Noonan Spectrum Disorders Panel

Indications for Ordering

Confirm diagnosis of a Noonan spectrum disorder
- Noonan syndrome (NS)
- Cardiofaciocutaneous syndrome (CFCS)
- Costello syndrome (CS)
- Legius syndrome (LS)
- LEOPARD (lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, deafness) syndrome
- Noonan-like syndrome
- Noonan-like syndrome with loose anagen hair (NS/LAH)
- Say-Barber-Biesecker-Young-Simpson (SBBYS) variant of Ohdo syndrome
- Martin-Probst syndrome (MPS)

Test Description

Targeted capture of all coding exons and intron/exon boundaries followed by massively parallel sequencing
- Reported variants are confirmed by Sanger sequencing

Tests to Consider

Primary test

Noonan Spectrum Disorders Panel, Sequencing, 15 Genes 2010772
- Preferred test for individuals with clinical phenotype of NS, CFCS, CS, LS, LEOPARD syndrome, or Noonan-like syndrome
- May be ordered on prenatal or postnatal specimens

Related tests

Noonan Syndrome (*PTPN11)* Sequencing with Reflex to *(SOS1)* Sequencing 2004189
- Acceptable initial test to confirm a clinical diagnosis of NS or LEOPARD syndrome
- Clinical sensitivity – ~70% for NS and 90% for LEOPARD syndrome

Noonan Syndrome (*PTPN11*) Sequencing 0051805
- Acceptable initial test to confirm a clinical diagnosis of NS or LEOPARD syndrome
- Clinical sensitivity – ~50-60% for NS and 90% for LEOPARD syndrome

Noonan Syndrome (*SOS1*) Sequencing 2004195
- Acceptable secondary test if no pathogenic variants are detected with *PTPN11* testing
- Clinical sensitivity – ~10% for NS

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence
- NS – 1/1,000-2,500
- Unknown for other Noonan spectrum disorders

Symptoms – see Table 1

Genetics

Genes tested – see Table 2

Inheritance
- X-linked for *RAB40AL* gene
- Autosomal dominant for all other analyzed genes

Penetrance
- Difficult to ascertain due to variable expressivity
- Noonan spectrum disorders are caused by variants in genes involved in the Ras/MAPK pathway
  - Also referred to as RASopathies

Variants

Variants in multiple genes appear to cause overlapping phenotypes for Noonan spectrum disorders

Test Interpretation

Clinical sensitivity – dependent on clinical phenotype
- 99% for CFCS
- ~95% for LEOPARD
- ~80-90% for CS
- ~75% for NS

Results
- Positive – pathogenic variants detected
  - Confirms diagnosis of a Noonan spectrum disorder
- Negative – no pathogenic variant detected
  - Reduces, but does not exclude, a possibility of Noonan spectrum disorder
- Inconclusive – variants of uncertain clinical significance may be identified

Limitations

- Not determined or evaluated
  - Variants in genes not included on the panel
  - Deep intronic and regulatory region variants
  - Large deletions/duplications
- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations
- Lack of detectable gene variant does not exclude a diagnosis of Noonan spectrum disorder

Table 1

Disorder	Major Clinical Features
NS	• Short stature • Developmental delay • Dysmorphic facial features • Congenital heart defects • Broad or webbed neck • Superior pectus carinatum and inferior pectus excavatum • Low-set nipples • Cryptorchidism • Intellectual disability • Coagulation and lymphatic disorders (including fetal cystic hygroma, increased nuchal translucency, and polyhydramnios)
CFCS	• Postnatal feeding difficulties with failure to thrive • Hypotonia • Skin abnormalities (eg, xerosis) • Congenital heart defects • Lymphedema • Dysmorphic facial features • Developmental delay • Short stature • Curly and sparse hair • Dystrophic nails • Intellectual disability • Relative macrocephaly • Seizures • Short webbed neck • Ocular abnormalities
CS	• Prenatal polyhydramnios (severe) and increased nuchal translucency • Neonatal lymphedema • Short stature • Postnatal feeding difficulties with failure to thrive • Hypotonia • Developmental delay • Intellectual disability • Dysmorphic (coarse) facial features • Curly and/or sparse fine hair • Cutaneous abnormalities (loose skin, deep palmar and plantar creases, facial and/or perianal papillomata) • Joint laxity with ulnar deviation of the wrists • Short humeri and femurs • Tight Achilles tendons • Congenital heart defects • Macrocephaly • Predisposition to malignant tumors (primarily rhabdomyosarcoma, neuroblastoma, and transitional cell carcinoma of the bladder) • Pectus carinatum or pectus excavatum • Cerebellar abnormalities (Chiari I malformation)
LEOPARD syndrome	• Lentigines and café au lait macules • ECG conduction abnormalities related to hypertrophic cardiomyopathy • Ocular hypertelorism • Congenital heart defects (pulmonic stenosis most common) • Abnormal genitalia (most often cryptorchidism) • Growth retardation (short stature) • Sensorineural deafness • Intellectual disability • Dysmorphic facial features • Broad neck
NS/LAH	• Short stature • Abnormal facial features • Short or webbed neck • Cardiovascular defects • Growth hormone deficiency • Sparse or loose anagen hair • Hyperpigmented skin
LS	• Café au lait spots • Axillary freckling • Macrocephaly • Characteristic Noonan-like facies • Lipomas • Hypotonia • Learning difficulties
MPS	• Short stature • Sensorineural hearing loss • Craniofacial dysmorphism • Intellectual disability • Renal insufficiency • Impaired hematopoiesis
SBBYS variant of Ohdo syndrome	• Congenital heart defects • Hypotonia • Feeding difficulties • Facial dysmorphism, including severe blepharophimosis • Dental anomalies • Thyroid dysfunction • Joint laxity • Intellectual disability

Table 2

Gene Symbol	Gene Name	NM #	OMIM #	Disorder(s)	Percentage of Associated Disorder(s) Attributed to Variants in This Gene
BRAF	V-raf murine sarcoma viral oncogene homolog b1	NM_004333	164757	CFCS, LEOPARD, NS	~75% of CFCS <5% of LEOPARD <1% of NS
CBL	Cas-Br-M (murine) ecotropic retroviral transforming sequence	NM_005188	165360	Noonan-like syndrome with or without juvenile myelomonocytic leukemia	Unknown
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	NM_005343	190020	CS, congenital myopathy with excess of muscle spindles (variant of CS)	~80-90% of CS
KAT6B	K(lysine) acetyltransferase 6B	NM_012330	605880	SBBYS, genitopatellar syndrome	Unknown
KRAS	V-ki-ras2 kirsten rat sarcoma viral oncogene homolog	NM_004985	190070	NS, CFCS	<5% of NS <2-3% of CFCS
MAP2K1 (*MEK1*)	Mitogen-activated protein kinase kinase 1	NM_002755	176872	CFCS, NS	~10-15% of CFCS <1% of NS
MAP2K2 (*MEK2*)	Mitogen-activated protein kinase kinase 2	NM_030662	601263	CFCS	~10-15% of CFCS
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog	NM_002524	164790	NS	<1% of NS
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11	NM_002834	176876	LEOPARD, NS	90% of LEOPARD 50-60% of NS
RAB40AL	RAB40A, member RAS oncogene family-like	NM_001031834	300405	MPS	Unknown
RAF1	V-raf-1 murine leukemia viral oncogene homolog 1	NM_002880	164760	NS, LEOPARD	3-17% of NS <5% of LEOPARD
RIT1	Ras-like without CAAX 1	NM_006912	609591	NS	Unknown
SHOC2	Soc-2 suppressor of clear homolog (C. elegans)	NM_007373	602775	NS/LAH	Unknown
SOS1	Son of sevenless homolog 1 (Drosophila)	NM_005633	182530	NS	10-13% of NS
SPRED1	Sprouty-related, EVH1 domain containing 1	NM_152594	609291	LS	Unknown