Deafness-Dystonia-Optic Neuronopathy Syndrome: **TIMM8A Gene Sequencing**

**Condition Description**

Deafness-dystonia-optic neuronopathy (DDON) syndrome is an X-linked disorder in males characterized by certain manifestations at different ages. Pre or postlingual sensorineural hearing impairment begins in early childhood; slowly progressive dystonia or ataxia manifests during the teens; slowly progressive decreased visual acuity from optic atrophy begins in the early 20s; and dementia begins around age 40. Additionally, psychiatric symptoms, such as personality change and paranoia, may be progressive from childhood. Age of onset and progression tends to be consistent for the hearing impairment; however the neurologic, visual, and neuropsychiatric signs vary in degree of severity and rate of progression. Females may have mild hearing impairment and focal dystonia.

Mutations in **TIMM8A** (Xq22) cause DDON. The **TIMM8A** gene encodes the mitochondrial import inner membrane translocase subunit Tim8 A protein and is involved in mitochondrial transport processes. DDON syndrome can also be part of a contiguous gene deletion syndrome at Xq22 which includes the **TIMM8A** and **BTK** genes and included X-linked agammaglobulinemia. The mutation detection rate is not yet known.

For patients with suspected DDON, 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.

**References:**
- Genetests

**Genes**

**TIMM8A**

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of deafness-dystonia-optic neuronopathy syndrome.
- Carrier testing in adults with a family history of deafness-dystonia-optic neuronopathy syndrome.

**Methodology**

PCR amplification of 2 exons contained in the **TIMM8A** 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.

**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%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**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\textsuperscript{TM} 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 \textit{TIMM8A} gene by CGH array is available for those individuals in whom sequence analysis is negative.
- 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 only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.