Smith-Magenis Syndrome: \textit{RAI1} Gene Sequencing

\textbf{Test Code:} SRAI1  
\textbf{Turnaround time:} 6 weeks  
\textbf{CPT Codes:} 81479 x1

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\textbf{Condition Description} \\
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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 \textit{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. \\

\textbf{References:}\n
- GeneReviews
- OMIM \#607642: \textit{RAI1} gene
- OMIM \#182290: SMS \\

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

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\textbf{Genes} \\
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\textit{RAI1} \\

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\textbf{Indications} \\
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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. \\

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\textbf{Methodology} \\
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\textbf{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. \\

\textbf{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: \sim 99\% \\

\textbf{Specimen Requirements} \\

\textit{Submit only 1 of the following specimen types} \\

\textbf{Type: Whole Blood (EDTA)} \\

\textbf{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 \\

\textbf{Specimen Collection and Shipping:} \\
Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze. \\

\textbf{Type: DNA, Isolated} \\

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\textbf{Disclaimer:} This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative. \\
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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: 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 RAIf 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.