Smith-Magenis Syndrome: RAI1 Gene Sequencing

Test Code: SRAI1
Turnaround time: 6 weeks
CPT Codes: 81479 x1

Condition Description

Smith-Magenis syndrome (SMS) is characterized by behavioral abnormalities, including the “self-hug” and “lick and flip” behaviors, significant sleep disturbances, and self-injurious behaviors; distinctive facial features that progress with age, mild to moderate intellectual disability, and developmental delay. Additionally, individuals with SMS have mild to moderate infantile hypotonia with feeding difficulties and failure to thrive, minor skeletal anomalies, short stature, eye abnormalities, otolaryngologic abnormalities, early speech delays with or without hearing loss, and peripheral neuropathy. SMS is caused by deletions or mutations of the RAI1 (17p11.2) gene.

For patients with suspected SMS, deletion/duplication analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by deletion/duplication analysis, full gene sequencing is appropriate.

References:
- GeneReviews
- OMIM #607642: RAI1 gene
- OMIM #182290: SMS

Deletion/Duplication testing should be ordered as the first tier test.

Genes

RAI1

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of Smith-Magenis syndrome in an individual in whom deletion/duplication analysis was negative.
- Carrier testing in adults with a family history of autosomal recessive Smith-Magenis syndrome in whom deletion/duplication analysis was negative.

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

5-10% of SMS mutations are detected by sequencing. 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

Type: DNA, Isolated

Specimen Requirements:
- Microtainer
- 8µg
- Isolation using the Perkin Elmer™Chemagen™ 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)

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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.

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.

Related Tests
- Deletion/duplication analysis of the RA11 gene is available and is required before sequencing analysis.
- 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.