Legius Syndrome

Indications for Ordering

- Confirm diagnosis of Legius syndrome (LS) in symptomatic individuals
- For individuals being evaluated for neurofibromatosis type 1 (NF1) who test negative for NF1 gene variants

Test Description

- Polymerase chain reaction followed by bidirectional sequencing of SPRED1 coding regions (exons 2-8) and intron/exon boundaries
- Multiplex ligation-dependent probe amplification of exons 2-8 to detect large deletions/duplications in SPRED1 gene

Tests to Consider

Primary tests
Legius Syndrome (SPRED1) Sequencing and Deletion/Duplication 2008347
- Preferred test to confirm LS for symptomatic individuals who test negative for NF1 gene variants

Legius Syndrome (SPRED1) Sequencing 2002945
- Acceptable diagnostic and predictive test for LS for symptomatic individuals who test negative for NF1 gene variants
- Detects most pathogenic variants

Related tests
Neurofibromatosis Type 1 (NF1) Sequencing and Deletion/Duplication 2007154
- Preferred test to confirm a suspected diagnosis of NF1 for individuals not meeting NIH clinical criteria

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence
- Unknown for LS
- 2% of individuals meeting the criteria for NF1 have an identifiable variant in the SPRED1 gene
- 3-25% of individuals being evaluated for NF1 who lack variants in the NF1 gene have variants in the SPRED1 gene

Symptoms
- Café au lait spots
- Axillary and inguinal freckling
- Lipomas
- Macrocephaly
- Learning disabilities
- Attention deficit hyperactivity disorder

Diagnostic issues
- Diagnosis is difficult due to overlapping symptoms with NF1
  - Neurofibromas, Lisch nodules (iris hamartomas), and central nervous system (CNS) tumors have not been reported in LS
  - Individuals with LS may meet clinical criteria for NF1 but test negative for NF1 gene variants
- Diagnosis of LS is difficult using only clinical features
  - Identification of a SPRED1 gene variant is necessary in order to make definitive diagnosis

Genetics

Gene – SPRED1
Inheritance – autosomal dominant
Penetrance – nearly 100%
De novo variants – 50%

Variants – single base-pair
- Nonsense
- Missense
- Frameshift

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity – unknown
- Analytical sensitivity/specificity – 99%

Results
- Positive – variant detected in SPRED1 gene
  - Diagnosis confirmed
- Negative – no variants detected in SPRED1 gene
  - Diagnosis of LS is less likely but not excluded
- Inconclusive – variant detected, but whether the variant is benign or pathogenic is unclear
Limitations

• Regulatory region and deep intronic variants will not be detected
• Large deletion/duplication breakpoints will not be determined
• Diagnostic errors can occur due to rare sequence variants