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

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