X-Linked Adrenoleukodystrophy Testing

X-linked adrenoleukodystrophy (X-ALD) is a rare X-linked metabolic disorder caused by variants in the *ABCD1* 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 (*ABCD1*) is recommended for diagnostic confirmation in individuals with clinical and/or biochemical presentation of X-ALD

DISEASE OVERVIEW

Incidence
1/14,700 live births

GENETICS

Gene
*ABCD1*

Structure
*ABCD1* gene, contains 10 exons

Inheritance
X-linked

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

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*)

Tests to Consider

See Testing Strategy

Very Long-Chain and Branched-Chain Fatty Acids Profile 2004250
Method: Liquid Chromatography-Tandem Mass Spectrometry
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 Test

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing
Useful when a pathogenic familial variant identifiable by sequencing is known
Sensitivity/Specificity

- Clinical sensitivity
  - Sequencing of ABCD1: ~97% \(^4\)
  - Deletion/duplication of ABCD1: ~3% \(^4\)
- 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


RELATED INFORMATION

X-Linked Adrenoleukodystrophy