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