

X-Linked Adrenoleukodystrophy

Disease Overview

X-linked adrenoleukodystrophy (X-ALD) is a rare X-linked metabolic disorder caused by variants in the *ABCD1* gene which cause a deficiency in adrenoleukodystrophy protein (ALDP) and subsequent accumulation of very long-chain fatty acids (VLCFA). VLCFA accumulation occurs in plasma and all tissue types, but primarily affects the adrenal cortex and white matter of the brain and spinal cord, resulting in a range of clinical outcomes.

Cerebral ALD (CALD), the most severe form, is a relentlessly progressive neurodegenerative disease phenotype that is generally fatal or severely debilitating. Allogeneic transplant has the potential to halt disease progression, but is only effective if administered prior to the onset of neurological symptoms. Early diagnosis is critical.

Adrenal insufficiency may be the initial presentation of X-ALD, and 21-hydroxylase antibody testing may confirm or exclude autoimmune etiology. In X-ALD, 21-hydroxylase antibody testing results will be normal; therefore, males with adrenal insufficiency and normal 21-hydroxylase antibody testing should be tested for X-ALD (VLCFA profile).

Incidence – ~1/20,000

- Most common peroxisomal disorder

Symptoms

- Multiple forms with varying severity
- Clinical presentation is variable, even within families
- No relevant genotype-phenotype correlation exists
- Cerebral form
 - Symptoms begin in childhood (typically 4-8 years)
 - Rapid progression of neurological disturbances, ending with death
 - Primary adrenocortical insufficiency may precede neurological symptoms
- Most common symptoms
 - Ataxia
 - Hearing loss
 - Hyperactivity
 - Loss of ability to speak or swallow
 - Paralysis
 - Seizures
 - Spasticity
 - Visual impairment

- Adrenomyeloneuropathy form
 - Typical onset at 20-30 years
 - Neurological disturbances over decades
 - Progressive spastic paraparesis, often in combination with impaired adrenocortical function
- “Addison disease only” form
 - Onset of symptoms ranging from childhood to adulthood
 - Adrenocortical impairment with symptoms of adrenal insufficiency
- Female carriers of a pathogenic variant
 - 18% under age 40 and 88% by age 60 develop neurological symptoms
 - Can present with progressive spastic paraparesis
 - Adrenal function tends to be normal

Genetics

Gene – *ABCD1*

Structure – *ABCD1* gene, contains 10 exons

Inheritance – X-linked

Penetrance – neurological symptoms are present in nearly 100% of males by adulthood

Variants

- Most are specific to a particular family (“private variants”)
- ~7% of individuals with X-ALD have a de novo variant

Diagnostic Testing

- VLCFA and branched-chain fatty acids (BCFA) profile is the first-line test for an individual with suspected X-ALD or adrenomyeloneuropathy
- Molecular testing (*ABCD1*) is recommended for diagnostic confirmation in individuals with clinical and/or biochemical presentation of X-ALD

Individuals recommended for testing

- At-risk family members of an affected individual (molecular testing and/or VLCFA profile)
- Infants with an abnormal newborn screening test for X-ALD (VLCFA profile)
- Males presenting with cognitive and neurological symptoms with white matter lesions on brain MRI (VLCFA profile)
- Males with adrenal insufficiency and normal 21-hydroxylase antibody testing (VLCFA profile)

Tests to Consider

Biochemical testing – VLCFA and BCFA

- Liquid chromatography/tandem mass spectrometry

[Very Long-Chain and Branched-Chain Fatty Acids Profile 2004250](#)

- Test measures concentration of VLCFA (C22-C26), pristanic acid, and phytanic acid
- Initial test to screen for disorders of peroxisomal biogenesis and/or function, including X-ALD and Zellweger syndrome
- Confirmatory test for abnormal newborn screening suggestive of X-ALD

Molecular testing – *ABCD1* gene

- Polymerase chain reaction followed by bidirectional sequencing of entire coding region and intron/exon boundaries of *ABCD1* gene
- Multiplex ligation-dependent probe amplification to detect large deletions/duplications in *ABCD1* gene

[Adrenoleukodystrophy, X-linked \(*ABCD1*\) Sequencing and Deletion/Duplication 2011906](#)

- Preferred test to
 - Confirm diagnosis of X-ALD following abnormal results from VLCFA profile test
 - Determine carrier status in females when familial variant is unknown
- Detects most pathogenic variants

[Adrenoleukodystrophy, X-linked \(*ABCD1*\) Sequencing 2011902](#)

- Useful to confirm diagnosis or carrier status for X-ALD
- Detects most pathogenic variants
- Sequencing does not detect deletions and duplications

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a pathogenic familial variant identifiable by sequencing is known

Test interpretation

Biochemical testing – VLCFA and BCFA

- Elevated VLCFA in males
- 85% of heterozygous female carriers will have elevated VLCFA

Molecular testing – *ABCD1*

Sensitivity/specificity

- Clinical sensitivity
 - Sequencing of *ABCD1* – ~93% (Kemp, 2012; Steinberg, 2012)
 - Deletion/duplication of *ABCD1* – ~6% (Steinberg, 2012)
- Analytical sensitivity/specificity – 99%

Results

- Positive
 - Pathogenic variant detected
 - Confirms X-ALD in males and carrier status in females
- Negative
 - No variant detected
 - X-ALD is less likely but not excluded
- Inconclusive
 - Variants of unknown clinical significance may be identified

Limitations

- Exons 7-10 are not evaluated by deletion/duplication analysis due to the presence of pseudogenes
- Breakpoints of large deletions/duplications will not be determined
- Diagnostic errors can occur due to rare sequence variations
- Not evaluated
 - Variants in genes other than *ABCD1*
 - Regulatory region variants
 - Deep intronic variants

References

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