## Condition Description

Legius syndrome, originally termed neurofibromatosis type 1 (NF1)-like syndrome, is caused by mutations in the **SPRED1** gene (15q13.2). Individuals with Legius syndrome frequently fulfill NIH diagnostic criteria for NF1 based on pigmented manifestations of café-au-lait spots and inguinal freckling, but do not have mutations in the **NF1** gene. Other characteristics may include macrocephaly, learning disabilities, and Noonan-like dysmorphology. To date, no affected individuals have been found to have neurofibromas, central nervous system tumors, NF1-type osseous lesions, or Lisch nodules.

A study by Messiaen et al. found that among 1086 patients fulfilling NIH criteria for a clinical diagnosis of NF1, an **NF1** mutation was found in 823 (76%), a **SPRED1** mutation in 21 (1.9%), and no **NF1/SPRED1** mutation in 243 (22%). Of 94 probands with familial café-au-lait spots with or without freckling and no other NF1 features, 69 (73%) had an **NF1** mutation and 18 (19%) had a **SPRED1** mutation; 7 (7%) did not have mutations in either gene. In another cohort in this study, 20 of 42 individuals (48%) with a **SPRED1** mutation fulfilled NIH NF1 diagnostic criteria. The dermatologic phenotype in young children with a **SPRED1** mutation could not be differentiated from NF1. The authors recommend that in cases of diagnostic uncertainty, the **NF1** gene be analyzed first and, if negative, **SPRED1** testing be considered in patients with café-au-lait spots with or without freckling and no other NF1 diagnostic features.

A study by Muram-Zborovski et al. found percentages similar to those seen in the Messiaen study. In 151 individuals who met NIH NF1 diagnostic criteria, 2 (1.3%) were found to have **SPRED1** mutations. The percentage increased to 20% when selecting for individuals who lacked Lisch nodules, optic gliomas, neurofibromas, long bone dysplasia and sphenoid wing dysplasia, or a family history. **SPRED1** analysis is recommended in individuals with dermatologic manifestations of NF1 after NF1 analysis is negative.

This testing is for mutations in the **SPRED1** gene only, and does NOT include analysis of the **NF1** gene.

### References:

- OMIM #611431 Legius Syndrome

### Genes

**SPRED1**

### Indications

This test is indicated for:

- Individuals with dermatologic manifestations of NF1 after NF1 gene analysis is negative

### Methodology

PCR amplification of 7 exons contained in the **SPRED1** gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

### Detection

Clinical Sensitivity: Molecular genetic testing identifies mutations in **SPRED2** in approximately 2% of individuals that meet NIH NF1 diagnostic criteria. That percentage rises to approximately 20% in individuals with only café-au-lait spots with or without freckling and no other NF1 features. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

### Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type:** Whole Blood
Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

### Related Tests

- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.