

Noonan Syndrome (*PTPN11*) 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 (lentiginos, 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.
- Mutations in at least four different genes are known to be causative for NS.
- Fifty percent of NS occurs due to *PTPN11* mutations, 13 percent due to *SOS1* mutations, 10 percent due to *RAF1* mutations, and <5 percent due to *KRAS* mutations.
- *PTPN11* mutations have also been observed in some individuals with LEOPARD or 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 for 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.

Indications for Ordering

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

Contraindications for Ordering

Once a causative mutation has been detected in an affected individual, targeted testing for the identified mutation should be offered to at-risk family members. Full-gene sequencing is not necessary.

Interpretation

- Identification of a known deleterious *PTPN11* mutation in a symptomatic individual confirms a diagnosis of NS.
- Lack of an identifiable *PTPN11* mutation does not rule out a diagnosis of NS, as only mutations within the *PTPN11* coding region and intron/exon borders will be detected.
- *PTPN11* mutations of unknown significance may be detected by this assay.

Limitations

- Large *PTPN11* gene deletions/duplications, intronic mutations, and regulatory region mutations are not evaluated.
- Mutations in other known causative genes, *SOS1*, *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.**
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is approximately 50 percent.

Related Tests

- [Familial Mutation, Targeted Sequencing \(2001961\)](#)
- [Familial Mutation, Targeted Sequencing, Fetal \(2001980\)](#)

Reference

Online GeneTests: Noonan Syndrome. www.genetests.org (accessed March 26, 2009).

Test Information

0051805 **Noonan Syndrome (PTPN11) Sequencing**

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.