**RAI1 Gene Analysis in Smith-Magenis Syndrome**

*Mendelian Inheritance in Man Number:* 182290 (Smith-Magenis Syndrome); 607642 (RAI1 gene)

**Clinical features:**
Smith-Magenis Syndrome (SMS) is characterized by facial dysmorphism, behavioral problems, sleep disturbances, growth retardation and moderate intellectual disability. The classic facial features tend to progress with age and include brachycephaly, mid-facial hypoplasia with broad flat midface, broad nasal bridge, and prognathism. Cognitive, psychomotor, and speech delays are common. Neurobehavioral features become more pronounced with age and can include hyperactivity, temper tantrums, attention-seeking, self-hugging, self-injurious behaviors, and sleep disturbances. A recent study of 26 patients with confirmed 17p11.2 deletions found that 90% met diagnostic criteria for autism spectrum disorders. About 40% of patients with the 17p11.2 deletion have structural or functional congenital heart defects. Hoarse voice, hearing loss, and eye abnormalities are frequently present as well. Hypercholesterolemia has been reported in 70% of affected patients.

**Inheritance pattern:** Autosomal dominant. Most cases are sporadic, but parental mosaicism and rare heritable chromosome rearrangements that lead to loss of 17p11.2 have been reported; therefore, parental testing is recommended.

**Reasons for referral:**
1. Confirmation of clinical diagnosis
2. Genetic counseling and recurrence risk estimation
3. Prenatal diagnosis

**Test method:**
Most cases (90%) of SMS are due to an interstitial deletion of the 17p11.2 critical region that includes the entire RAI1 gene (and other genes). Of those patients with deletions, 70% carry a recurrent 3.7-Mb deletion. GeneDx offers whole genome oligonucleotide microarray analysis (GenomeDx), which can detect the common 17p11.2 deletion as well as other microdeletion/microduplication syndromes with clinical features overlapping with Smith Magenis. Alternatively, FISH analysis with the RAI1 gene probe is also available to detect the common 17p11.2 deletion.

For those SMS cases in which the classic 3.7-Mb deletion is not identified, GeneDx performs bi-directional sequence analysis of exon 3 of the RAI1 gene and its flanking intron sequences. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of individual exons within the RAI1 gene. Exon 3 represents approximately 95% of the coding sequence of this gene and is where all RAI1 mutations have been reported to date. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

**Test sensitivity:**
The FISH test for SMS deletion is positive in 90% of cases. Studies of 17p11.2 deletion-negative SMS patients have described a total of 14 different RAI1 mutations identified by sequence analysis. Disease-causing mutations in exon 3 of the RAI1 gene are identified in approximately 10-11% of individuals with Smith Magenis syndrome who have had a negative FISH test.
Mutation spectrum:
A vast majority (90%) of SMS cases are due to an interstitial deletion in 17p11.2 and most of these deletions (70%) are 3.7-Mb in size, representing a recurrent rearrangement between segmental duplication loci. A small number of cases demonstrate a smaller deletion but still include the critical RAI1 gene. Among sequence mutations, the majority of reported novel RAI1 mutations are frameshift mutations typically due to a deletion of a single “C” nucleotide in one of the regions with a poly-C tract. Missense and nonsense mutations have also been described in patients with Smith-Magenis syndrome. A genotype-phenotype correlation study revealed that 21 of 30 SMS features resulted from haploinsufficiency of the RAI1 gene. Whereas cardiac anomalies, renal anomalies, speech and motor delay, hypotonia, short stature, and hearing loss were more associated with 17p11.2 deletions, polyembolokoilamania, self-hugging, muscle cramping, and dry skin were more associated with RAI1 mutations. The variable clinical presentation and severity of SMS are thought to be due to deletions of other genes within the 17p11.2 region (contiguous gene deletion syndrome). A reciprocal duplication of the SMS region is now known to cause Potocki-Lupski syndrome, which features a phenotype that is distinct from SMS.

Specimen Requirements and Shipping/Handling:
- **Blood**: For sequence analysis and deletion/duplication analysis (ExonArrayDx), submit a single tube with 1-5 mL whole blood in EDTA (lavender top tube). Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Blood**: For FISH testing, submit a single tube with 1-5 mL whole blood in sodium heparin (green top tube). Ship overnight at ambient temperature, using a cool pack in hot weather.
- **Buccal Brushes**: CANNOT be accepted for this test.
- **Prenatal Diagnosis**: Prenatal testing for the recurrent deletion and for pathogenic sequence variants is available. For prenatal testing for a known mutation in the RAI1 gene, please refer to the specimen requirements table on our website: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

For test codes, prices, CPT codes and turn-around-times, please refer to the “Smith-Magenis syndrome” page on our website: www.genedx.com.

Required Forms:
- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

References: