

Neurofibromatosis Type 2 via NF2 Gene Sequencing --Test #118

Brief Description of Clinical Features: Neurofibromatosis Type 2 (NF2, OMIM 101000) is a tumor prone disease of the nervous system, with bilateral vestibular schwannoma (BVS) as the hallmark. Patients with NF2 may also develop schwannoma at other locations and other tumors such as meningioma, glioma, neurofibroma, astrocytoma and skin tumors. Posterior subcapsular lens opacities are common in NF2. Other common symptoms include hearing loss, imbalance, tinnitus, facial weakness and headache (Parry et al. *Am J Med Genet* 52:450-461, 1994; Kanter et al. *Neurology* 30:851-859, 1980). Two clinical subtypes are recognized. The first is characterized by an early onset, severe features, rapid progression and predisposition to meningioma and spinal tumors, in addition to the BVS. The second subtype has a late onset, a comparatively benign course and a low incidence of meningioma and spinal tumors (Bruder et al. *Hum Mol Genet* 10:271-282, 2001). NF2 affects people worldwide with an incidence of 1 in 30,000-40,000 live births (Evans et al. *J Med Genet* 29:841-846, 1992). See also Evans, GeneReviews, 2009 at www.genetests.org.

Genetics: NF2 is inherited as an autosomal dominant trait, with high penetrance, in about half of cases, and is caused by *de novo* mutations in the other half (Evans et al. *J Med Genet*, 29:841-846, 1992). NF2 is caused by mutations in the *NF2* gene (Trofatter et al. *Cell* 72:791-800, 1993; Rouleau et al. *Nature* 363:515-521, 1993). To date, over 350 *NF2* germline mutations have been identified. Of these, ~ 85% were missense, nonsense, splicing, small insertions/deletions and indels; and the remaining 15 % consisted of gross insertions/deletions or complex rearrangements. About 25 % of patients with sporadic NF2 are mosaic as the result of postzygotic mutations in the early stage of embryonic development (Evans et al. *Am J Hum Genet* 63:727-736, 1998; Kluwe et al. *J Med Genet* 40:109-114, 2003).

Description of this Particular Test: The *NF2* gene is a tumor-suppressor and encodes the Merlin protein. This test will detect missense, nonsense, small insertions/deletions and splicing mutations in the *NF2* 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_000022.9** mRNA and protein: **CCDS 13862.1**

Indications for Test: Patients with clinical features consistent with NF2.

Sensitivity of Test: This test detects mutations in ~ 73 % of patients with an established family history of NF2 and ~ 60 % of sporadic cases (Evans et al. *J Med Genet* 44:424-428, 2007). Somatic mosaicism is likely to account for the lower mutation detection rate in patients with sporadic NF2 (Evans et al. *Am J Hum Genet* 63:727-736, 1998).

Turn Around Time: Maximum of 40 calendar days.

Specimen Requirement: See page 4 of the Requisition Form.

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| Prices: | Sequencing of all NF2 exons: | \$ 840 |
| CPT Codes: | | |
| Sample Ascertainment x1 | 83890 \$ 30 | DNA Isolation x1 83891 \$ 40 |
| Amplification x21 | 83898 \$ 250 | Sequencing x21 83904 \$ 380 |
| Separation x1 | 83894 \$ 60 | Interpretation/Report x1 83912 \$ 80 |

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

Contact for info: Dr. Khemissa Bejaoui, khemissa@preventiongenetics.com, www.preventiongenetics.com