Noonan Spectrum Disorders Panel

Noonan spectrum disorders (NSDs) 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

- Approximately 99% for cardiofaciocutaneous syndrome (CFCS)[1]
- Approximately 80-90% for Costello syndrome (CS)[2,3,4,5]
- Approximately 70-80% for NS[6-13]

Featured ARUP Testing

Noonan Spectrum Disorders Panel, Sequencing 2010772

Method: Massively Parallel Sequencing

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)

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

Contraindications: This panel should not be ordered in individuals with primary juvenile myelomonocytic leukemia (JMML) as the assay may not detect mosaicism for somatic variants associated with malignancy.

Noonan Spectrum Disorders Panel, Sequencing, Fetal 2010769

Method: Massively Parallel Sequencing

Confirm a diagnosis of an NSD in a pregnancy with clinically suggestive findings, such as increased nuchal translucency, cystic hygroma, and cardiac defects. For a fetus with ultrasonographic abnormalities, genomic microarray should be ordered prior to the NSD panel.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

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	Analytic Sensitivity (PPA) Estimate[a] (%)	Analytic 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 NS 1 NS 7 LEOPARD syndrome 3
CBL	CBL2, RNF55, c-Cbl	165360	NS-like disorder with or without juvenile myelomonocytic
HRAS	HRAS1	190020	Melanocytic Nevus syndrome, congenital Schimmelpenning-Feuerstein-Mims syndrome CS
KRAS	KRAS2, KRAS1	190070	Schimmelpenning-Feuerstein-Mims syndrome NS 3 CFCS 2
LZTR1	LZTR-1, BTBD29	600574	NS 10

Gene	Alias Symbol(s)	MIM Number	Disorder
MAP2K1	PRKMK1, MEK1, MAPKK1	176872	NS 1 CFCS 3
MAP2K2	PRKMK2, MEK2	601263	CFCS 4
NRAS	N-ras	164790	Schimmelpenning-Feuerstein-Mims syndrome NS 6
PTPN11	NS1, BPTP3, SH-PTP2, SHP-2, PTP2C, SHP2	176876	LEOPARD syndrome 1 NS 1
RAF1	Raf-1, c-Raf, CRAF	164760	NS 5 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

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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)

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