

# Noonan Syndrome, *PTPN11* Sequencing with Reflex to *SOS1* Sequencing

*TO CONFIRM A CLINICAL DIAGNOSIS OF NOONAN SYNDROME (NS), LEOPARD SYNDROME, OR NOONAN-LIKE/MULTIPLE GIANT-CELL LESION SYNDROME*

## Disease Overview

- Characteristics of Noonan Syndrome (NS) include: developmental delay, dysmorphic facial features, short stature, broad or webbed neck, congenital heart defect, superior pectus carinatum and inferior pectus excavatum, low-set nipples, cryptorchidism, coagulation disorders, and lymphatic dysplasias.
- Heart defects occur in up to 80 percent of affected individuals, with pulmonary valve stenosis and hypertrophic cardiomyopathy being the most common.
- Up to one third of individuals have mild mental retardation.
- Ocular findings, such as strabismus, amblyopia, nystagmus, and refractive errors, are present in 95 percent of those affected.
- Following diagnosis, several evaluations are recommended, including: physical, neurologic, developmental, cardiac, ophthalmologic, hearing, renal ultrasound, radiographic assessment of spine and rib cage, brain and cervical MRI, and genetics consultation.
- Clinical findings in LEOPARD syndrome (lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, deafness) show significant overlap with those of NS.
- Noonan-like/multiple giant-cell lesion syndrome has some features of NS and giant-cell lesions of bone and soft tissues.

## Epidemiology

- Incidence of NS is estimated to be between one in 1,000 to one in 2,500 individuals.

## Genetics

- NS inheritance is autosomal dominant. Up to 70 percent of cases may result from new mutations.
- Penetrance is unknown due to ascertainment bias and variable expressivity.
- Mutations in at least four different genes are known to be causative for NS.
- 50 to 60 percent of NS occurs due to *PTPN11* mutations, 10 percent due to *SOS1* mutations, 10 percent due to *RAF1* mutations, and <5 percent due to *KRAS* mutations. Mutations causing NS are all detectable by sequencing. No large deletions or duplications in the above genes have been identified in affected individuals.

- *PTPN11* and *RAF1* mutations are believed to be causative for LEOPARD syndrome in 90 and 3 percent of cases, respectively.
- *PTPN11* and *SOS1* mutations have also been observed in some individuals with Noonan-like/multiple giant-cell lesion syndrome.
- If a causative mutation is found in an affected child, molecular testing for the same mutation is recommended for the parents. If no parental mutation is identified, the risk of another child being affected is <1 percent. If one parent is found to have the same NS-causing mutation as the child, then the recurrence risk in future offspring is 50 percent.

## Indication for Ordering

- To confirm a clinical diagnosis of NS, LEOPARD syndrome, or Noonan-like/multiple giant-cell lesion syndrome.

## Contraindication for Ordering

- Once a causative mutation has been detected in an affected individual, [Familial Mutation, Targeted Sequencing \(ARUP test #2001961\)](#) should be offered to the patient's parents and other at-risk family members.
- A copy of the affected individual's result should accompany the test requisition.

## Interpretation

- Identification of a known pathogenic *PTPN11* or *SOS1* mutation in a symptomatic individual confirms a diagnosis of NS, LEOPARD syndrome, or Noonan-like/multiple giant-cell lesion syndrome.
- Lack of an identifiable *PTPN11* or *SOS1* mutation does not rule out a diagnosis of NS, as only mutations within the coding region and intron/exon borders of the two genes will be detected. *RAF1* and *KRAS* are not evaluated by this assay.
- *PTPN11* or *SOS1* mutations of unknown significance may be detected.

## Limitations

- Large *PTPN11* and *SOS1* gene deletions/duplications, intronic mutations, and regulatory region mutations are not evaluated.
- Mutations in other known causative genes, *RAF1* and *KRAS*, as well as possible undiscovered genes, will not be detected.
- Rare diagnostic errors can occur due to primer-site mutations.

### Methodology

- Bidirectional sequencing of the entire *PTPN11* coding region and intron-exon boundaries. If no pathogenic mutations are detected, bidirectional sequencing of the entire *SOS1* coding region and intron-exon boundaries is performed.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity for NS is approximately 70 percent.

### Related Tests

- Noonan Syndrome (*PTPN11*) Sequencing (0051805)
- Noonan Syndrome (*SOS1*) Sequencing (2004195)
- Familial Mutation, Targeted Sequencing (2001961)

### Reference

1. Online GeneTests: Noonan Syndrome. [www.genetests.org](http://www.genetests.org) (accessed on April 12, 2010).

## Test Information

**2004189**

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For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).