Condition Description

Alpha-mannosidosis is an autosomal recessive disorder due to deficiency in the lysosomal enzyme alpha-mannosidase. The enzyme is responsible for catalyzing the removal of the mannose sugar residues during the breakdown of proteins that contain sugar groups (called glycoproteins), such as oligosaccharides. Deficiency of the alpha-mannosidase activity results in accumulation of mannose-rich oligosaccharides chains, leading to swelling of the lysosome and impairment of normal cellular functions.

Alpha-mannosidosis is a heterogeneous condition that is classified into overlapping types. Clinical symptoms of Type I, the mildest form, are typically noticeable after 10 years of age and do not include skeletal abnormalities. Clinical symptoms of Type 2, the intermediate form, include skeletal abnormalities and typically onset before 10 years of age. Type 3 is the most severe form with early childhood onset of symptoms and rapid progression of the disease, leading to death. Individuals with alpha-mannosidosis have: delayed motor development, mental retardation, hearing loss, typical facies (a Hurler-like face), bone disease, immunodeficiency, ocular findings and hepatosplenomegaly. In addition, psychiatric problems are common.

Mutations in the MAN2B1 gene are responsible for alpha-mannosidosis(1). More than 20 different disease causing mutations have been identified. These mutations include missense, nonsense, splice site, frameshift and large deletions(2). These mutations lead to partial or complete loss of enzymatic activity.

For questions about testing for alpha-mannosidosis, call EGL Genetics at 470-378-2200 or 855-831-7447. For further clinical information about lysosomal storage diseases, including management and treatment, call the Emory Lysosomal Storage Disease Center at (404) 778-8565 or (800) 200-1524.

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array KU.

References:

Genes

**MAN2B1**

Indications

- Confirmation of a clinical diagnosis of alpha-mannosidosis
- Prenatal testing for known familial mutation(s).
- Assessment of carrier status in high risk family members - known mutation analysis.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Next Generation Sequencing: 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/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype. Analytical Sensitivity: ~99%.

Prevalence: The estimated prevalence of all lysosomal storage disorders is 2-5 per 100,000. The prevalence of alpha-mannosidosis disease is not specifically known, but is likely to be rare and may vary by ethnicity.

Specimen Requirements
Submit only 1 of the following specimen types

Type: Saliva

**Specimen Requirements:**
Oragene™ Saliva Collection Kit
Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated

**Specimen Requirements:**
Microtainer
8µg
Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

**Specimen Requirements:**
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Special Instructions**
Submit copies of diagnostic biochemical test results with the sample. 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. Contact the laboratory if further information is needed.

**Related Tests**
- Known mutation analysis (Custom Diagnostics) is available to test family members.
- A deletion/duplication assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor for specific requirements for prenatal testing before collecting a fetal sample.