

Legius Syndrome (*SPRED1*) Sequencing & (*NF1*) Sequencing Exon 22 (Exon 17)

TO DETERMINE THE CAUSAL MUTATION IN INDIVIDUALS WITH ISOLATED PIGMENTARY FINDINGS OF NEUROFIBROMATOSIS TYPE 1 (NF1) SYMPTOMS

Disease Overview

- NF1-like syndromes are caused by germline mutations in genes that act as negative regulators of Ras-mitogen-activated protein kinase (MAPK) signaling. MAPK pathway gene mutations lead to a group of neuro-cardio-facial-cutaneous syndromes including: NF1, Noonan, LEOPARD, Costello, and cardio-facio-cutaneous (CFC).
- Legius Syndrome (LS) is an NF1-like syndrome with the following characteristics: café au lait spots, axillary and inguinal freckling, learning disability, and macrocephaly. Noonan-like dysmorphism has been described in some affected individuals.
- LS is caused by mutations in the *SPRED1* (Sprouty-related, EVH1 domain1) gene.
- Although LS has many overlapping features with NF1, neurofibromas, lisch nodules, and CNS tumors have not been reported in LS.
- Affected individuals may meet the clinical diagnostic criteria for NF1 based on pigmentary findings but do not have an *NF1* gene mutation. These isolated pigmentary findings may also be seen with an inframe exon 22* deletion (c.2970-2972delAAT). However, these individuals do have NF1 and may develop other characteristic features of NF1.

Epidemiology

Incidence is unknown. LS may represent 0.5 percent of NF1 clinical diagnoses and 8 percent of individuals with only café-au-lait spots and/or freckling with no neurofibromas or Lisch nodules.

Genetics

- LS is autosomal dominant and shows complete penetrance. It is caused by loss of function mutations in *SPRED1*.
- SPRED1* is located on chromosome 15q13.2 and has seven coding exons.
- Mutations detectable by sequencing (single base pair nonsense, missense, and frameshift) have been described in LS, as well as large exonic copy number mutations requiring deletion/duplication analysis for detection.
- Individuals with a 3 base pair inframe deletion of *NF1* exon 22 (c.2970-2972delAAT) may present with isolated pigmentary findings associated with NF1; thus, they may appear to have LS. However, these individuals do have NF1 and may develop other characteristic features of NF1.

Indications for Ordering

- To confirm a clinical diagnosis of LS in individuals with NF1-like characteristics but lacking the neurofibromas, Lisch nodules, and CNS tumors observed in NF1.
- To confirm a clinical diagnosis of LS in individuals without an identifiable *NF1* mutation.
- To determine if at-risk family members have a *SPRED1* mutation when the familial mutation is unknown and affected relatives are not available for testing.

Contraindications

- Testing for individuals with a previously identified familial *SPRED1* or *NF1* exon 22 mutation. To test individuals for a specific mutation, it is more cost-effective to order Familial Mutation, Targeted Sequencing (ARUP test #2001961) and provide a copy of the lab report detailing the familial mutation.
- Prenatal testing.

Interpretation

- Identification of a known pathogenic *SPRED1* mutation in a symptomatic individual confirms a diagnosis of LS.
- Identification of the 3-base pair inframe deletion of exon 22 (c.2970-2972 delAAT) confirms a diagnosis of NF1.
- Lack of an identifiable *SPRED1* mutation in a clinically affected individual decreases, but does not exclude, a diagnosis of LS. Medical management should rely on clinical findings and family history.
- Lack of an identifiable *NF1* exon 22 mutation does not exclude a diagnosis of NF1. Full gene sequencing for NF1 in the appropriate clinical situation is recommended.
- SPRED1* and *NF1* sequence variants of unknown clinical significance may be detected.

Methodology

- Bi-directional sequencing of the *SPRED1* coding regions (exons 1–7) and intron-exon boundaries, as well as bidirectional sequencing of exon 22 of the *NF1* gene and intron-exon boundaries.
- Clinical sensitivity for LS is unknown.
- Analytical sensitivity and specificity of sequencing are 99 percent.

Limitations

- Deep intronic *SPRED1* mutations, large deletions/duplications, and regulatory region mutations are not detected.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Mutations, other than those targeted in *SPRED1* or *NF1* exon 22, will not be detected.

Related Tests

- Neurofibromatosis (*NF1*) Deletion/Duplication (2001952)
- Familial Mutation, Targeted Sequencing (2001961)

References

1. Bentires-Alj M, et al. Stops along the RAS pathway in human genetic disease. *Nat Med* 2006;12;283–5.

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3. National Institutes of Health. National Institutes of Health Consensus Development Conference Statement: Neurofibromatosis. *Arch Neurol Chicago* 1988;45:575–8.
4. Pasmant E, et al. *SPRED1* germline mutations caused a neurofibromatosis type 1 overlapping phenotype. *J Med Gen* 2009;46;425–30.
5. Upadhyaya M, et al. An absence of cutaneous neurofibromas associated with a 3 bp inframe deletion in exon 17 of the *NF1* gene (c.2970-2972delAAT): evidence of a clinical significant *NF1* genotype-phenotype correlation. *Am J Hum Genet* 2007;80:140–51.
6. Spurlock G, et al. *SPRED1* mutations (Legius syndrome): another clinically useful genotype for dissecting the *NF1* phenotype. 2009;46:431–7.

* Exon 22 by NCBI nomenclature is exon 17 by NF Consortium nomenclature (GenBank Ref #*NM_001042492.1*)

Test Information

2002945 Legius Syndrome (*SPRED1*) Sequencing and (*NF1*) Sequencing Exon 22 (Exon 17)

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.