

Neurofibromatosis Type 1 and Related Disorders via *NF1* Gene Sequencing -- Test #117

Brief Description of Clinical Features: Neurofibromatosis type 1 (NF1, OMIM 162200) is characterized by an extensive clinical variability between individuals with regards to age of onset, tumor burden, and disease progression. The most typical clinical features of NF1 include cutaneous neurofibromas, Café-au-Lait Spots, iris hamartoma (Lisch nodules) and freckling of axillary and inguinal regions; these features usually become apparent during puberty. Additional features include plexiform neurofibromas, optic glioma, macrocephaly, short stature, scoliosis, pseudoarthritis, overgrowth and learning difficulties (Riccardi, Am J Hum Genet 53:301-304, 1993). NF1 affects 1 in 3,000 people (Rasmussen and Friedman Am J Epidemiol 151:33-40, 2000). For additional information see Friedman, GeneReviews, 2007 at www.genetests.org.

Genetics: NF1 is caused by defects in the *NF1* gene. NF1 is inherited as an autosomal dominant trait in about half of cases, and is caused by *de novo* mutations in the other half. Over 1,050 *NF1* germline mutations have been reported. About 90% of the mutations have been missense, nonsense, splicing, and small insertions/deletions, about 9% comprised partial or whole deletions of the gene, and less than 1% included gross insertions and complex rearrangements. Nearly all *de novo* mutations occurred in the paternal chromosomes (Jadayel et al. Nature 343:558-559, 1990), with the exception of large deletions, which occurred in maternal chromosomes (Lázaro et al. Hum Genet 98:696-699, 1996; Upadhyaya et al Hum Genet 102:591-597, 1998). Parental germline mosaicism has been reported (Lázaro et al. N Engl J Med 331:1403-1407, 1994).

Mutations in the *NF1* gene have been detected in patients with Neurofibromatosis-Noonan Syndrome (NFNS, OMIM 601321; Baralle et al. Am J Med Genet Part A 119A:1-8, 2003), patients with Familial Spinal Neurofibromatosis (FSNF, OMIM 162210; Ars et al. Am J Hum Genet 62:834-841, 1998), patients with Juvenile Myelomonocytic Leukemia (JMML, OMIM 607785; Tartaglia et al. Nat Genet 34:148-150, 2003), and patients with Watson Syndrome (WS, OMIM 193520; Watson Arch Dis Child 42:303-307, 1967). WS is also referred to as Pulmonic Stenosis with Café au Lait Spots.

Description of this Particular Test: The *NF1* gene encodes the neurofibromin protein. This test will detect missense, nonsense, small insertions/deletions, and many splicing mutations in the *NF1* gene. The test involves bidirectional sequencing of all coding exons and splice sites of the gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will sequence any single or double exons in family members of patients with known mutation or to confirm previous results.

Reference Sequences: Genomic: **NC_000017.9** mRNA and protein: **CCDS 42292.1**

Indications for Test: Patients with NF1, NFNS, FSNF, JMML and WS are candidates.

Sensitivity of Test: This test will detect *NF1* mutations in ~ 90% of patients with NF1 (Friedman, GeneReviews, 2007).

Turn Around Time: Maximum of 40 calendar days.

Specimen Requirement: See page 4 of the Requisition Form.

Prices:		Sequencing of all NF1 exons:		\$ 2490	
CPT Codes:	Description	Price	CPT Codes:	Description	Price
83890	Sample Ascertainment	\$ 30	83891	DNA Isolation	\$ 40
83898	Amplification (x 58)	\$ 860	83904	Sequencing (x58)	\$1280
83894	Separation	\$ 150	83912	Interpretation/Report	\$ 130

Accreditation Info. CLIA ID #: **52D1027685** (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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