Legius Syndrome (SPRED1)

Legius syndrome (LS) is a rare genetic disorder characterized primarily by cutaneous findings such as café au lait spots, axillary and intertriginous freckling, and lipomas. Distinguishing LS from neurofibromatosis type 1 (NF1) may be difficult because of overlapping clinical features, especially in younger patients who have not yet developed other clinical features particular to NF1 (eg, neurofibromas and Lisch nodules). *SPRED1* molecular testing can help identify patients who do not need routine surveillance for NF1-related tumors and other complications.[1]

Disease Overview

Prevalence

- May represent 0.5% of NF1 diagnoses or 8% of those with isolated café au lait spots
- 3-25% of individuals being evaluated for NF1 who lack variants in the *NF1* gene have variants in the *SPRED1* gene[1]

Clinical Findings

- Café au lait spots[1]
- Axillary and intertriginous freckling[1]
- Lipomas[1]
- Macrocephaly[1]
- Learning disabilities, attention deficit hyperactivity disorder (ADHD), and developmental delays[1]

Diagnostic Considerations

Diagnosis can be difficult due to clinical overlap with NF1. Patients with LS may have pigmentary symptoms of NF1 (ie, café au lait macules and/or intertriginous freckling); however, they lack the nonpigmentary manifestations (eg, Lisch nodules, neurofibromas).[1]

Identification of a pathogenic *SPRED1* gene variant is necessary to make a definitive diagnosis of LS.[1]

Genetics

Gene

SPRED1

Inheritance

Autosomal dominant[1]

De novo variants

Approximately 39%[2]

Tests to Consider

Legius Syndrome (SPRED1) Sequencing and Deletion/Duplication 2008347

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Use to confirm a suspected diagnosis of Legius syndrome in individuals with a negative NF1 Sequencing and Deletion/Duplication test

Related Tests

Neurofibromatosis Type 1 (NF1) Sequencing and Deletion/Duplication 2007154

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Preferred test to confirm a suspected diagnosis of NF1

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

Variants

Most variants are of the following types:

- Sequence variants[1] (88% of detected variants in one study[3])
- Large deletions (multiexonic, or whole gene[1]; 10% of detected variants in one study[3])

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: unknown
- Analytical sensitivity/specificity: 99%

Results

Results	Result Description	Interpretive Data
Positive	Pathogenic variant detected in *SPRED1* gene	Diagnosis of LS confirmed
Negative	No pathogenic variants detected in *SPRED1* gene	Diagnosis of LS less likely, but not excluded
Inconclusive	Variant of unknown significance detected	Inconclusive

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 variations

References

1. Stevenson D, Viskochil D, Mao R. Legius syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews, University of Washington, 1993-2020. [Last update: Aug 2020; Accessed: Feb 2020]

2. Brems H, Legius E. Legius syndrome, an update. Molecular pathology of mutations in *SPRED1*. Keio J Med. 2013;62(4):107-112. PubMed

3. Spencer E, Davis J, Mikhail F, et al. Identification of SPRED1 deletions using RT-PCR, multiplex ligation-dependent probe amplification and quantitative PCR. Am J Med Genet A. 2011;155A(6):1352-1359. PubMed

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