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

This fact sheet has general information about X-Linked Adrenoleukodystrophy (X-ALD) in females. 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 she definitely has X-ALD or is a carrier**. 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 focuses on female carriers of X-ALD. For information about males with X-ALD, see our X-ALD in Males Fact Sheet.

Peroxisomal Disorders:

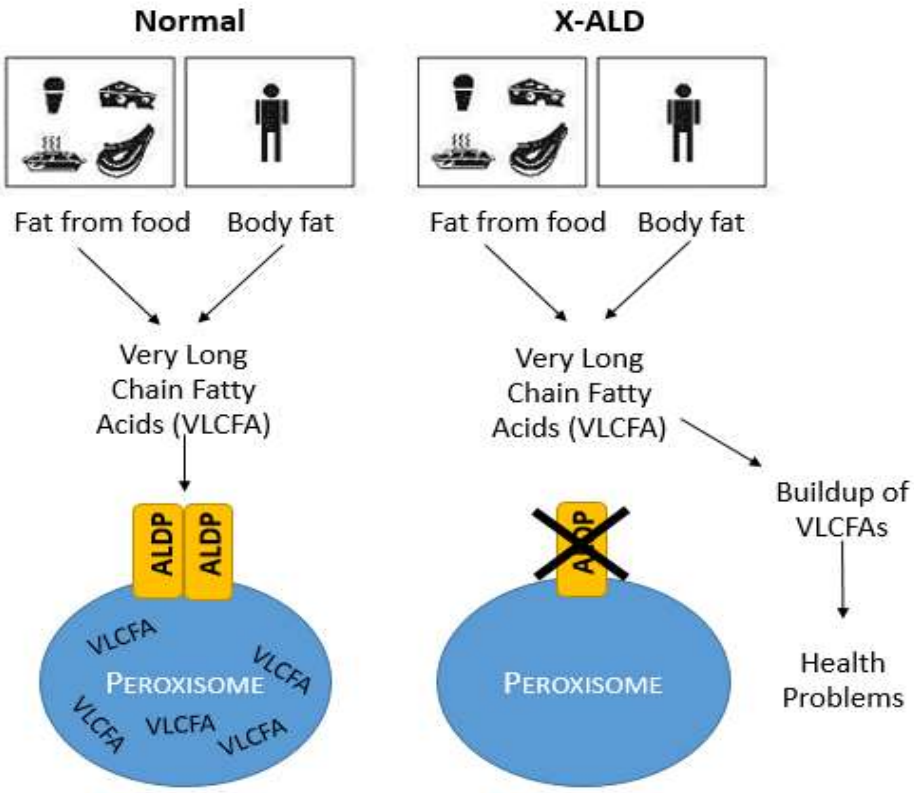
Peroxisomes are like recycling centers for cells. They are small sacs filled with enzymes and proteins that do different jobs. Some enzymes help to break down large molecules into smaller molecules that the body can use. Other proteins help to transport molecules into the peroxisomes.

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?

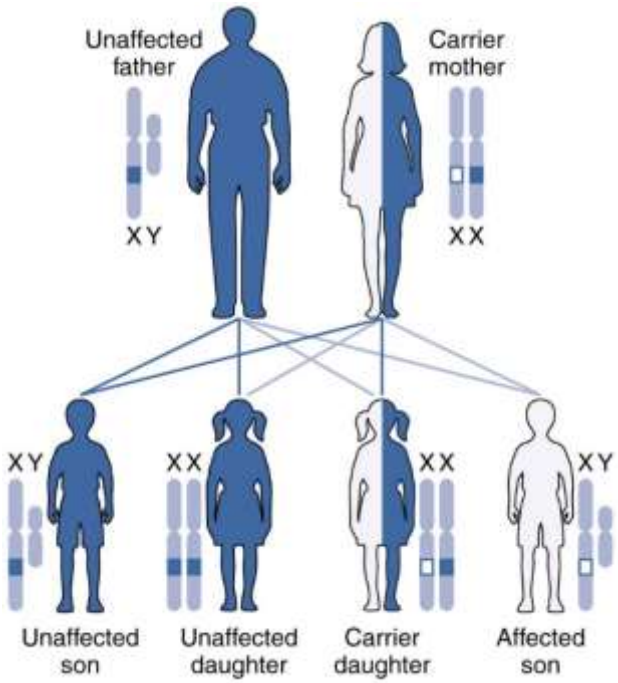
X-ALD is inherited in an X-linked pattern. In some families, an affected baby is the first person in the family to have a non-working copy of ABCD1. In those babies, X-ALD is not inherited from a parent.

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 female carriers?

Females who are carriers of X-ALD can sometimes show symptoms of X-ALD. However, they usually will not have as many symptoms as males who have X-ALD and develop symptoms at an older age than boys with X-ALD.

Adrenomyeloneuropathy
Up to 50% of female carriers of X-ALD will develop a condition called adrenomyeloneuropathy (AMN) in adulthood. AMN affects the nerves in the spinal cord and gets worse over time. Female carriers of X-ALD typically develop symptoms of AMN in their thirties or later

Symptoms of AMN in females affect the spinal cord and peripheral nerves, and include:

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

Other symptoms of ALD
Males with X-ALD may develop Addison disease (adrenal insufficiency) and cerebral ALD.

It is very rare for female carriers of X-ALD to have Addison disease or to develop cerebral ALD with less than 1% of female carriers developing these conditions. However, it is still important for female carriers to have regular monitoring and to be aware of all of the symptoms of X-ALD.

While it is very rare, if female carriers experience any symptoms for Addison disease or cerebral ALD, it is important for them to seek medical care as soon as possible.

Symptoms of Addison disease include unexplained nausea and vomiting, abdominal pain, weakness, fatigue, dehydration, coma, and increased pigment in the skin. Addison disease usually occurs in males with X-ALD between age 2 to adulthood, typically by age 7-8.

Symptoms of cerebral ALD include behavioral and learning problems, difficulties comprehending speech, clumsiness, vision problems, hyperactivity, aggressive behavior, and seizures. In boys, cerebral ALD usually does not occur before the age of 3, and most commonly begins between ages of 4 to 8 and before the age of 18. Early treatment is very important in cerebral ALD.

What is the treatment of X-ALD in female carriers?

If a female carrier of X-ALD experiences symptoms that might indicate they have Addison disease, they should be seen by an endocrinologist as soon as possible for testing for adrenal insufficiency.

If they are experiencing symptoms of cerebral ALD, they should be seen by a neurologist. Regular brain MRIs are not usually recommended for female carriers of X-ALD because of how rare cerebral ALD is in females.

When they are adults, female carriers of X-ALD should consider having regular assessments by a neurologist to monitor for symptoms of adrenomyeloneuropathy, and for appropriate management as needed.

What happens when X-ALD is treated?

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

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

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 she definitely is a carrier of 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 VLCFA in blood from females is often not enough to determine whether a female is a carrier of X-ALD, as some carriers have normal levels of VLCFAs.

Therefore, 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. 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 20,000 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?

Genetics Home Reference
ghr.nlm.nih.gov/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/

National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov/disorders/adrenoleukodystrophy/adrenoleukodystrophy.htm

The Stop ALD Foundation
www.stopald.org

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