

ABCD1 Gene Analysis in X-Linked Adrenoleukodystrophy

CLINICAL FEATURES

X-linked adrenoleukodystrophy (X-ALD) is the most common inherited peroxisomal disorder, with an incidence of ~1:17,000 newborn males and females.¹ The disorder is characterized by demyelination of the central nervous system and damage to the adrenal cortex. A spectrum of clinical phenotypes has been described ranging from a childhood onset cerebral form to an adult onset form in which symptoms may only involve the adrenal gland. The onset of cerebral adrenoleukodystrophy (CALD) generally occurs within the first decade of life, however adolescent and adult presentations can occur. Initial signs include behavioral issues, difficulty with visuospatial and visuomotor tasks, hyperactivity, cognitive and neurological deficits including hemiplegia, cerebellar ataxia, impaired central auditory discrimination, visual field defects, cortical blindness, and seizures. Adrenal insufficiency is reported in greater than 50% of affected males with CALD.¹⁻³ Adrenomyeloneuropathy (AMN) typically presents between the ages of 20-30 years and mainly affects the spinal cord and peripheral nervous system resulting in symptoms such as spastic paraplegia, ataxia, incontinence, and leg pain.¹⁻³ Approximately 20-30% of males with AMN will develop cerebral demyelination as the disease progresses.⁴ Adrenal insufficiency only, also known as Addison's disease, has been reported in ~10-13% of patients diagnosed in childhood. The majority of patients with Addison's disease will develop AMN by middle age.^{2,3}

It is estimated that greater than 65% of heterozygous females will develop neurological symptoms by the age of 60 years, however symptoms generally occur later in life and are milder compared to males.^{3,6} Neurological symptoms are similar to that of AMN in males and may include sensory ataxia, fecal incontinence, and leg pain. Cases of cerebral involvement in females have been reported but are rare, as is adrenocortical insufficiency.⁶

Evaluation of clinical symptoms, along with biochemical analysis demonstrating elevation of very long chain fatty acids (VLCFA), specifically C24:0 and C26:0, by an experienced lab can establish the diagnosis of X-ALD in most affected males. Newborn screening for X-ALD has been included as part of the Recommended Uniform Screening Panel (RUSP) since September 2015⁷ and is performed through tandem mass spectrometry to evaluate for C:26 and C:24 lysophosphatidylcholines.⁸

INHERITANCE PATTERN

X-Linked

GENETICS

X-linked adrenoleukodystrophy is caused by pathogenic variants in the *ABCD1* gene. The *ABCD1* gene contains 10 exons and is located at Xq28. *ABCD1* encodes the adrenoleukodystrophy protein (ALDP) which is involved in transporting VLCFA into peroxisomes for beta-oxidation. Deficiency of ALDP results in a reduction of beta-oxidation of VLCFA causing abnormally high levels of C24:0 and C26:0 fatty acids in the body which can be toxic to the adrenal cortex and myelin.¹ Hemizygous males almost always have elevated VLCFA, while ~85% of heterozygous females have elevated VLCFA.⁵

Loss of function pathogenic variants in the *ABCD1* gene include missense, nonsense, small insertions/deletions, and exonic deletions.^{9,10} Exonic deletions account for ~3-6% of pathogenic variants.^{2,9,14} The majority of causative variants are private familial variants. There is no reported genotype-phenotype correlation, as variable clinical phenotypes have been described in individuals harboring the same pathogenic variants.^{11,12} De novo pathogenic variants are reported to occur in ~4-5% of affected probands.^{10,13}

TEST METHODS

Analysis is performed by bi-directional sequencing of the coding regions (exons 1-10) and splice sites of the ABCD1 gene. Concurrently, multiplex ligation-dependent probe amplification (MLPA) is performed to evaluate for a deletion or duplication of most exons in this gene. This test does not include deletion/duplication testing of exon 9. Any variant is confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR, or other appropriate methods.

The methods used by GeneDx are expected to be greater than 99% sensitive in detecting variants identifiable by sequencing.

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