Screening, Technology, and Research in Genetics is a multi-state project to improve information about the financial, ethical, legal, and social issues surrounding expanded newborn screening and genetic testing – http:// www.newbornscreening.info

Disorder name: X-Linked Adrenoleukodystrophy
Acronym: X-ALD

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- **To watch a video that includes a summary of some information included in this written factsheet, you can visit https://youtu.be/gRoTOcaRRn4.**

This fact sheet has general information about X-Linked Adrenoleukodystrophy (X-ALD) in males (boys, men). Every child is different and some of this information may not apply to your child specifically. Certain treatments may be recommended for some children but not others. If you have specific questions about X-ALD and available treatments, you should contact your doctor.

If your newborn has had a positive screen for X-ALD after newborn screening, it **does not yet mean that he definitely has X-ALD**. There are usually other medical tests (for example, blood tests) that need to be done to confirm whether your baby actually has X-ALD.

What is X-ALD?

X-linked adrenoleukodystrophy (X-ALD) is an inherited condition that affects the brain, nervous system, and adrenal glands. People with X-ALD have problems breaking down a certain type of fat. X-ALD is the most common type of peroxisomal disorder.

X-ALD mainly affects males, but females who are carriers of X-ALD can also develop symptoms. This fact sheet is focused on X-ALD in males. For information about X-ALD in females, please see the X-ALD Fact Sheet for Females.

Peroxisomal Disorders:

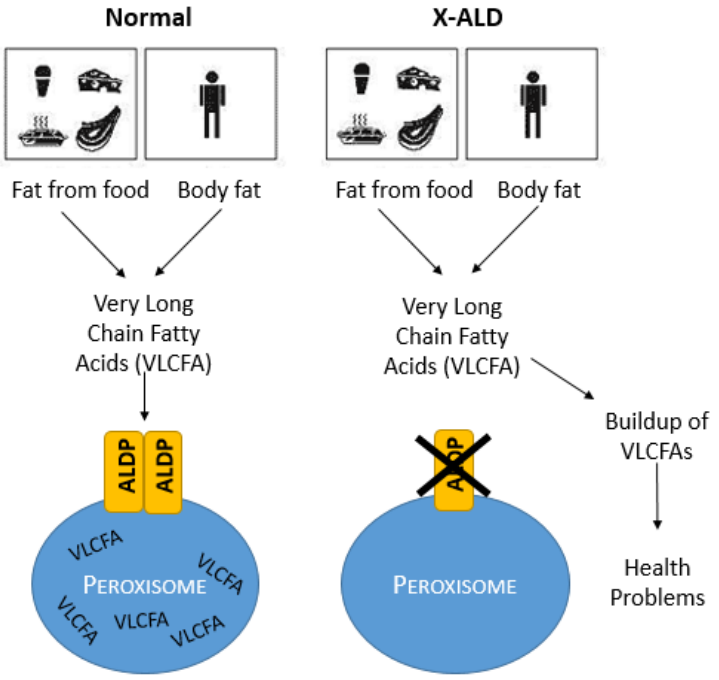
Peroxisomes are like recycling centers for cells. They are small sacs filled with enzymes and proteins that do different jobs. Some enzymes help to break down large molecules into smaller molecules that the body can use. Other proteins help to transport molecules into the peroxisomes.

People with peroxisomal disorders have missing or non-working enzymes/proteins. As a result, these people have problems breaking down certain large molecules into usable forms. This leads to a buildup of these molecules, which causes a variety of problems.

The symptoms and treatment vary between different peroxisomal disorders. They can also vary from person to person with the same peroxisomal disorder.

What Causes X-ALD?

X-ALD occurs when a protein called adrenoleukodystrophy protein (ALDP) is either missing or not working properly. This protein's job is to transport certain fats (very long chain fatty acids, or VLCFAs) from the body into the peroxisome so they can be broken down. When ALDP is not working, VLCFAs build up and can be very harmful to different parts of the body. This buildup of VLCFAs causes the symptoms of X-ALD.



The gene that tells our cells to make ALDP is called ABCD1.

How is X-ALD inherited?

X-ALD is inherited in an X-linked pattern. In some families, an affected baby is the first person in the family to have a non-working copy of *ABCD1*. In those babies, X-ALD is not inherited from a parent.

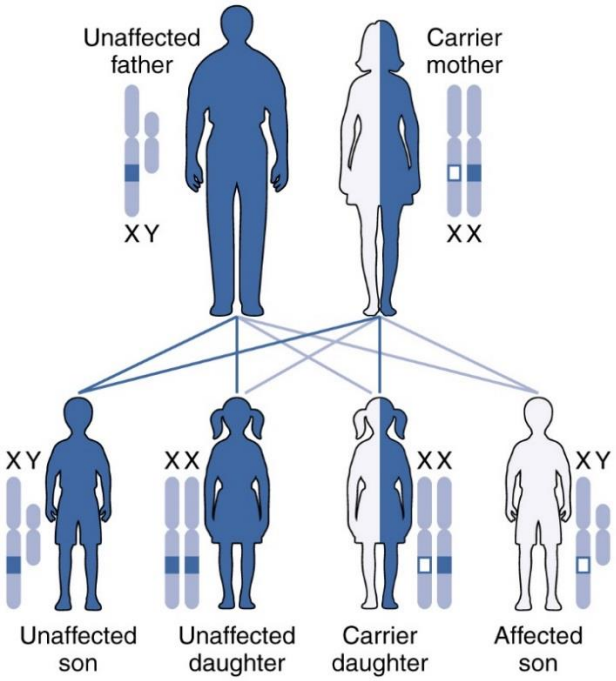
X-Linked Inheritance
In this type of inheritance, the gene associated with the condition is located on the X chromosome, which is one of the sex chromosomes. X-ALD is caused by changes in the ABCD1 gene which is located on the X chromosome.

Genes usually come in pairs, with each parent giving one copy to their child. The sex chromosomes, however, are different. A male inherits one X chromosome from his mother, and one Y chromosome from his father. Males have only one X chromosome. A female inherits two X chromosomes, one from each parent.

A male with a non-working ABCD1 gene on his X chromosome will have X-ALD. This is because he does not have a second X chromosome with a working copy of the ABCD1 gene. Therefore, it is more common for males to have X-ALD than females.

When a female has a non-working copy of the ABCD1 gene on one of her X chromosomes, she will be a carrier of X-ALD. She has a second, working copy of the

ABCD1 gene on her other X chromosome. Female carriers of X-ALD most often will not have symptoms of X-ALD, but if she does, they are usually not as severe as males.



Source: OpenStax CNX

If a mother has one non-working copy of the ABCD1 gene, she is called a carrier. For carriers, there is a 50% chance that each male pregnancy will have X-ALD (affected son). For carriers, there is a 50% chance that each female pregnancy will be a carrier (carrier daughter), like her mother.

A father passes his Y chromosome to his sons and his X chromosome to his daughters. Therefore, if a father has X-ALD, none of his sons will have X-ALD and all of his daughters will be carriers.

What are the symptoms of X-ALD in males?

The symptoms of X-ALD vary from person to person and can begin at different ages, ranging from infancy to middle age. It is important to remember that every child with X-ALD is different and it is not possible to predict how severely a child may be affected.

There are three major symptom sets, or 'presentations,' of X-ALD in males.

1. **Addison disease (adrenal insufficiency)**

Adrenal insufficiency, also known as Addison disease, usually occurs in males with X-ALD between age 2 to adulthood, typically by age 7-8. About 80% of males with X-ALD will develop adrenal sufficiency before adulthood, and almost all males with X-ALD will develop it at some point in their life.

The adrenal glands are responsible for producing some hormones. Adrenal insufficiency causes a shortage of certain hormones in the body.

Initial symptoms of adrenal insufficiency include:

- Nausea and vomiting, abdominal pain
- Weakness and fatigue, loss of appetite
- Dehydration
- Coma
- Increased skin pigmentation

Most boys with X-ALD who only have adrenal insufficiency in childhood will develop adrenomyeloneuropathy later in life.

2. **Adrenomyeloneuropathy**

Adrenomyeloneuropathy (AMN) occurs in virtually all men with X-ALD. However, the age of onset and rate of progression can vary. Typically, AMN is diagnosed between 20-30 years of age. AMN affects the nerves in the spinal cord and gets worse over time.

Symptoms in affected males include:

- Progressive stiffness and weakness of legs
- Urge incontinence (sudden urge to urinate)
- Spastic gate (stiff, abnormal walking)
- Impotence
- Early balding

About 70% of men with AMN also have Addison disease. Between 10-20% of men with AMN will develop cerebral ALD. We cannot predict which men with AMN will develop cerebral ALD, or at what age they will develop it.

3. **Cerebral ALD**

Cerebral ALD can occur in childhood, adolescence, or adulthood. Symptoms of cerebral ALD can be rapidly progressive. A newborn baby boy has a 35-40% risk of developing childhood cerebral ALD (before the age of 18). Cerebral ALD usually does not occur before the age of 3, and most commonly begins between ages of 4 to 8.

Symptoms in affected males include:

- Behavioral or learning problems, sometimes diagnosed as attention deficit disorder or hyperactivity (ADHD)
- “Spacing out” in school, inattention
- Deteriorating handwriting skills
- Difficulty understanding speech, reading, comprehension of writing

- Clumsiness, visual problems
- Aggressive behavior
- Seizures

Without early detection and treatment, cerebral ALD can progress rapidly and cause total disability within six months to two years, and can be fatal at an average of two years after symptoms begin.

Occasionally, symptoms are more atypical and do not fit one of these presentations. Other symptoms could include headaches, visual problems, speech problems, paralysis, dementia, poor coordination and balance, and inability to control urine and bowel movements. Some patients have not had any symptoms at all.

What is the treatment for X-ALD in males?

People with X-ALD should be treated by a team of specialists who are familiar with the disorder. This may include an endocrinologist (hormone doctor), neurologist (brain doctor), neuromuscular specialist (muscle doctor), geneticist (genetics doctor) such as a biochemical genetics doctor or metabolic genetics doctor, rehabilitation specialist (i.e., physical therapist), and a genetic counselor. Certain treatments may be advised for some children but not others, and some treatments are only recommended once the different symptoms associated with X-ALD occur.

It is very important that your child is regularly monitored for the development of symptoms of X-ALD, which can occur at any age.

The following monitoring and treatments are usually recommended for males with X-ALD.

1. **Brain MRI**
   It is very important for males with X-ALD to have a brain MRI to check for cerebral ALD starting at age 6 months – 1 year. From age 3 to age 10, brain MRIs should be done every 6 months as this is the high-risk period for developing cerebral X-ALD; after age 10 until age 18, brain MRIs should be done yearly. Signs of cerebral ALD can be seen on brain MRIs before symptoms develop, and early detection of cerebral ALD is vital for potential treatment.
2. **Hematopoietic Stem Cell Transplant (HSCT**)
   Hematopoietic stem cell transplant (also known as bone marrow transplant) is a treatment for cerebral ALD. If it is successful, the progression of cerebral ALD will stop. In HSCT, a patient receives healthy stem cells from a matched donor. HSCT is only recommended for males who show signs of cerebral ALD on MRIs, but are still in the early stages of cerebral disease. HSCT is not used to treat males with AMN because the risks of the procedure are thought to outweigh the benefits.

3. **Gene Therapy**
   The FDA has approved a gene therapy for X-ALD. In this gene therapy, the patient's own blood stem cells are used and working copies of the ABCD1 gene are added to the patient's cells. These new cells may help the body to break down the VLCFAs and slow the progression of damage to the brain and the decline in neurologic function.
4. **Treatment of Addison disease**
   Addison disease occurs when the adrenal glands do not produce the level of hormones that they should. Newborn males with X-ALD should have an initial blood test to check for adrenal insufficiency. They should then have blood testing for adrenal insufficiency every 6 months, and a yearly exam by an endocrinologist. If someone with X-ALD is found to have adrenal insufficiency, this is treated with corticosteroid replacement therapy (oral medication).
5. **Treatment of Adrenomyeloneuropathy (AMN)**
   Physical therapy can help to relieve symptoms like muscle spasms and reduce muscle rigidity that develops in AMN. Occupational therapy can help develop and maintain motor skills needed for daily living and work tasks. Some medications may also be prescribed to treat nerve pain, abnormal movement, and bladder control problems.

There are other therapies that have been tried for X-ALD, some of these therapies are still under research investigation.

What happens when X-ALD is treated?

Adrenal insufficiency can cause major health problems. Corticosteroid replacement therapy for people with Addison disease is essential to prevent symptoms and problems associated with adrenal insufficiency.

HSCT in males with early cerebral ALD can stop the progression of cerebral ALD, which is the main cause of death in X-ALD. The best results of HSCT are seen in males where the beginning brain changes are seen on MRIs but before symptoms are seen. HSCT does not treat or cure adrenal insufficiency. It is not yet known for certain if successful HSCT has an impact on the development of AMN.

Physical and occupational therapy can improve overall well-being and help to manage the symptoms of AMN.

Is genetic testing available?

X-ALD is caused by changes, also called variants in the ABCD1 gene. Genetic testing, also called DNA testing, can be done on a blood sample, and looks for variants in the ABCD1 gene. DNA testing for X-ALD is typically done to confirm the diagnosis.

DNA testing can also be helpful for carrier testing or prenatal diagnosis, discussed below.

If a genetic variant in the ABCD1 gene is not found, additional biochemical testing or genetic testing for other genetic disorders may be necessary.

What other testing is available?

Newborn Screening

Newborn screening for X-ALD is only done in some states. A blood spot from a needle prick on a baby's heel is used to screen for many different conditions. Newborn screening detects X-ALD by looking for the amount of a certain type of VLCFA in the blood spot.

If a baby has a positive result on the initial X-ALD newborn screen, it **does not** yet mean that he or she definitely has X-ALD. The increased amount of VLCFA can also indicate other types of peroxisomal disorders or other genetic conditions. A positive screening result is followed up by repeat testing of VLCFA in blood, and often DNA testing to confirm the diagnosis.

When someone else in the family has been diagnosed with X-ALD newborn screening results are not enough to rule out X-ALD disease in a newborn baby. In this case, more sensitive diagnostic testing should be done in addition to newborn screening, even if the newborn screening result is negative. Your healthcare provider or genetic counselor can help you obtain the proper tests.

Confirmatory Testing

Measuring the concentration of VLCFA in blood in males who show symptoms can usually be enough to diagnose X-ALD.

Genetic testing of the ABCD1 gene is often necessary after a positive newborn screening result.

Can you test for X-ALD during a future pregnancy?

If a genetic variant is found in the ABCD1 gene that causes X-ALD in your family has been identified, DNA from the fetus can be tested. The sample for this testing is obtained by either CVS or amniocentesis.

Parents may choose to have testing during pregnancy or wait until after birth to have the baby tested. Parents may also choose to use assisted reproductive techniques to decrease the chance that their future children would have X-ALD. A genetic counselor can talk to you about your choices and answer questions about prenatal testing or testing your baby after birth.

Can other members of the family have X-ALD or be carriers?

Only some states offer newborn screening for X-ALD. It is very important that other family members are told that they could be at risk of having X-ALD or being carriers. A healthcare provider or genetic counselor can help them obtain expanded newborn screening.

Having X-ALD

Each full brother (same mother and father) of a baby with X-ALD has a 50% (1 in 2) chance of having X-ALD, even if they have had no symptoms. Finding out whether other children in the family have X-ALD is important because early treatment can prevent more serious health problems. Talk to your doctor or genetic counselor about testing your other children for X-ALD.

In addition, the father of a female baby who is found to be a carrier of X-ALD after newborn screening could also have X-ALD and not yet noticed or experienced any symptoms. It is important for both parents of a female carrier of X-ALD to be tested.

X-ALD Carriers

The mother of a boy with X-ALD is usually, but not always, a carrier of X-ALD. It is important for mothers to have carrier testing to determine the chance of other children or future pregnancies also having X-ALD. It is also important because mothers who are carriers of X-ALD can develop some symptoms of the condition and should have regular follow-up.

If the mother is found to be a carrier, her daughters have a 50% risk to be carriers as well.

Can other family members be tested?

If the genetic variant has been found in your child, other male family members can have DNA testing as well to see if they have X-ALD. Other blood tests may be recommended in addition to DNA testing. Other female family members can also consider DNA testing to see if they are carriers. This testing could also be important for extended family members.

How many people have X-ALD?

About 1 in 15,000 individuals are born with X-ALD.

Does X-ALD happen more often in a certain ethnic group?

No, X-ALD does not happen more often in any specific race, ethnic group, geographical area, or country.

Does X-ALD go by any other names?

X-ALD is sometimes referred to as:

- Addison disease with cerebral sclerosis
- Adrenoleukodystrophy (ALD)
- Adrenomyeloneuropathy (AMN)
- Siemerling-Creutzfeldt disease
- Addison-Schilder disease

Where can I find more information?

MedlinePlus
https://medlineplus.gov/genetics/condition/x-linked-adrenoleukodystrophy/

Baby's First Test
http://www.babysfirsttest.org/newborn-screening/conditions/adrenoleukodystrophy

ALD Connect
www.aldconnect.org

ALD Info
https://adrenoleukodystrophy.info/

The Stop ALD Foundation
www.stopald.org

ALD Alliance
www.aldalliance.org
Parent's guide www.aldnewbornscreening.org

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