

## Noonan and Leopard Syndromes via *RAF1* Gene Sequencing (Test #375)

**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, 2007; van der Burgt Orphanet J Rare Diseases 2:4, 2007). A number of other symptoms including mild mental retardation and ectodermal features are sometimes observed. Symptoms are quite variable even among family members carrying the same mutation. Diagnosis is often made in infancy or early childhood. Prevalence is roughly 1 in 2000 births. See also the Noonan Syndrome Support Group, Inc. ([www.noonansyndrome.org](http://www.noonansyndrome.org)). LEOPARD Syndrome (OMIM 151100) is characterized by skin pigmentation abnormalities including lentigines and café au lait patches, characteristic facial features, heart defects particularly hypertrophic cardiomyopathy, and deafness (Legius et al. J Med Genet 39:571-574, 2002; Sarkozy et al. J Med Genet 41:e68, 2004).

**Genetics:** NS is an autosomal dominant disorder, although *de novo* mutations are found in a substantial fraction of patients. Mutations in the *PTPN11*, *SOS1*, *RAF1* and *KRAS* genes have been reported to be causative for NS. Roughly 50% of NS patients carry causative mutations in *PTPN11*. Of the remainder, perhaps 7% have mutations in *SOS1* and 2% in *KRAS*. *RAF1* is the newest NS gene. Fourteen different causative missense mutations were reported in three *RAF1* exons (7, 14 and 17) (Pandit et al. Nat Genet 39:1007-1012, 2007; Razzaque et al. Nat Genet 39:1013-1017, 2007). *RAF1* mutations were found in 3% of Causasian NS patients (Pandit et al. 2007) and 17% of Japanese NS patients (Razzaque et al. 2007). Nearly all the patients with mutations in *RAF1* exon 7 had hypertrophic cardiomyopathy. Pandit et al. also reported that roughly 3% of LEOPARD Syndrome patients carried *RAF1* mutations.

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of exons 7, 14 and 17 of the *RAF1* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. We will sequence any single exon in family members of patients with known mutations, and to confirm research results (\$190).

**Reference Sequences:** Genomic: NC\_000003.10 mRNA: NM\_002880.2 protein: NP\_002871.1

**Indications for Test:** All NS and LEOPARD Syndrome patients that are negative for *PTPN11* mutations are candidates for this test. For NS patients with hypertrophic cardiomyopathy, it may be better to perform the *RAF1* test ahead of the *SOS1* and *KRAS* gene sequencing tests.

**Sensitivity of Test:** As described above under **Genetics**, a small, but significant fraction of NS and LEOPARD Syndrome patients have *RAF1* mutations.

**Turn Around Time:** Maximum of 40 days, although many of these tests are completed in 2-3 weeks.

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

**Price:** Sequencing of exons 7, 14 and 17 of *RAF1* Gene **\$ 370**

**CPT Codes:**

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x3	83898	\$ 90	Sequencing x3	83904	\$ 130
Separation	83894	\$ 30	Interpretation/Report	83912	\$ 50

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

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