Noonan Syndrome: *PTPN11* Gene Deletion/Duplication

**Condition Description**

Noonan syndrome (NS) is an autosomal dominant dysmorphology syndrome characterized by short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymhatic dysplasias, ocular abnormalities, and deafness. Characteristic facies include hypertelorism (74%), downward sloping palpebral apertures (38%), epicanthal folds (39%), ptosis (48%), and low-set posteriorly rotated ears. Early feeding difficulties such as poor suck or gastrointestinal dysfunction are also common. Although birth length is usually normal, final adult height approaches the lower limit of normal. Up to one-third of affected individuals have mild intellectual disability.

Congenital heart disease occurs in 50%-80% of individuals with NS. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy is found in 20%-30% of individuals, and may be congenital or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot.

NS is clinically diagnosed. Affected individuals have normal chromosome studies. Molecular genetic testing identifies mutations in *PTPN11* in over 50% of affected individuals. (Other genes known to be involved include *KRAS* in fewer than 5% of affected individuals, *SOS1* in approximately 13%, and *RAF1* in 3%-17%.) The *PTPN11* gene (12q24.1) encodes a nontransmembrane protein-tyrosine phosphatase. One study showed that pulmonic stenosis was more prevalent among the group of individuals with NS who had *PTPN11* mutations than it was in the group without them (70.6% vs 46.2%), while hypertrophic cardiomyopathy was less prevalent among those with *PTPN11* mutations (5.9% vs 26.2%). The prevalence of other congenital heart malformations, short stature, pectus deformity, cryptorchidism, and developmental delay did not differ between the two groups. Mutations in the *NRAS*, *BRAF*, and *MAP2K1* genes have been reported in less than 1% of cases.

Many affected individuals have de novo mutations; however, an affected parent is recognized in 30%-75% of families. When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low (<1%). Noonan syndrome has an estimated incidence of 1 in 1,000 to 2,500 live births.

LEOPARD syndrome can also be caused by mutations in the *PTPN11* gene. LEOPARD is an acronym for multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness. Sequence analysis of *PTPN11* detects missense mutations in about 90% of individuals tested. Unlike the activating mutations found in NS, LEOPARD syndrome mutations are catalytically defective and act as dominant-negative mutations that interfere with growth factor/ERK-MAPK-mediated signaling.

[Click here](#) for the GeneTests summary on this condition.

### Genes

**PTPN11**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Noonan syndrome in individuals who have tested negative for sequence analysis

### Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

### Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:
In EDTA (purple top) or ACD (yellow top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Sequence analysis of the *PTPN11* gene is available and is required before deletion/duplication analysis.
- Sequence and deletion/duplication analysis for the *NRAS, KRAS, RAF1* and *SOS1* genes are also available.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.