Test Specific Guidelines

Legius Syndrome Genetic Testing

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Introduction

Legius syndrome testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure code
SPRED1 Deletion/Duplication Analysis	81479
SPRED1 Known Familial Mutation Analysis	81403
SPRED1 Sequencing	81405

What Is Legius Syndrome?

Definition

Legius syndrome is an inherited disorder characterized by multiple café-au-lait macules and axillary or inguinal freckling, without neurofibromas or other tumor symptoms of Neurofibromatosis type 1 (NF1).[1,2]

Prevalence

The prevalence of Legius syndrome is estimated at 1/46,000 to 1/75,000.[3] Studies have shown that approximately 2% of individuals meeting the diagnostic criteria for NF1 have Legius syndrome.[1]

Symptoms

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 an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The diagnosis of Legius syndrome can be made in in individual without an affected parent if both of the following are present:[4]

"Six or more café au lait macules ... bilaterally distributed and no other NF1-related diagnostic criteria except for axillary or inguinal freckling"

"A heterozygous pathogenic variant in SPRED1 with a variant allele fraction of 50% in apparently normal tissue such as white blood cells"

"A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of Legius syndrome if one or more of the criteria [above] are present."

SPRED1 sequencing variants, such as missense, nonsense, and splice site variants, account for up to 89% of mutations seen in Legius syndrome.[3] Approximately 10% of the disease-causing variants in Legius syndrome are multi-exon and whole gene deletions.[5,6]

Management

Management of Legius syndrome includes therapies for developmental delays, learning disorders, and ADHD, if present.[3]

Survival

Lifespan does not appear to be affected by Legius syndrome. Current knowledge is based on the clinical history of fewer than 300 individuals with a confirmed diagnosis of Legius syndrome.[3,5]

Test Information

Introduction

Testing for Legius syndrome may include known familial mutation analysis, sequence analysis, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

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

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and Evidence

Introduction

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

Selected Relevant Publication

A 2020 expert-authored review stated:[3]

"Opinions differ on the appropriate approach when clinical information and family history cannot distinguish between NF1 and Legius syndrome. This is the case in individuals with only cafe au lait macules with or without freckling but no other signs of NF1. The assessment of pros and cons 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

Odds of identifying a diagnosis of NF1 versus Legius syndrome in those with a phenotype limited to pigmentary findings."*:*

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 by a method that would detect the familial mutation, AND

SPRED1 mutation identified in 1st degree biological relative

SPRED1 Sequence Analysis

No previous sequencing analysis of SPRED1, AND

No known, pathogenic SPRED1 mutation in the member's close biologic relatives, AND

No known, pathogenic NF1 mutation in the member or the member's close 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 member, AND

Rendering laboratory is a qualified provider of services per the Health Plan policy.

SPRED1 Deletion/Duplication Analysis

Criteria for SPRED1 sequencing are met, AND

No previous deletion/duplication analysis of SPRED1, AND

No mutation detected in full sequencing of SPRED1, AND

Rendering laboratory is a qualified provider of services per the Health Plan policy.

References

Introduction

This guideline cites the following references.

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