

## Neurofibromatosis-Noonan Syndrome *via NF1* Gene Sequencing – Test #115

**Brief Description of Clinical Features:** Patients with Neurofibromatosis-Noonan syndrome (NFNS, OMIM 601321) present with clinical features characteristic of both neurofibromatosis type 1 (NF1, OMIM 162200) and Noonan syndrome (NS, OMIM 163950). The NF1 features observed in patients with NFNS include café-au-lait spots, freckling, neurofibromas, hamartoma of the iris (Lisch nodules), optic gliomas, and other MRI findings, such as unidentified bright objects (UBO). The NS features in these patients include facial anomalies such as hypertelorism, low-set ears, short stature, congenital heart defects, primary pulmonary valve stenosis, webbed neck and thoracic abnormalities. In NFNS patients, features common to both NF1 and NS include macrocephaly, scoliosis, mental retardation or learning difficulties (Allanson et al. *Am J Med Genet* 21:457-462, 1985; De Luca et al. *Am J Hum Genet* 77:1092-1101, 2005).

**Genetics:** The vast majority of NFNS cases are sporadic, although several families transmitting the trait in an autosomal dominant manner have been reported (Quattrin et al. *Am J Med Genet* 26:645-649, 1987; Abuelo et al. *Am J Med Genet* 29:937-941, 1988; Colley et al. *Clin Genet* 49:59-64, 1996). Recently, heterozygous mutations in the *NF1* gene were reported in patients with NFNS, including sporadic and familial cases (Baralle et al. *Am J Med Genet Part A* 119A:1-8, 2003; De Luca et al. 2005; Stevenson et al. *Clin Genet* 69:246-253, 2006; Huffmeier et al. *Am J Med Genet Part A* 140A:2749-2756, 2006). These data led the authors to suggest that NFNS represents an allelic variation of NF1. Most NFNS patients investigated to date showed mutations in the *NF1* gene, and none had mutations in the *PTPN11* gene, the primary gene associated with NS (Tartaglia et al. *Nat Genet* 29:465-468, 2001), except for one patient with heterozygous mutations in both *NF1* and *PTPN11* genes (Carey et al. *Proc Greenwood Genet Center* 17:152-153, 1997). At least 21 different mutations in the *NF1* gene were detected in patients with NFNS. The majority of the NFNS-causing mutations are clustered in exons 27 to 35. Four of the NFNS-causing mutations were found in patients with classic NF1; these mutations, however, were outside of exons 27-35. Mutations in *NF1* were also detected in patients with Watson syndrome (WS, OMIM 193520).

**Description of this Particular Test:** The *NF1* gene encodes the neurofibromin protein and is ubiquitously expressed. Neurofibromin functions as a tumor suppressor. *NF1* testing for NFNS at PreventionGenetics is performed in two tiers. In Tier 1, we bidirectionally sequence the coding regions plus ~ 50 bp of flanking-coding DNA on either side of exons 27 to 35. If Tier 1 is negative, we sequence the remaining exons. Single exon sequencing is also available for \$ 190.

**Reference Sequences:** Genomic: 000017.9 mRNA and protein: **CCDS: 42292.1**

**Indications for Test:** All patients with symptoms suggestive of NFNS, as described above.

**Sensitivity of Test:** This test allows the detection of mutations in ~ 94 % of patients presenting with NFNS symptoms (De Luca et al. 2005).

**Turn Around Time:** Maximum of 40 calendar days.

**Specimen Requirement:** See page 4 of the Requisition Form.

**Prices:** Tier 1 alone \$ 540 Tier 2 alone \$ 2390 Tiers 1 and 2 together \$ 2490

CPT Codes	Description	Tier 1 only	Tier 2 only	Tier 1 and 2 together
83890	Ascertainment	\$ 30 (x 1)	\$ 30 (x 1)	\$ 30 (x 1)
83891	DNA Isolation	\$ 40 (x 1)	\$ 40 (x 1)	\$ 40 (x 1)
83898	Amplification	\$ 200 (x 9)	\$ 820 (x 49)	\$ 860 (x 58)
83904	Mutation Ident. by Sequencing	\$ 140 (x 9)	\$ 1240 (x 49)	\$ 1280 (x 58)
83894	Separation	\$ 50 (x 1)	\$ 140 (x 1)	\$ 150 (x 1)
83912	Interpretation and Report	\$ 80 (x 1)	\$ 120 (x 1)	\$ 130 (x 1)
	<b>Totals</b>	<b>\$ 540</b>	<b>\$ 2390</b>	<b>\$ 2490</b>

**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](mailto:khemissa@preventiongenetics.com), [www.preventiongenetics.com](http://www.preventiongenetics.com)