

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 (lentiginos, 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

- Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants
- For fetal specimens, all clinically significant reported sequence variants are confirmed by Sanger sequencing

Tests to Consider

Primary test

[Noonan Spectrum Disorders Panel, Sequencing 2010772](#)

- Preferred test for individuals with clinical phenotype of NS, CFCS, CS, LS, LEOPARD syndrome, or Noonan-like syndrome

[Noonan Spectrum Disorders Panel, Sequencing, Fetal 2010769](#)

- Prenatal testing for fetus with ultrasound findings suggestive of Noonan syndrome, such as cystic hygroma, increased nuchal translucency, or polyhydramnios

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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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

Disorder	Major Clinical Features
CS	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Lentiginos 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	<ul style="list-style-type: none"> • Short stature • Abnormal facial features • Short or webbed neck • Cardiovascular defects • Growth hormone deficiency • Sparse or loose anagen hair • Hyperpigmented skin
LS	<ul style="list-style-type: none"> • Café au lait spots • Axillary freckling • Macrocephaly • Characteristic Noonan-like facies • Lipomas • Hypotonia • Learning difficulties
MPS	<ul style="list-style-type: none"> • Short stature • Sensorineural hearing loss • Craniofacial dysmorphism • Intellectual disability • Renal insufficiency • Impaired hematopoiesis
SBBYS variant of Ohdo syndrome	<ul style="list-style-type: none"> • 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
<i>BRAF</i>	V-raf murine sarcoma viral oncogene homolog b1	NM_004333	164757	CFCS, LEOPARD, NS	~75% of CFCS <5% of LEOPARD <1% of NS
<i>CBL</i>	Cas-Br-M (murine) ecotropic retroviral transforming sequence	NM_005188	165360	Noonan-like syndrome with or without juvenile myelomonocytic leukemia	Unknown
<i>HRAS</i>	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
<i>KAT6B</i>	K(lysine) acetyltransferase 6B	NM_012330	605880	SBBYS, genitopatellar syndrome	Unknown
<i>KRAS</i>	V-ki-ras2 kirsten rat sarcoma viral oncogene homolog	NM_004985	190070	NS, CFCS	<5% of NS <2-3% of CFCS
<i>MAP2K1 (MEK1)</i>	Mitogen-activated protein kinase kinase 1	NM_002755	176872	CFCS, NS	~10-15% of CFCS <1% of NS
<i>MAP2K2 (MEK2)</i>	Mitogen-activated protein kinase kinase 2	NM_030662	601263	CFCS	~10-15% of CFCS
<i>NRAS</i>	Neuroblastoma RAS viral (v-ras) oncogene homolog	NM_002524	164790	NS	<1% of NS
<i>PTPN11</i>	Protein tyrosine phosphatase, nonreceptor type 11	NM_002834	176876	LEOPARD, NS	90% of LEOPARD 50-60% of NS
<i>RAB40AL</i>	RAB40A, member RAS oncogene family-like	NM_001031834	300405	MPS	Unknown
<i>RAF1</i>	V-raf-1 murine leukemia viral oncogene homolog 1	NM_002880	164760	NS, LEOPARD	3-17% of NS <5% of LEOPARD
<i>RIT1</i>	Ras-like without CAAX 1	NM_006912	609591	NS	Unknown
<i>SHOC2</i>	Soc-2 suppressor of clear homolog (C. elegans)	NM_007373	602775	NS/LAH	Unknown
<i>SOS1</i>	Son of sevenless homolog 1 (Drosophila)	NM_005633	182530	NS	10-13% of NS
<i>SPRED1</i>	Sprouty-related, EVH1 domain containing 1	NM_152594	609291	LS	Unknown