Legius Syndrome Genetic Testing

Introduction

Legius syndrome testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is Legius Syndrome

Definition

Legius syndrome is an autosomal dominant condition characterized by multiple café-au-lait macules and axillary or inguinal freckling, without neurofibromas or other tumor symptoms of Neurofibromatosis type 1 (NF1).¹

Incidence or Prevalence

The exact incidence of Legius syndrome is unknown. Studies have shown that approximately 2% of individuals meeting the diagnostic criteria for NF1 have Legius syndrome.¹

Symptoms/Diagnosis

Individuals with Legius syndrome have multiple café-au-lait macules and may have axillary or inguinal freckling. Other clinical features reported in some patients with Legius syndrome include macrocephaly, Noonan-like facial features, pectus excavatum or carinatum, developmental concerns, attention deficit hyperactivity disorder (ADHD), and learning difficulties.²

Genetic testing may be indicated in a patient with café-au-lait macules to confirm a diagnosis and direct long term management and surveillance. Approximately 3%-25% of individuals evaluated for NF1 who do not have an identifiable mutation in the NF1 gene are noted to have a SPRED1 pathogenic variant.³ Individuals with NF1 require
long-term surveillance due to an increased risk of tumor development and other complications. Thus, the diagnosis of Legius syndrome may include molecular testing of the SPRED1 gene, and in some cases the NF1 gene.

**Cause**

Legius syndrome is caused by mutations in the SPRED1 gene. The protein product of this gene interacts with neurofibromin, the protein product of the NF1 gene.²

**Inheritance**

Legius syndrome is inherited in an autosomal dominant fashion. When a parent has a SPRED1 mutation, each offspring has a 50% risk of inheriting the mutation.³

**Treatment**

Management of a child with Legius syndrome includes therapies for developmental delays, learning disorders, and ADHD.³

**Survival**

Lifespan does not appear to be affected by Legius syndrome. Current knowledge is based on the clinical history of less than 200 individuals with confirmed diagnosis of Legius syndrome.⁴

**Test Information**

**Introduction**

Testing for Legius syndrome may be performed by SPRED1 sequencing or SPRED1 deletion/duplication analysis. Known familial mutation analysis is also available.

**SPRED1 sequencing analysis**

SPRED1 sequencing variants, such as missense, nonsense, and splice site variants, account for up to 88% of mutations seen in Legius syndrome.³

**SPRED1 deletion/duplication analysis**

About 10% of the disease-causing variants in Legius syndrome are multi-exon and whole gene deletions.⁴⁵

**Known familial mutation analysis**

Analysis for known familial mutations is typically performed by Sanger sequencing, but if available, a targeted mutation panel that includes the familial mutation may be performed.
Known familial mutations analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing.

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to Legius syndrome testing.

Expert Authored Review

"There are different opinions on the appropriate approach when clinical information and family history cannot distinguish between Neurofibromatosis type 1 and Legius syndrome. The pros and cons assessment of molecular testing requires the consideration each individual’s unique circumstances, including (but not limited to):

- Clinical findings and family history
- Age of the individual
- Differences in recommended clinical management when the diagnosis of NF1 or Legius syndrome is established with certainty versus when the diagnosis of neither can be established with confidence
- Psychological burden of a diagnosis or lack thereof
- Cost of testing and surveillance "

Criteria

Introduction

Requests for SPRED1 testing are reviewed using the following clinical criteria.

SPRED1 Known Familial Mutation Analysis

Genetic Counseling:

- Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Diagnostic Testing for Symptomatic Individuals:

- No previous genetic testing of SPRED1, AND
- SPRED1 mutation identified in 1st degree biological relative
SPRED1 Sequencing

- No previous genetic testing of SPRED1, AND
- No known, pathogenic SPRED1 mutation in the member’s biologic relatives, AND
- No known, pathogenic NF1 mutation in the member or the member’s biologic relatives, AND
- Member has at least one of the following pigmentary findings suggestive of Legius syndrome:
  - Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals, with or without freckling in the axillary or inguinal regions, or
  - Six or more café-au-lait macules over 15 mm in greatest diameter in postpubertal individuals, with or without freckling in the axillary or inguinal regions, AND
- Member’s personal and/or family history are not consistent with neurofibromatosis type 1 (e.g., neurofibromas, optic glioma, Lisch nodules, sphenoid dysplasia or tibial pseudoarthrosis are not present), AND
- The results of the test will directly impact the diagnostic and treatment options that are recommended for the patient, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

SPRED1 Deletion/Duplication

- Criteria for SPRED1 sequencing are met, AND
- No previous deletion/duplication analysis of SPRED1, AND
- No mutation detected in full sequencing of SPRED1

References

Introduction

This guideline cites the following references.
