Noonan Spectrum Disorders Panel

Noonan spectrum disorders (NSD) are a group of genetic syndromes caused by pathogenic germline variants in genes in the Ras/mitogen activated protein kinase (MAPK) pathway, which controls the cell cycle and cell differentiation. The vast majority of causative variants increase pathway signaling; thus, the resulting syndromes exhibit phenotypic overlap and share a predisposition for developing malignancies.

DISEASE OVERVIEW

Symptoms of Noonan Syndrome (NS)
- Characteristic facial features
- Short stature
- Broad webbed neck (fetal cystic hygroma/increased nuchal translucency)
- Congenital heart defect
- Developmental delay
- Undescended testes
- Coagulation defects
- Lymphatic dysplasias

Etiology of NSDs
Pathogenic sequence variants in Ras pathway genes

Prevalence
NS – 1/1,000-2,500

Inheritance
Autosomal dominant for all analyzed genes

Genotype-Phenotype Correlation
Variants in multiple genes cause overlapping phenotypes for NSD

TEST DESCRIPTION

See Genes Tested table for genes included in this panel.

Clinical Sensitivity
Dependent on clinical phenotype
- ~99% for cardiofaciocutaneous syndrome (CFCS) (Rauen, 2013)
- ~80-90% for Costello syndrome (CS) (Aoki, 2005; Estep, 2006; Gripp, 2006; Kerr, 2006)
- ~70-80% for NS (Tartaglia, 2002; Roberts, 2007; Tartaglia, 2007; Aoki, 2016; Schubbert, 2006; Brasil, 2010; Sarkozy, 2009; Nava, 2007)

Limitations
- A negative result does not exclude a diagnosis of a MAPK pathway disorder.
Diagnostic errors can occur due to rare sequence variations.
Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
The following will not be evaluated:
- Variants outside the coding regions and intron-exon boundaries of the targeted genes
- Regulatory region variants and deep intronic variants
- Large deletions/duplications
- Noncoding transcripts
The following may not be detected:
- Deletions/duplications/insertions of any size by massively parallel sequencing
- Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
- Low-level somatic variants

Analytic Sensitivity
For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region (%)</th>
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</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
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<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
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<tr>
<td>Deletions 11-44 bp</td>
<td>100</td>
<td>87.8-100</td>
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<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
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<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
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</tbody>
</table>

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
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<tbody>
<tr>
<td>BRAF</td>
<td>BRAF1</td>
<td>164757</td>
<td>CFCS 1&lt;br&gt;NS 1&lt;br&gt;NS 7&lt;br&gt;LEOPARD syndrome 3</td>
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<td>CBL</td>
<td>CBL2, RNF55, c-Cbl</td>
<td>165360</td>
<td>NS-like disorder with or without juvenile myelomonocytic</td>
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<td>HRAS</td>
<td>HRAS1</td>
<td>190020</td>
<td>Melanocytic Nevus syndrome, congenital&lt;br&gt;Schimmelpenning-Feuerstein-Mims syndrome CS</td>
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<td>KRAS</td>
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<td>190070</td>
<td>Schimmelpenning-Feuerstein-Mims syndrome&lt;br&gt;NS 3&lt;br&gt;CFCS 2</td>
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<td>LZTR1</td>
<td>LZTR-1, BTBD29</td>
<td>600574</td>
<td>NS 10</td>
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<td>MAP2K1</td>
<td>PRKMK1, MEK1, MAPKK1</td>
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<td>NS 1&lt;br&gt;CFCS 3</td>
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<td>MAP2K2</td>
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<td>CFCS 4</td>
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<td>NRAS</td>
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<td>Schimmelpenning-Feuerstein-Mims syndrome&lt;br&gt;NS 6</td>
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<td>PTPN11</td>
<td>NS1, BPTP3, SH-PTP2, SHP-2, PTP2C, SHP2</td>
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<td>LEOPARD syndrome 1&lt;br&gt;NS 1</td>
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<tr>
<td>Gene</td>
<td>Alias Symbol(s)</td>
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<td>Disorder</td>
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<td>RAF1</td>
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<td>RASA2</td>
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<td>SHOC2</td>
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<td>SOS1</td>
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<td>NS 9</td>
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<td>SPRED1</td>
<td>FLJ33903, PPP1R147</td>
<td>609291</td>
<td>Legius syndrome</td>
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</table>

REFERENCES

RELATED INFORMATION

Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder Laboratory Testing - Neurocognitive Impairments

ARUP Consult® Algorithm

Testing for Genetic Syndromes Related to Developmental Delay (DD), Intellectual Disability (ID), and Autism Spectrum Disorder (ASD)

RELATED TESTS

Noonan Syndrome (PTPN11) Sequencing with Reflex to (SOS1) Sequencing 2004189
Method: Polymerase Chain Reaction/Sequencing

Noonan Syndrome (PTPN11) Sequencing 0051805
Method: Polymerase Chain Reaction/Sequencing

Noonan Syndrome (SOS1) Sequencing 2004195
Method: Polymerase Chain Reaction/Sequencing

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing