

Neurofibromatosis Type 1 (NF1) Deletion/Duplication

*TO DETERMINE IF A CLINICAL DIAGNOSIS OF
NEUROFIBROMATOSIS TYPE 1 IS CAUSED BY LARGE NF1
GENE DELETIONS OR DUPLICATIONS*

Disease Overview

- Diagnostic criteria for neurofibromatosis type I (NF1) were developed at an NIH conference and include having any two of the following characteristics:
 - Six or more café au lait macules
 - Axillary or inguinal freckling
 - Two or more dermal fibromas
 - Two or more iris Lisch nodules (iris hamartomas)
 - Optic glioma
 - Specific osseous lesion, such as tibial pseudarthrosis or sphenoid dysplasia
 - First-degree relative with diagnosis of NF1
- Other common characteristics include: learning disabilities (50 percent), scoliosis, vertebral dysplasia, hypertension, and overgrowth. More serious complications may include plexiform neurofibromas, vasculopathy, and malignant peripheral nerve sheath tumors.
- Patients with large *NF1* locus deletions are at increased risk for malignant peripheral nerve sheath tumors (MPNT).
- NF1 is characterized by extreme clinical variability, even among affected individuals within a single family.
- Of children with NF1 findings and no family history, half can be clinically diagnosed by age 1 and nearly all by age 8.
- Affected individuals should undergo annual physical and ophthalmologic examinations by physicians familiar with NF1 in addition to regular blood pressure monitoring.
- The average life expectancy is reduced by 15 years in affected individuals, mostly due to malignancies and vasculopathy.

Epidemiology

Incidence at birth is one in 3,000.

Genetics

- Autosomal dominant with 100 percent penetrance by adulthood.
- 50 percent of cases result from a de novo mutation.
- The *NF1* gene is located on chromosome 17q11.2 and produces neurofibromin.
- The *NF1* gene consists of 60 exons; over 500 mutations have been identified.
- NF1 locus deletions and smaller intragenic deletions represent 5 percent and 1 percent of *NF1* mutations, respectively.
- Genotype/phenotype correlations predict individuals with NF1 locus deletions to have a severe phenotype including: frequent, early-appearing cutaneous neurofibromas, more significant learning disabilities, and sometimes overgrowth, large hands and feet, or dysmorphic facial features.
- Sequence analysis detects approximately 89 percent of causative mutations.

Indications for Ordering

- To determine if a large deletion or duplication is responsible for NF1 in a clinically affected person.
- Testing at-risk family members of an affected relative known to have a large *NF1* deletion or duplication.

Contraindications

- Prenatal diagnosis.
- Confirmation of an NF1 diagnosis in a patient meeting NIH clinical criteria.

Additional Ordering Notes

If there is a family history of NF1, please provide the relationship of the relative to the individual being tested, as well as the specific mutation identified in the family member.

Interpretation

- Identification of large *NF1* locus deletion is predictive of severe disease.
- A negative result does not rule out neurofibromatosis since only 6 percent of NF1 is caused by large *NF1* locus or intragenic deletions/duplications.
- For individuals with unclear or negative results, medical management should rely on clinical findings and family history.

Methodology

- Multiplex ligation-dependent probe amplification (MLPA) for large deletion/duplication analysis of the *NF1* gene.
- Analytic sensitivity and specificity are 99 percent. Clinical sensitivity is approximately 6 percent.

Limitations

- Breakpoints of large *NF1* locus and intragenic deletions/duplications will not be determined.
- Rare diagnostic errors may occur due to probe-site mutations.
- NF1* base-pair substitutions, small deletions/duplications, and deep intronic and regulatory region mutations will not be detected.

Reference

- Friedman, JM. Neurofibromatosis 1. www.genetests.org (accessed on June 18, 2009).

Test Information

2001952 Neurofibromatosis Type 1 (NF1) Deletion/Duplication

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.