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 spots¹
- Axillary and intertriginous freckling¹
- Lipomas¹
- Macrocephaly¹
- Learning disabilities, attention deficit hyperactivity disorder (ADHD), and developmental delays¹

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 dominant¹

De novo variants

Approximately 39%²
Variants

Most variants are of the following types:

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

Test Interpretation

Sensitivity/Specificity

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

Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Result Description</th>
<th>Interpretive Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Pathogenic variant detected in $SPRED1$ gene</td>
<td>Diagnosis of LS confirmed</td>
</tr>
<tr>
<td>Negative</td>
<td>No pathogenic variants detected in $SPRED1$ gene</td>
<td>Diagnosis of LS less likely, but not excluded</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Variant of unknown significance detected</td>
<td>Inconclusive</td>
</tr>
</tbody>
</table>

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


ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
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