# 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)[1]
- ~80-90% for Costello syndrome (CS)[2,3,4,5]
- ~70-80% for NS[6,7,8,9,10,11,12,13]

## Tests to Consider

### Noonan Spectrum Disorders Panel, Sequencing 2010772

**Method:** Massively Parallel Sequencing

#### Ordering Indications

Confirm a suspected clinical diagnosis of:

- Noonan syndrome (NS)
- Cardiofacial cutaneous syndrome (CFCS)
- Costello syndrome (CS)
- Legius syndrome (LS)
- Noonan syndrome with multiple lentigines (LEOPARD syndrome)
- Noonan-like syndrome
- Noonan-like syndrome with loose anagen hair (NS/LAH)

#### Contraindications

This panel should not be ordered in individuals with primary JMML as the assay may not detect mosaicism for somatic variants associated with malignancy.

#### Testing Strategy

Given the genotypic and phenotypic overlap among Noonan spectrum disorders (NSDs), the NSD panel is the recommended first-line test for determining a genetic etiology.

### Noonan Spectrum Disorders Panel, Sequencing, Fetal 2010769

**Method:** Massively Parallel Sequencing

#### Ordering Indications

Confirm a diagnosis of a NSD in a pregnancy with clinically suggestive findings, such as increased nuchal translucency, cystic hygroma, and cardiac defects.

#### Testing Strategy

For a fetus with ultrasonographic abnormalities, genomic microarray should be ordered prior to the NSD panel.

See Related Tests

## 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:

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) | Analytical Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|
| SNVs | 99.2 | 96.9-99.4 |
| Deletions 1-10 bp | 93.8 | 84.3-98.2 |
| Deletions 11-44 bp | 100 | 87.8-100 |
| Insertions 1-10 bp | 94.8 | 86.8-98.5 |
| Insertions 11-23 bp | 100 | 62.1-100 |

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

## Genes Tested

| Gene | Alias Symbol(s) | MIM Number | Disorder |
|---|---|---|---|
| *BRAF* | BRAF1 | 164757 | CFCS 1<br>NS 1<br>NS 7<br>LEOPARD syndrome 3 |
| *CBL* | CBL2, RNF55, c-Cbl | 165360 | NS-like disorder with or without juvenile myelomonocytic |
| *HRAS* | HRAS1 | 190020 | Melanocytic Nevus syndrome, congenital<br>Schimmelpenning-Feuerstein-Mims syndrome<br>CS |
| *KRAS* | KRAS2, KRAS1 | 190070 | Schimmelpenning-Feuerstein-Mims syndrome<br>NS 3<br>CFCS 2 |
| *LZTR1* | LZTR-1, BTBD29 | 600574 | NS 10 |

| Gene | Alias Symbol(s) | MIM Number | Disorder |
|---|---|---|---|
| *MAP2K1* | PRKMK1, MEK1, MAPKK1 | 176872 | NS 1<br>CFCS 3 |
| *MAP2K2* | PRKMK2, MEK2 | 601263 | CFCS 4 |
| *NRAS* | N-ras | 164790 | Schimmelpenning-Feuerstein-Mims syndrome<br>NS 6 |
| *PTPN11* | NS1, BPTP3, SH-PTP2, SHP-2, PTP2C, SHP2 | 176876 | LEOPARD syndrome 1<br>NS 1 |
| *RAF1* | Raf-1, c-Raf, CRAF | 164760 | NS 5<br>LEOPARD syndrome 2 |
| *RASA2* | GAP1M | 601589 | |
| *RIT1* | RIT, RIBB, ROC1, MGC125864, MGC125865 | 609591 | NS 8 |
| *SHOC2* | KIAA0862, SOC2, SUR-8, SOC-2, SUR8 | 602775 | NS-like disorder with loose anagen hair 1 |
| *SOS1* | GINGF, HGF, GF1 | 182530 | NS 4 |
| *SOS2* | | 601247 | NS 9 |
| *SPRED1* | FLJ33903, PPP1R147 | 609291 | Legius syndrome |

## References


1. Rauen KA. The RASopathies. Annu Rev Genomics Hum Genet. 2013;14:355-369. PubMed
2. Aoki Y, Niihori T, Kawame H, et al. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nat Genet. 2005;37(10):1038-1040. PubMed
3. Estep AL, Tidyman WE, Teitell MA, et al. HRAS mutations in Costello syndrome: detection of constitutional activating mutations in codon 12 and 13 and loss of wild-type allele in malignancy. Am J Med Genet A. 2006;140(1):8-16. PubMed
4. Gripp KW, Lin AE, Stabley DL, et al. HRAS mutation analysis in Costello syndrome: genotype and phenotype correlation. Am J Med Genet A. 2006;140(1):1-7. PubMed
5. Kerr B, Delrue MA, Sigaudy S, et al. Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. J Med Genet. 2006;43(5):401-405. PubMed
6. Tartaglia M, Kalidas K, Shaw A, et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet. 2002;70(6):1555-1563. PubMed
7. Roberts AE, Araki T, Swanson KD, et al. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. Nat Genet. 2007;39(1):70-74. PubMed
8. Tartaglia M, Pennacchio LA, Zhao C, et al. Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. Nat Genet. 2007;39(1):75-79. PubMed
9. Aoki Y, Niihori T, Inoue Sichi, et al. Recent advances in RASopathies. J Hum Genet. 2016;61(1):33-39. PubMed
10. Schubbert S, Zenker M, Rowe SL, et al. Germline KRAS mutations cause Noonan syndrome. Nat Genet. 2006;38(3):331-336. PubMed
11. Brasil ASalem, Pereira AC, Wanderley LTurolla, et al. PTPN11 and KRAS gene analysis in patients with Noonan and Noonan-like syndromes. Genet Test Mol Biomarkers. 2010;14(3):425-432. PubMed

Biomarkers. 2010;14(5):423-432. PubMed

12. Sarkozy A, Carta C, Moretti S, et al. Germline BRAF mutations in Noonan, LEOPARD, and cardiofaciocutaneous syndromes: molecular diversity and associated phenotypic spectrum. Hum Mutat. 2009;30(4):695-702. PubMed

13. Nava C, Hanna N, Michot C, et al. Cardio-facio-cutaneous and Noonan syndromes due to mutations in the RAS/MAPK signalling pathway: genotype-phenotype relationships and overlap with Costello syndrome. J Med Genet. 2007;44(12):763-771. PubMed

## Related Information

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

## Related Tests

Noonan Syndrome (PTPN11) Sequencing 0051805

**Method:** Polymerase Chain Reaction/Sequencing

Familial Mutation, Targeted Sequencing 2001961

**Method:** Polymerase Chain Reaction/Sequencing

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