Noonan Syndrome: S0S1 Gene Deletion/Duplication

Test Code: DS0S1  
Turnaround time: 2 weeks  
CPT Codes: 81228 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, S0S1 (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 S0S1 gene has been reported in a family with gingival fibromatosis.

Please note that this test is for the S0S1 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: S0S1 gene
- OMIM #610733: NS
- OMIM #135300: Gingival Fibromatosis

Genes

S0S1

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of Noonan syndrome in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of Noonan syndrome in whom sequence analysis was negative.

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

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 SOS1 gene is available and is required before deletion/duplication analysis.
- 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.