SickKids | Genome Diagnostics

# Neurofibromatosis Type 1/ Legius Syndrome

**Neurofibromatosis type 1** (NF1) is the most common neurological disorder caused by a single gene, the *NF1* gene. A clinical diagnosis of NF1 is met when two or more of the following features are present in an individual:

- 6 or more café-au-lait macules (>5mm in prepubertal individuals,
- >15mm in post pubertal individuals
- 2 or more neurofibromas or 1 plexiform neurofibroma
- Axillary or inguinal freckling; optic pathway glioma
- 2 or more Lisch nodules
- Distinctive bony lesion
- 1st degree relative with NF1 (as defined by the above criteria).

Only 50% of children with NF1 with no known family history of NF1 meet these clinical criteria for diagnosis by 1 year of age, but almost all do by age 8, since many of the features of NF1 are age-dependent. These diagnostic criteria are both highly sensitive and specific in adults with NF1.

**Legius syndrome**, which is caused by pathogenic variants in the *SPRED1* gene, has marked similarity to NF1. Similar to NF1, individuals with Legius syndrome have multiple café-au-lait macules. Some may also have axillary or inguinal freckling. However unlike NF1, there is notable absence of neurofibromas, Lisch nodules, bony lesions, or optic pathway gliomas in individuals with Legius syndrome. Since café-au-lait macules and axillary/inguinal freckling are common to both NF1 and Legius syndrome, these two conditions may be clinical indistinguishable from each other in childhood.

Molecular analysis of the *NF1* and *SPRED1* genes can help delineate these overlapping syndromes.

## Genetics

Both NF1 and Legius syndrome are inherited in an autosomal dominant pattern. Approximately 50% of individuals with NF1 have the condition as a result of a *de novo* pathogenic *NF1* variant. Individuals with Legius syndrome may have the condition as a result of a *de novo* pathogenic *SPRED1* variant, or may have inherited it from an affected parent.

## Who Should be Tested?

- Individuals clinically suspected of being affected with NF1 or Legius syndrome.
- The relatives of a proband with identified pathogenic variant(s) in the *NF1* or *SPRED1* genes.
- Pregnancies at increased risk due to a family history of NF1 or Legius syndrome.

## Test Methods

- Complete sequencing of the coding region and flanking intron/exon boundaries of the *NF1* and/or *SPRED1* genes.
- Quantitative testing of the *NF1* and/or *SPRED1* genes to detect large deletions or duplications, using MLPA (Multiplex-Ligation Probe Amplification).

~95% of individuals with NF1 will have a pathogenic variant in *NF1* identified by sequence analysis; ~5% will have a whole gene deletion.

~88% of individuals with Legius syndrome will have a pathogenic variant in *SPRED1* identified by sequence analysis; ~10% will have an exonic or whole gene deletion.

### For More Information

**GeneReviews**
www.ncbi.nlm.nih.gov/books/NBK1109/
www.ncbi.nlm.nih.gov/books/NBK47312/

**OMIM** www.ncbi.nlm.nih.gov/omim/
NF1 #162200
Legius syndrome #611431

**SickKids Genomic Diagnostics Laboratory:**
www.sickkids.ca/genome-diagnostics

**To locate a genetics center near you:**

Canadian Association of Genetic Counsellors (CAGC):
www.cagc-accg.ca

National Society of Genetic Counselors (NSGC):
www.nsgc.org/

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*1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of NF1 or Legius syndrome.*

*2. The clinical course or severity of symptoms cannot be predicted by molecular analysis.*

*3. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.*

*4. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.*