Noonan Syndrome: RAF1 Gene Deletion/Duplication

Test Code: DRAF1
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, SOS1 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.

Mutations in the RAF1 gene (3p25) has been correlated with hypertrophic cardiomyopathy, with 95% of affected individuals with RAF1 mutations showing this feature, in comparison with the overall prevalence in NS of 18%. This suggests that pathologic cardiomyocyte hypertrophy occurs because of increased Ras signaling.

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 RAF1 gene. LEOPARD is an acronym for multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness. LEOPARD syndrome is caused by gain-of-function mutations in RAF1. About one-third of families affected with LEOPARD syndrome without PTPN11 mutations have a mutation in RAF1.

For patients with suspected RAF1-related Noonan syndrome, 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.

Click here for the GeneReviews Noonan syndrome summary.
Click here for the GeneReviews LEOPARD syndrome summary.

Genes

RAF1

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 RAF1 gene is available and is required before deletion/duplication analysis.
- Sequence and deletion/duplication analysis of the PTPN11, SOS1, RAF1, NRAS and KRAS 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.