SPRED1 Gene Analysis in Legius Syndrome

Clinical Features:
Neurofibromatosis 1-like syndrome, or Legius syndrome, is an autosomal dominant disorder resembling neurofibromatosis 1 with cafe-au-lait spots, axillary freckling, macrocephaly, learning disabilities, ADHD, developmental delays, and dysmorphic facial features similar to Noonan syndrome. Other typical NF1 features such as Lisch nodules of the iris, neurofibromas and central nervous system tumors are systematically absent. Two studies revealed that approximately 2% of individuals fulfilling diagnostic criteria for NF1 have SPRED1 variants.

Genetics:
The SPRED1 gene encodes a protein involved in the regulation of growth factor-induced activation of the MAP kinase pathway. Pathogenic variants in SPRED1 result in defective inhibition of Raf1 kinase activation and thus, in increased Ras signal propagation.

Pathogenic variants in SPRED1 are inherited in an autosomal dominant manner. The majority of reported variants in the SPRED1 gene are nonsense, frameshift, splice site or large deletions that lead to loss-of-function. However, a small number of pathogenic missense variants have also been reported in association with a neurofibromatosis 1-like phenotype.

Test Methods:
Bi-directional sequence analysis of the coding regions and splice sites of the SPRED1 gene. Any variant or reportable variant will be confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. In individuals who do not harbor a SPRED1 variant identifiable by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of the SPRED1 gene.

Test Sensitivity:
SPRED1 variants have been reported in approximately 2% of individuals who meet NIH NF1 diagnostic criteria, and in 8% who met NF1 criteria and were negative for an NF1 gene variant. SPRED1 variants have also been reported in approximately 1.3% of individuals with a clinical diagnosis of NF1 and who have had no previous genetic testing. However, the sensitivity of SPRED1 sequencing for the cohort discussed by Muram-Zborovski et al. increased to 20% if patients with an affected parent, optic pathway tumor, Lisch nodules, neurofibromata, long bone dysplasia, or sphenoid wing dysplasia were excluded. Deletions of the SPRED1 gene account for approximately 10% of all variants identified in the SPRED1 gene.
The frequency of SPRED1 variants among patients with suspected Noonan syndrome is currently unknown.

The majority of reported variants in the SPRED1 gene are nonsense, frameshift, splice site or large deletions, which lead to loss-of-function. However, a small number of missense variants have also been reported in association with a neurofibromatosis 1-like phenotype. 3,9

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