Marinesco-Sjogren Syndrome: \textit{SIL1} Gene Sequencing

\textbf{Test Code:} SSIL1  
\textbf{Turnaround time:} 4 weeks  
\textbf{CPT Codes:} 81479 x1

\section*{Condition Description}

Marinesco-Sjogren syndrome (MSS) is characterized by cerebellar ataxia with cerebellar atrophy, early-onset (not necessarily congenital) cataracts, mild to severe mental retardation, hypotonia, and muscle weakness. Additional features include short stature, various skeletal abnormalities including scoliosis, hypergonadotropic hypogonadism, dysarthria, strabismus, and nystagmus. Children with MSS usually present with muscular hypotonia in early infancy; distal and proximal muscular weakness is noticed during the first decade of life. Later, cerebellar findings of truncal ataxia, dysdiadochokinesia, and dysarthria become apparent. Motor function worsens progressively for some years, then stabilizes at an unpredictable age and degree of severity. Cataracts can develop rapidly and typically require lens extraction in the first decade of life. Although many adults are severely handicapped, life span in MSS seems to be near normal.

Diagnosis is based on clinical, radiographic, and neuroimaging studies. Serum CK concentrations are normal or moderately increased (usually 2-4 times the upper normal limits). Light microscopy shows variation in muscle fiber size, atrophic fibers, fatty replacement, and rimmed vacuole formation. Electron microscopy reveals autophagic vacuoles, membranous whorls, and electron-dense double-membrane structures associated with nuclei, which are thought to be a specific ultrastructural feature of MSS. \textit{SIL1} (5q31) is the only gene known to be associated with Marinesco-Sjogren syndrome and mutations in \textit{SIL1} are identified in 50-60\% of individuals fulfilling diagnostic criteria.

MSS is inherited in an autosomal recessive manner. MSS has previously been called Garland-Moorhouse syndrome, Marinesco-Garland syndrome, and hereditary oligophrenic cerebello-lental degeneration. MSS is panethnic; the prevalence is not known, but the carrier frequency in Finland is estimated to be approximately 1 in 96.

For patients with suspected Marinesco-Sjogren 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.

\section*{References}

\section*{Genes}

\textbf{\textit{SIL1}}

\section*{Indications}

This test is indicated for:
- Confirmation of a clinical diagnosis of Marinesco-Sjogren syndrome
- Carrier testing in adults with a family history of Marinesco-Sjogren syndrome

\section*{Methodology}

PCR amplification of 9 exons contained in the \textit{SIL1} 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.

\section*{Detection}

Clinical Sensitivity: Mutations in \textit{SIL1} are identified in 50-60\% of individuals fulfilling diagnostic criteria. 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: \textasciitilde99\%

\section*{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:

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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.

### 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 SIL1 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 to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.