Noonan Syndrome: SOS1 Gene Sequencing

Test Code: SSOS1
Turnaround time: 4 weeks
CPT Codes: 81406 x1

**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, lymphatic 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** (2p22-p21) in approximately 13%, and **RAF1** in 3%-17%. 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.

Additionally, a mutation in the **SOS1** gene has been reported in a family with gingival fibromatosis.

Please note that this test is for the **SOS1** gene only.

For patients with suspected NS, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**References:**
- GeneReviews
- OMIM #182530: SOS1 gene
- OMIM #610733: NS
- OMIM #135300: Gingival Fibromatosis

**Genes**

**SOS1**

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of Noonan syndrome.
- Carrier testing in adults with a family history of Noonan syndrome.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity: Molecular genetic testing identifies mutations in the **SOS1** gene in approximately 13% of affected individuals. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

**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.

### Related Tests

- Deletion/duplication analysis of the **SOS1** gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Sequencing and deletion/duplication analysis of the **PTPN11**, **RAF1**, **NRAS** and **KRAS** genes are available.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.