ABCD1 Gene Sequencing and Deletion/Duplication Analysis by MLPA

Disease:

X-Linked Adrenoleukodystrophy (X-ALD)

Description:

The *ABCD1* gene encodes the Adrenoleukodystrophy protein. Defects in this gene result in abnormal peroxisomal beta-oxidation, causing accumulation of very long chain fatty acids (VLCFAs) in all body tissues, especially in the white matter and the adrenal cortex. Pathogenic hemizygous variants in the *ABCD1* gene are associated with a broad phenotypic spectrum of disorders in males. While up to seven disease subtypes have been previously described, three primary subtypes are found in the majority of affected individuals:

- Childhood cerebral adrenoleukodystrophy (CCALD)
- Adrenomyeloneuropathy (AMN)
- Addison Disease

CCALD is present in approximately 35% of affected individuals. Onset of symptoms begin between four to eight years of age, initially presenting with changes in behavior or learning difficulty followed by rapid progressive cognitive impairment, vision and hearing loss, impaired motor function, and adrenocortical insufficiency. This subtype is expected to result in a limited lifespan. AMN occurs in approximately 45% of affected individuals and is characterized by early adult onset of adrenocortical insufficiency, progressive stiffness, loss of bladder and bowel control, and sexual dysfunction. This subtype may lead to variable but progressive cognitive impairment. The Addison Disease subtype occurs in 10% of affected individuals and has variable age of onset, beginning in early childhood through adulthood. The primary feature is adreno-cortical insufficiency, with rare cases of neurologic decline occurring later in life.

In females, heterozygous ABCD1 pathogenic variants may cause mild-to-moderate AMN-like features in adulthood, such as gradual spastic paraparesis in the legs with bowel or bladder difficulties. Most carrier females have normal adrenal function; however 85% of female carriers may have elevated VLCFA concentra-tion in blood serum or plasma.

Some males have a combined deletion involving the 5' end of ABCD1 and the gene BCAP31 (previously known as DXS1375E). This variant causes Contiguous ABCD1 DXS1375E Deletion Syndrome (CADDS). CADDS is characterized by neonatal onset hypo-tonia, failure to thrive, developmental delay, and cholestatic liver disease which can lead to premature death in infancy.

Indications:

- Confirmation of diagnosis in a symptomatic individual
- Confirmation of diagnosis in males following positive newborn screening results for X-ALD
- Pre-symptomatic or carrier testing for at-risk relatives
- Prenatal diagnosis in families with an identified *ABCD1* variant

Methodology:

PCR-based Sanger sequencing of the coding regions and their exon/intron boundaries of the *ABCD1* gene. *ABCD1* deletion/duplication analysis is performed by multiple ligation-dependent probe amplification (MLPA).

Clinical Sensitivity:

It is estimated that ~ 97.5% of *ABCD1* pathogenic variants that cause X-ALD can be detected by Sanger sequencing. Remaining ~2.5% are large deletions/duplications that cannot be detected by Sanger sequencing, but assays such as MLPA can detect (Mallack et al. 2022).

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Turn-Around Time:

28 days

Specimen:

At least 3 mls whole blood in a lavender top (EDTA) tube or saliva in an Oragene saliva kit . Please call the lab at 513-636-4474 for a free saliva collection kit. Label the tube with the patient's name, birth date, and date of collection. Alternatively, 1 mcg of DNA extracted by a CLIA certified lab may be submitted.

CPT Codes:

ABCD1 full gene sequencing: **81405**
ABCD1 known gene sequencing: **81403**
ABCD1 deletion/duplication analysis by MLPA: **81479**

Shipping Instructions:

Please enclose **test requisition** with sample. **All information must be completed before sample can be processed.**

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Saturday.

Ship to:

Genetics and Genomics Diagnostic Laboratory
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

References:

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Corzo, D., et al. (2002). Contiguous deletion of the X-linked adrenoleukodystrophy gene (ABCD1) and DXS1357E: a novel neonatal phenotype similar to peroxisomal biogenesis disorders. American journal of human genetics, 70(6), 1520–1531.

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Moser, H. W., Raymond, G. V., & Dubey, P. (2005). Adrenoleukodystrophy: new approaches to a neurodegenerative disease. JAMA, 294(24), 3131–3134.

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