Neurofibromatosis Type 1

Indications for Ordering

- Confirm a suspected diagnosis of neurofibromatosis type 1 (NF1) in individuals not meeting National Institutes of Health (NIH) clinical criteria
- 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

Neurofibromatosis Type 1 (*NF1*) Deletion/Duplication 2001952

- Useful when a familial large deletion is known
- Does not detect sequence variations

Related tests

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

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

- Preferred test for confirming diagnosis of Legius syndrome in symptomatic individuals who test negative for *NF1* gene variants
- Useful for individuals with café au lait macules and/or axillary/inguinal freckling only, but no pathogenic *NF1* gene variants

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

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

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – ~84-93% (Minkelen, 2014; Pasmant, 2015; Wimmer, 2006)
  - Sequencing – 77-86%
  - Deletion/duplication analysis – 7%
- Analytical sensitivity/specificity – 99%

Results

- Positive – diagnosis confirmed
- Negative – diagnosis of NF1 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 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

- Minkelen R, van Bever Y, et al. A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. Clin Genet. 2014;85:318-327
- Pasmant E, Parfait B, 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;23:596–601
- Wimmer K, Yao S, et al. Spectrum of single- and multiexon NF1 copy number changes in a cohort of 1,100 unselected NF1 patients. Genes Chromosomes Cancer. 2006;45:265–276