X-Linked Adrenoleukodystrophy: \textit{ABCD1} Gene Deletion/Duplication

\textbf{Condition Description}

X-linked adrenoleukodystrophy (X-ALD) is a disorder of fatty acid oxidation caused by mutations in the \textit{ABCD1} gene (Xq28). X-ALD can present at a variety of ages and with different manifestations depending on the presence and type of neurologic findings. The condition has three main phenotypes seen in males. In the childhood cerebral form, symptoms appear between ages four and eight years and include inattention, hyperactivity, and emotional lability. Progressive impairment of cognition, behavior, vision, hearing, and motor function follow the initial symptoms and often lead to total disability within two years. The second phenotype, adrenomyeloneuropathy (AMN), manifests most commonly in the late twenties as progressive paraparesis, sphincter disturbances, sexual dysfunction, and often, impaired adrenocortical function; all symptoms are progressive over decades. The third phenotype, “Addison disease only,” presents with primary adrenocortical insufficiency between age two years and adulthood (most commonly by age 7.5 years), without evidence of neurologic abnormality. Some degree of neurologic disability (most commonly AMN), however, usually develops later. Varying phenotypes often coexist in the same kindred or sibship. Approximately 20\% of carrier females develop neurologic manifestations that resemble adrenomyeloneuropathy, but have later onset (age 35 years or later) and milder disease than affected males.

The \textit{ABCD1} gene encodes the ATP-binding cassette sub-family D member 1 protein, which is located in the peroxisomal membrane. Gene product is absent in 70\% of affected individuals. The principal biochemical abnormality is the accumulation of saturated very long chain fatty acids (VLCFA) due to an apparent defect in peroxisomal beta oxidation, particularly hexacosanoic (C26:0) and tetracosanoic (C24:0) fatty acid, a function that normally takes place in the peroxisome. Testing for plasma concentration of VLCFA reveals abnormal levels in 99.9\% of males with X-ALD. Increased concentration of VLCFA in plasma and/or cultured skin fibroblasts is present in approximately 85\% of affected females; 20\% of known carriers have normal plasma concentration of VLCFA.

About 93\% of index cases have inherited the \textit{ABCD1} mutation from one parent; at most, 7\% of individuals with X-ALD have de novo mutations. PCR and sequence analysis identified mutations in 229 of 249 (92\%) hemizygous males or obligate heterozygote females. Sixteen of the 20 individuals (in the series of 249 individuals) without a mutation identified by sequence analysis had a deletion detected by Southern blot analysis. In one of the four remaining individuals, Southern blot results suggested a duplication or rearrangement, for a total detection rate of 98\%. The prevalence is estimated to be between 1:20,000 and 1:50,000. The minimum frequency of hemizygotes identified in the United States is estimated to be 1:21,000 and that of hemizygotes plus heterozygotes (i.e., carrier females) is 1:16,800. The prevalence appears to be approximately the same in all ethnic groups.

Due to the presence of a pseudogene for the \textit{ABCD1} gene, analysis of deletion or duplication of exons 7-10 cannot be included in this assay.

For patients with suspected X-ALD, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

\textbf{Genes}

\textit{ABCD1}

\textbf{Indications}

This test is indicated for:

- Confirmation of a clinical diagnosis of X-ALD in individuals who have tested negative for sequence analysis
- Carrier testing in adult females with a family history of X-ALD who have tested negative for sequence analysis

\textbf{Methodology}

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

\textbf{Detection}

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

\textbf{Specimen Requirements}

Submit only 1 of the following specimen types

- Preferred specimen type: Whole Blood

\textbf{Type: Whole Blood}
Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the ABCD1 gene is available and is required before deletion/duplication analysis.
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.