

# NEUROFIBROMATOSIS Type 1-like or Legius Syndrome – *SPRED1* testing

Target Mutation Analysis - **Test 2**

- updated 08-10-09 -

## DESCRIPTION

Mendelian Inheritance in Man number: [611431](#)

Click here for [Gene Reviews](#) Clinical Summary.

Recently, a new autosomal dominant condition resembling NF1 was described, consisting of mainly multiple CAL-spots, freckling and macrocephaly. Some patients also have learning disabilities or hyperactivity. In none of the adult patients identified so far, neurofibromas or central nervous system tumors were observed (Brems et al, 2007). A Noonan-like dysmorphism was observed in some individuals. In the five multi-generation families initially ascertained, several affected individuals fulfilled the NIH diagnostic criteria for NF1. The disorder is caused by germline loss-of-function mutations in *SPRED1*. Analysis of 86 unrelated individuals who presented with multiple CAL-spots only with or without a family history of CAL-spots, revealed a mutation in 7 of them (~8%). All were minor-lesion mutations (nonsense, frameshift and 1 missense mutation); no dosage alterations (total gene deletion or one/multi-exon copy number change) were found in Brems et al, but we have since identified them in our cohort of patients (Messiaen L, unpublished results). At the recent European NF meeting in Killarney (Ireland), it was decided by the community to refer to this condition as “Legius syndrome.”

*SPRED1* is a member of the *SPROUTY/SPRED* family of proteins that act as negative regulators of RAS-RAF interaction and mitogen-activated protein kinase (MAPK) signaling.

## INDICATIONS FOR DIRECT TESTING

- Relatives of patients with a known *SPRED1* mutation

## TESTING METHODOLOGY

We offer a **targeted detection** of a previously characterized *SPRED1* mutation within the family. Targeted testing involves direct sequencing of a specific region or copy number analysis by MLPA and quantitative PCR.

Test 2 is provided **free of charge** to all relevant relatives of a proband in whom a novel **missense** alteration was found that needs further clarification to come to a final conclusion. As the final conclusion on the pathogenicity of a missense alteration relies on accurate phenotypic data, the testing in relevant relatives is provided free of charge only if a phenotypic checklist is filled out by a healthcare professional that made the clinical assessment of the relatives. The correct interpretation of the results also relies on the correct disclosure of the biological relationships.

## SPECIMEN REQUIREMENTS

We require 1 milliliter of whole blood. Blood samples must be collected in EDTA (purple topped) tubes.

## TRANSPORT

If specimen is from clinics within UAB or Kirklin Clinic, please call 934-7107 for pick-up. If specimens are being sent from some other location, please ship via UPS or Federal Express.

1. Be sure that the shipping air bill is marked “**Priority**”, either Domestic or International.
2. Specimens must be packaged to prevent breakage and absorbent material must be included in the package to absorb liquids in the event that breakage occurs. Also, the package must be shipped in double watertight containers (e.g. a specimen pouch + the shipping companies Diagnostic Envelope). **You can use our collection kits, which we will send to physicians directly upon request.**

## TURN AROUND TIME

2 weeks

## CPT CODES AND PRICES

**Please note that prices listed correspond to institutional rates; please contact the lab for insurance rates.**

\$250, - USD ([currency converter](#))

83891 (x1), 83894 (x4), 83898 (x4), 83904 (x3), 83912 (x1)

## REQUIRED FORMS

[SPRED1 Test Requisition including the phenotypic data form](#)  
[Form for Customs \(International shipment\)](#)

**Note:** Requests for Molecular Genetic testing for *SPRED1* will **not** be accepted for the following reasons:

- No label (patient’s full name and date of collection) on the specimens
- No referring physician’s or genetic counselor’s names and addresses
- No billing information if this is a fee for service test
- No informed consent
- **No phenotypic checklist:** we offer **free of charge** targeted testing to all relevant relatives of a proband in whom a **novel missense variant** was identified. Testing of these relatives may allow us to make a final conclusion on the pathogenicity of the novel missense variant and allow us to provide better counseling now and in the future. Free of charge targeted testing will only be provided if the necessary **phenotypic information on the proband and relatives filled out by a healthcare professional** accompanies the samples. If no phenotypic information is provided, we will charge the institution for the test.

**For more information, test requisition forms, or sample collection and mailing kits, please call: 205-934-5562.**

## **REFERENCES**

Brems H, Chmara M, Sahbatou M, Denayer E, Taniguchi K, Kato R, Somers R, Messiaen L, De Schepper S, Fryns J-P, Cools J, Marynen P, Thomas G, Yoshimura A, Legius E – Germline loss-of function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. Nat Genet 39: 1120-1126, 2007. ([pubmed](#))