What is X-ALD?

X-linked adrenoleukodystrophy (X-ALD) is a rare peroxisomal disorder caused by mutations in the ABCD1 gene, which results in a buildup of very long chain fatty acids (VLCFAs) that damage the white matter of the brain, spinal cord, and adrenal glands. X-ALD is more severe in males than females. There are usually no signs of X-ALD at birth and there is wide variability in severity and age of onset of symptoms, even within a family.

There are three forms of X-ALD that primarily affect males:

• **Childhood Cerebral form** – This type of X-ALD affects the brain and adrenal glands. Males appear normal at birth but usually develop symptoms at 4-8 years of age, although some may have symptoms before age 2. Symptoms may include hyperactive behavior, loss of developmental and motor skills, poor coordination, seizures, difficulty swallowing, and loss of vision and hearing.

• **Adrenomyeloneuropathy (AMN)** – AMN affects the spinal cord. Symptoms typically begin in the late twenties and include weakness in the legs, sphincter abnormalities, and adrenal insufficiency.

• **Addison disease** – In this type, patients develop adrenocortical insufficiency, which can be life threatening if not treated. Symptoms can begin in childhood or adulthood.

Because the ABCD1 gene is on the X chromosome, females are carriers of the condition. Although most do not exhibit any symptoms, some may display mild symptoms later in life, usually after age 35. Symptoms may include progressive stiffness, weakness, numbness, pain in the joints, and urinary problems.

How is X-ALD identified and diagnosed?

The North Carolina State Laboratory of Public Health (NCSLPH) screens specimens from every infant born in North Carolina for X-ALD by measuring certain biomarkers from the blood spot sample obtained at birth. The positive screen must be confirmed by additional blood tests which will be ordered during a confirmatory testing appointment at UNC. Results will take approximately 7 to 21 days. If the infant is found to have elevated VLCFAs and a disease-causing mutation in the ABCD1 gene, this will confirm the X-ALD diagnosis.

There are other peroxisomal disorders that can lead to a positive newborn screen when measuring VLCFAs including Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Additional tests may be needed to differentiate these disorders.
How to handle an abnormal screen for X-ALD?

- Once you have spoken with the UNC X-ALD Newborn Screening Coordinator, contact the family immediately to describe the newborn screening result. Emphasize that a diagnostic test is needed to confirm whether the infant has X-ALD. Notify the family that the UNC X-ALD Newborn Screening Coordinator will be contacting them to make an appointment within a week to order confirmatory testing. Provide the family with contact information for the UNC follow-up team (919-966-4202).
- Page the UNC X-ALD Newborn Screening Coordinator (919-216-1622) once you have called the family.
- Call UNC Scheduling (984-974-1401) to make a referral to UNC Pediatric Genetics and Metabolism. Information about referrals can be found on their website (see the QR codes and resource links below). The geneticist will refer the infant to a pediatric endocrinologist and neurologist if X-ALD is confirmed.

How is X-ALD monitored and treated?

Long-term surveillance will be needed to monitor for symptoms of X-ALD by different specialists. There are different treatments for each type of X-ALD.

- For the childhood cerebral form of X-ALD, early hematopoietic stem cell transplant (HSCT)/bone marrow transplant can prevent progression of the disease in affected males. An appropriate time for transplant can be determined on the basis of specific changes in the brain identified by specialized MRI and other tests. Referrals to a transplant expert will be made by the treatment team.
- For AMN, treatment includes physical therapy, counseling, and corticosteroid replacement.
- Treatment for Addison disease includes corticosteroid replacement therapy.

Where do I go for more information?

- Genetics Home Reference: https://medlineplus.gov/genetics/condition/x-linked-adrenoleukodystrophy/
- ALD Alliance https://www.aldalliance.org/