Neurofibromatosis Type 1

Indications for Ordering

- Confirm a suspected clinical diagnosis of neurofibromatosis type 1 (NF1)
- Confirm diagnosis in child with clinically significant tumor (eg, optic glioma) to optimize medical screening and management

Test Description

- Bidirectional sequencing of *NF1* coding regions and intron/exon boundaries
- Multiplex ligation-dependent probe amplification to detect large deletions/duplications

Tests to Consider

Primary tests

Neurofibromatosis Type 1 (*NF1*) Sequencing and Deletion/Duplication 2007154

- Preferred test to confirm a suspected diagnosis of NF1 in individuals not meeting NIH clinical criteria

Neurofibromatosis Type 1 (*NF1*) Sequencing 2007159

- Acceptable test to confirm a suspected diagnosis of NF1 in individuals not meeting NIH clinical criteria
- Does not detect large duplications/deletions

Related tests

Legius Syndrome (*SPRED1*) Sequencing and Deletion/Duplication 2008347

- Preferred test for confirming diagnosis of Legius syndrome in symptomatic individuals who test negative for pathogenic *NF1* variants by sequencing and deletion/duplication analysis

Familial Mutation, Targeted Sequencing 2001961

- Useful for confirming a diagnosis when a pathogenic sequence variant has been identified in family member

Deletion/Duplication Analysis by MLPA 3003144

- Useful for confirming a diagnosis when a large deletion/duplication has been identified in family member

Disease Overview

Incidence: 1/3,000 worldwide

NIH diagnostic criteria include ≥2 of the following:

- ≥6 café au lait macules
- Axillary or inguinal freckling
- >2 neurofibromas of any type or >1 plexiform neurofibroma
- ≥2 Lisch nodules (iris hamartomas)
- Optic glioma
- Specific osseous lesion (eg, tibial pseudarthrosis, sphenoid dysplasia)
- First-degree relative with a diagnosis of NF1

Other common findings

- Learning disabilities (occurs in 50% of affected individuals)
- Scoliosis
- Skeletal dysplasia
- Hypertension
- Overgrowth

Serious complications

- Plexiform neurofibromas
- Vasculopathy
- Malignant peripheral nerve sheath tumors (MPNT)

Clinical phenotype: highly variable

Genetics

Gene: *NF1*

Inheritance: autosomal dominant

Penetrance

- 100% by adulthood
- 50% of affected children meet diagnostic criteria by age 1 and nearly all by age 8

De novo variants: 50% of cases

Variants

- >2,500 identified
- Large locus deletions associated with increased risk of MPNT or other severe phenotypes

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity of *NF1* gene sequencing and deletion/duplication: ~84-93% (Minkelen, 2014; Pasmant, 2015; Wimmer, 2006)
  - Sequencing: 77-86%
  - Deletion/duplication analysis: 7%

- Clinical sensitivity of *SPRED1* sequencing and deletion/duplication: unknown
    - 2% of individuals meeting NIH diagnostic criteria for NF1 have pathogenic variant in *SPRED1* (Stevenson, 2015)
- Analytical sensitivity/specificity: 99%

Results

- Positive: diagnosis confirmed
- Negative: diagnosis is less likely but not excluded
- Inconclusive: gene variant detected, but it is unclear whether the variant is benign or pathogenic

Limitations

- Does not detect:
    - Large *NF1* deletions/duplications of exons 11 and 20
    - Regulatory region or deep intronic variants
- Diagnostic errors can occur due to rare sequence variations
- Large deletion/duplication breakpoints will not be determined

References

van Minkelen R, van Bever Y, Kromosoeto JN, et al. A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. Clin Genet. 2014;85(4):318-327. PubMed

Pasmant E, Parfait B, Luscan A, et al. Neurofibromatosis type 1 molecular diagnosis: what can NGS do for you when you have a large gene with loss of function mutations? Eur J Hum Genet. 2015;23(5):596-601.

Legius E, Stevenson D. Legius syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews. University of Washington, Seattle; 1993-2021. [Last update: Jan 2015; Accessed: Feb 2020]

Wimmer K, Yao S, Claes K, et al. Spectrum of single- and multiexon NF1 copy number changes in a cohort of 1,100 unselected NF1 patients. Genes Chromosomes Cancer. 2006;45(3):265-276. PubMed