood onset

- Symptoms first appear between ages 4 and 8.
- Symptoms include learning and behavioral problems, gradual decline in vision, hearing and motor function.

2. Adult onset (adrenomyeloneuropathy)

- Symptoms typically appear in early adulthood to middle age.
- Symptoms include progressive stiffness, weakness of the legs, issues with urinary and genital function, changes in cognition and behavior

3. Adrenal insufficiency only (Addison disease)

- Symptoms can appear between childhood and adulthood.
- Individuals have **no neurological symptoms** but have adrenal insufficiency
- Symptoms include loss of appetite, weight loss, nausea, vomiting, muscle weakness, increased skin pigmentation.

What causes ALD?

ALD is caused by changes in the *ABCD1* gene. This gene provides instructions to produce a protein known as the ABC transporter which helps transport a group of fats called very long chain fatty acids (VLCFAs). In individuals with ALD, changes in the *ABCD1* gene disrupt the transport and breakdown of VLCFAs. This leads to a buildup of VLCFAs in the body, which may be toxic to the adrenal glands and to the myelin of nerves.

The *ABCD1* gene is located on the X chromosome. As boys have one X and one Y chromosome, they are usually more severely affected than females who have two X chromosomes.

How is ALD diagnosed?

Testing to confirm the clinical suspicion of ALD can include:

- A blood test to measure the levels of VLCFA. Increased levels of VLCFA indicate disruption in the breakdown of VLCFA.
- ACTH stimulation test which tests the function of the adrenal glands.
- MRI brain which shows typical changes in the white matter and can be scored to show how severe the brain involvement is (Loes score).
- Genetic testing to look for changes in the *ABCD1* gene.

In some parts of the world, cALD can be diagnosed from newborn screening tests.

How is ALD inherited?

All men have only one copy of the 'X' chromosome whereas all women have two copies. As a result of this any man with a variant in their X chromosome might suffer from a X-linked condition and women with this variant may not develop any symptoms during their lifetime or may only have mild symptoms, but there is a 50% chance that they might pass it on to their children.

Figure A.

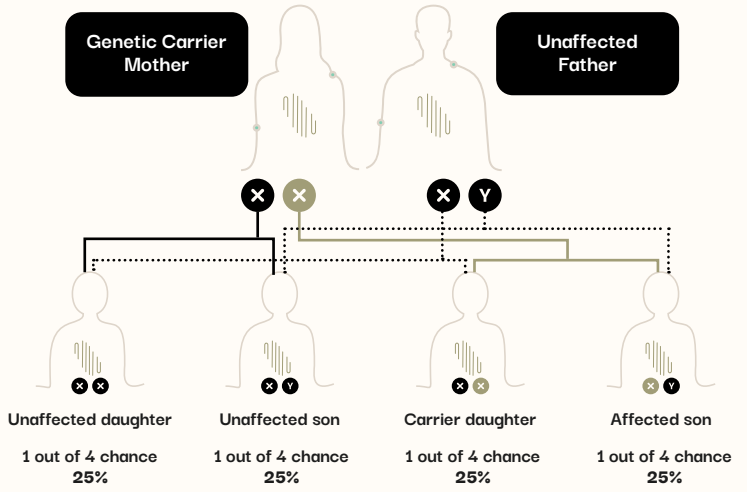

Figure B.

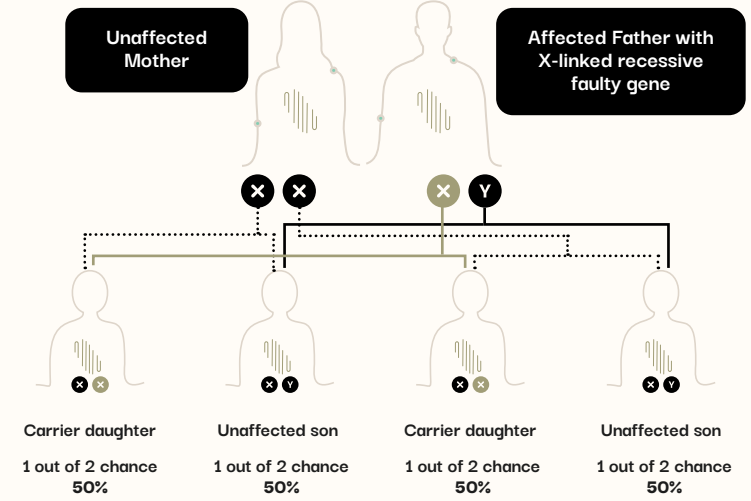

Figure A. A carrier mother's chance of transmitting the variant.
Figure B. An affected male's chance of transmitting the variant.
Source: genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-9-x-linked-recessive-inheritance

Can ALD be treated?

- Adrenal insufficiency is treated with steroid replacement.
- cALD can be treated if diagnosed early when the boy is either asymptomatic or has only mild symptoms and a normal or mildly affected brain MRI. Treatment is a bone marrow transplant from a donor to populate the patient with cells that can produce the correct amounts of the ABC transporter protein. This treatment cannot reverse the condition but may stop its progression.
- For boys with advanced cALD (based on their MRI score), there is no specific treatment and management is aimed at symptoms. Bone marrow transplant in boys with advanced cALD usually accelerates the disease and shortens the boy's life.
- Researchers are investigating new treatment options including gene therapy.

Support and resources:

- **ALD Alliance** aldalliance.org
- **ALD Connect** aldconnect.org
- **ALD Foundation** aldfoundation.org
- **Brian's Hope** brianshope.org
- **Stop ALD** stopald.org
- **Navigating ALD** navigatingald.com
- **ALD Newborn Screening Toolkit** bluebirdbio.com/patients-and-advocacy/newborn-screening-toolkit-for-ALD
- **A parent's guide to living with ALD** leuko.org.au/wp-content/uploads/2020/06/ALD_brochure_2020_downloadable.pdf
- **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=ald&term=&cntry=&state=&city=&dist=