Allan-Herndon-Dudley Syndrome: \textit{SLC16A2} Gene Sequencing

\textbf{Condition Description}

Allan-Herndon-Dudley syndrome is an X-linked recessive disorder caused by mutations in the \textit{SLC16A2} (also called \textit{MCT8}) gene (Xq13.2). Common characteristics of this disorder include moderate to severe mental retardation, impaired speech, hypotonia, muscle weakness, and contractures. Symptoms seen in infancy and childhood can consist of hypotonia, weakness, reduced muscle mass, and delay of developmental milestones. Facial characteristics are not distinctive, but the face tends to be elongated with bifrontal narrowing, and the ears are often simply formed or cupped. Some patients have myopathic facies. Generalized weakness is manifested by excessive drooling, forward positioning of the head and neck, failure to walk independently, or ataxia in those who do walk. Speech is dysarthric or absent altogether.

Hypotonia gives way in adult life to spasticity. The hands exhibit dystonic and writhing posturing and fisting. Cognitive development is severely impaired. No major malformations occur and head circumference and genital development are usually normal. Behavior tends to be passive, with little evidence of aggressive or disruptive behavior.

Mutations in the \textit{SLC16A2} gene impair thyroid hormone transport. Although clinical signs of thyroid dysfunction are usually absent in affected males, the disturbances in blood levels of thyroid hormones can be seen, such as increased serum T3 levels. Some female carriers may have mild serum thyroid hormone abnormalities but no neurologic manifestations. Both point mutations and partial gene deletions have been reported in this gene.

For patients with suspected Allan-Herndon-Dudley syndrome, 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{MCT8, SLC16A2}

\textbf{Indications}

This test is indicated for:

- Confirmation of a clinical diagnosis of Allan-Herndon-Dudley syndrome
- Carrier testing in adult females with a family history of Allan-Herndon-Dudley syndrome

\textbf{Methodology}

PCR amplification of 6 exons contained in the \textit{SLC16A2} gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

\textbf{Detection}

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

\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) or ACD (yellow 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.

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**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 Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Deletion/duplication analysis of the SLC16A2 gene by CGH array is available for those individuals in whom sequence analysis is negative (YG).
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.