Ataxia with Oculomotor Apraxia Type 2: *SETX* Gene Sequencing

**Test Code:** SSETX  
**Turnaround time:** 6 weeks  
**CPT Codes:** 81479 x1

### Condition Description

Mutations in the *SETX* gene (9q34) are associated with three different conditions: ataxia with oculomotor apraxia type 2 (AOA2), juvenile amyotrophic lateral sclerosis (ALS4) and autosomal dominant ataxia.

AOA2 is characterized by cerebellar ataxia, axonal sensorimotor neuropathy, oculomotor apraxia, and elevated serum concentration of alpha-fetoprotein. Other characteristics include marked cerebellar atrophy on MRI and signs of axonal neuropathy on EMG. The age of onset is between ages three and 30 years. There is a slow progression of the phenotype. Cardiac involvement, cancer predisposition, and immunodeficiency are usually absent. Ataxia is often the first sign of AOA2 and causes the majority of disability early in the disease progression. Later in the disease course, peripheral sensorimotor neuropathy, especially in the lower limbs, causes the majority of disease progression.

Both sequence alterations and partial or whole gene deletions and duplications of the *SETX* gene have been reported. AOA2 is inherited in an autosomal recessive manner. Carriers are asymptomatic.

ALS4 is associated with three different autosomal dominant missense mutations in the *SETX* gene: T3I, L389S, R2136H. It is characterized by severe distal muscle weakness and atrophy and signs associated with degeneration of motor neurons in the central nervous system. Individuals with ALS4 have normal sensation, onset before the age of 25, slow disease progression, and a normal life span.

Two mutations in cis in the *SETX* gene have been identified in a family with an autosomal dominant form of ataxia. Affected individuals in this family had cerebellar ataxia with atrophy of the cerebellum, dysarthria, oculomotor defects, and tremor. Mental status, reflexes, sensation, muscle tone, and levels of alpha-fetoprotein were in the normal range.

### References:

- GeneReviews

### Genes

**SETX**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of AOA2.  
- Carrier testing in adults with a family history of AOA2.

### 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

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 clinical and/or 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) tube:

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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.

**Related Tests**

- 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.