X-Linked Adrenoleukodystrophy Testing

X-linked adrenoleukodystrophy (X-ALD) is a rare X-linked metabolic disorder caused by variants in the \( A B C D1 \) gene that cause a deficiency in adrenoleukodystrophy protein (ALDP) and subsequent accumulation of very long-chain fatty acids (VLCFAs). 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.

Adrenal insufficiency may be the initial presentation of X-ALD, and 21-hydroxylase antibody testing may confirm or exclude an 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).

Testing Strategy

Diagnostic Testing

- VLCFA and branched-chain fatty acid (BCFA) profile is the first-line test for an individual with suspected X-ALD or adrenomyeloneuropathy
- Molecular testing (\( A B C D1 \)) is recommended for diagnostic confirmation in individuals with clinical and/or biochemical presentation of X-ALD

Disease Overview

Incidence

1/14,700 live births\(^1\)

Genetics

Gene

\( A B C D1 \)

Structure

\( A B C D1 \) gene, contains 10 exons\(^2\)

Inheritance

X-linked

Penetrance

Neurologic symptoms are present in nearly 100% of males by adulthood.

Tests to Consider

See Testing Strategy

**Very Long-Chain and Branched-Chain Fatty Acids Profile 2004250**

**Method:** Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

- Biochemical test to measure concentration of very long-chain fatty acids (VLCFAs) 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

**Adrenoleukodystrophy, X-Linked (ABCD1) Sequencing and Deletion/Duplication 2011906**

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

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

**Adrenoleukodystrophy, X-Linked (ABCD1) Sequencing 2011902**

**Method:** Polymerase Chain Reaction/Sequencing

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

Related Tests

**Familial Mutation, Targeted Sequencing 2001961**

**Method:** Polymerase Chain Reaction/Sequencing

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

- Most are specific to a particular family ("private variants")
- ~4-19% of individuals with X-ALD have a de novo variant

For more information on the disease including testing strategy, disease overview, and genetics, visit the X-Linked Adrenoleukodystrophy topic in ARUP Consult.

Test Interpretation

Biochemical testing (VLCFAs and BCFAs)

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

Molecular testing (ABCD1)

Sensitivity/Specificity

- Clinical sensitivity
  - Sequencing of ABCD1: ~97%
  - Deletion/duplication of ABCD1: ~3%
- 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
- Variants in genes other than ABCD1, regulatory region variants, and deep intronic variants are not evaluated

References


Additional Resources
Related Information

X-Linked Adrenoleukodystrophy