RAI1 Gene Analysis in Smith-Magenis Syndrome

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.[1] 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[2].

GENETICS

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.[3]

TEST METHODS

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.[3] GeneDx offers whole genome oligonucleotide microarray analysis (MicroarrayDx), which can detect the common 17p11.2 deletion as well as other microdeletion/microduplication syndromes with clinical features overlapping with Smith Magenis.[3] Alternatively, FISH analysis with the RAI1 gene probe is also available to detect the common 17p11.2 deletion.[4] 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 RAI1gene. Exon 3 represents approximately 95% of the coding sequence of this gene and is where all RAI1 variants have been reported to date. Variants 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 variants identified by sequence analysis.[6,7] pathogenic variants 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.[3, 6]

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