

Noonan Syndrome via *PTPN11* Gene Sequencing

Sequential (Standard) Test – Test #373; Tier 1 Only – Test #371; Tier 2 Only – Test #374

Brief Description of Disorder: Noonan Syndrome (NS) (OMIM 163950) is a relatively common dysmorphic syndrome characterized by short stature, heart defects, broad or webbed neck, and characteristic facial features (Tartaglia and Gelb Ann Rev Genomics Hum Genet 6:45-68, 2005; Allanson Gene Reviews, 2008; van der Burgt Orphanet J Rare Diseases 2:4, 2007). A number of other symptoms including mild mental retardation, coagulation defects and lymphatic dysplasias are sometimes observed. Symptoms are quite variable even among family members carrying the same mutation. Diagnosis is often made in infancy or early childhood. Symptoms often lessen with increasing age. Prevalence is roughly 1 in 2000 births. See also the Noonan Syndrome Support Group, Inc. (www.noonansyndrome.org).

Genetics: NS is an autosomal dominant disorder, although *de novo* mutations are found in a substantial fraction of patients. About half of NS patients carry mutations in the *PTPN11* gene. All causative mutations reported to date have been missense resulting in amino acid substitutions, except for two 3 bp deletions resulting in loss of a single amino acid (Jongsma et al. Am J Med Genet A 134:165-170, 2005; Tartaglia et al. Am J Hum Genet 78:279-290, 2006). These mutations appear to activate the gene product (SHP2 protein). Genotype/phenotype correlations are slowly being made. In particular, several groups have shown that pulmonary stenosis is more common in *PTPN11* mutation-positive patients, and hypertrophic cardiomyopathy more common in *PTPN11* mutation-negative patients. *PTPN11* mutations are also found in two related, rarer disorders: LEOPARD Syndrome (OMIM 151100) and Noonan-like syndrome with multiple giant cell lesions (OMIM 163955). Recently, mutations in the *RAF1*, *SOS1* and *KRAS* genes have also been found in NS patients (see test descriptions for those genes).

Description of This Particular Test: *PTPN11* testing for NS at PreventionGenetics is performed in two tiers. In Tier 1, we bidirectionally sequence the complete coding regions plus flanking intronic DNA for exons 3, 7, 8, and 13. Approximately 90% of causative *PTPN11* mutations reported to date are found in these four exons. If Tier 1 is negative, we go on to sequence the remaining eleven exons in Tier 2. Single exon sequencing is also available for \$190.

Reference Sequences: Genomic: **NC_000012.10** mRNA: **NM_002834.3** protein: **NP_002825.3**

Indications for Test: All patients with clinical features of NS are candidates for this test. Clinical features of NS overlap with those for Cardio-Facio-Cutaneous (CFC) and Costello Syndromes. NS patients who test negative for the mutations in *PTPN11*, *RAF1*, *SOS1* or *KRAS* may be candidates for CFC (*BRAF*, *MAP2K1* and *MAP2K2* genes) or Costello (*HRAS* gene) testing. Conversely, CFC or Costello Syndrome patients who test negative for those genes may be candidates for all or a portion of NS DNA testing.

Sensitivity of Test: Pathogenic mutations in the *PTPN11* gene have been identified in ~50% of NS patients.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form

Prices: Tier 1 only \$390 Tier 2 only \$690 Tiers 1 and 2 together \$890

CPT Codes:

Codes	Description	Tier 1 Only	Tier 2 Only	Tier 1 + Tier 2
83890	Ascertainment	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	DNA Isolation	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	Amplification	\$110 (x4)	\$190 (x11)	\$260 (x15)
83904	Mutation Ident by Sequencing	\$120 (x4)	\$300 (x11)	\$400 (x15)
83894	Separation	\$ 30 (x1)	\$ 50 (x1)	\$ 60 (x1)
83912	Interpretation and Report	\$ 60 (x1)	\$ 80 (x1)	\$100 (x1)
Totals:		\$390	\$690	\$890

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

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