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

- 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