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[1]

Genetics

Gene

ABCD1

Structure

ABCD1 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[3]

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[3]

Molecular testing (*ABCD1*)

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

1. Huffnagel IC, Dijkgraaf MGW, Janssens GE, et al. Disease progression in women with X-linked adrenoleukodystrophy is slow. Orphanet J Rare Dis. 2019;14(1):30. PubMed

2. Kemp S, Berger J, Aubourg P. X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects. Biochim Biophys Acta. 2012;1822(9):1465-1474. PubMed

3. Wiesinger C, Eichler FS, Berger J. The genetic landscape of X-linked adrenoleukodystrophy: inheritance, mutations, modifier genes, and diagnosis. Appl Clin Genet. 2015;8:109-121. PubMed

4. Raymond GV, Moser AB, Fatemi A. X-linked adrenoleukodystrophy. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Last Update: Feb 2018; Accessed: Jun 2020]

Additional Resources

Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364-389. PubMed

Related Information

X-Linked Adrenoleukodystrophy

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