THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Noonan syndrome

Clinical Features:

Noonan syndrome is autosomal dominant condition characterized by short stature, facial dysmorphism, congenital heart defects, and developmental delay. Pulmonary valve stenosis is the most common heart defect in patients with Noonan syndrome, followed by hypertrophic cardiomyopathy. Additional features identified in patients with Noonan syndrome include: broad and/or webbed neck, spine and chest abnormalities, cryptorchidism, coagulation defects, lymphatic dysplasias and ocular abnormalities. Up to one fourth of individuals with Noonan syndrome have mild intellectual disability and language impairments. 30-75% of individuals with Noonan syndrome inherit a pathogenic variant from an affected parent.

A number of syndromes related to genes in the RAS/MAPK pathway have phenotypic overlap with Noonan syndrome. These include cardiofaciocutaneous (CFC) syndrome, Costello syndrome, neurofibromatosis type 1, and Noonan syndrome-like disorders. CFC syndrome and Noonan syndrome have the greatest similarity in features, with similar cardiac and lymphatic findings. However, individuals with CFC typically have a greater degree of intellectual disability coupled with central nervous system abnormalities, gastrointestinal issues, and coarser facies (1).

Molecular Genetics:

The genes associated with Noonan syndrome are involved in the Ras/mitogen activated protein kinase (RAS/MAPK) pathway, which is essential in the regulation of cell cycle processes including differentiation, growth and senescence. To date, mutations in genes included on the Noonan syndrome panel account for approximately 75% of affected individuals (1).

Pathogenic variants in the *PTPN11* gene are the most common cause of Noonan syndrome, and are identified in 50% of affected individuals. Mutations in *PTPN11* have been shown to be more prevalent in patients with pulmonary stenosis, and less common in patients with hypertrophic cardiomyopathy (2). Mutations in *SOS1*, *RAF1,* and *RIT1* represent 23% of pathogenic variants identified in individuals with Noonan syndrome. More rare causes of Noonan syndrome include mutations in *NRAS, BRAF,* and *MAP2K1.*

Heterozygous mutations in the *CBL* gene are associated with a Noonan-like disorder characterized by developmental delay, facial dysmorphism, cardiac disease, reduced growth and musculoskeletal anomalies. Mutations in *CBL* are also associated with an increased risk for juvenile myelomonocytic leukemia (3).

SHOC2 mutations have been identified in patients with Noonan-like features as well as growth hormone deficiency, hyperactive behavior, slow growing and sparse hair (loose anagen hair), and skin abnormalities These patients have a higher rate of mitral valve abnormalities and septal defects than seen in patients with Noonan syndrome (4).

Mutations in *BRAF, MAP2K1, MAP2K2* and *KRAS* are associated with cardiofaciocutaneous (CFC) syndrome. CFC syndrome is characterized by distinct facial features, heart defects, intellectual disability, and abnormalities of the hair and skin including sparse, dry hair and keratosis of the skin.

Heterozygous mutations in *HRAS* are associated with Costello syndrome, a multi-system disorder characterized by developmental delay and intellectual disability, short stature, distinctive facial and hand features, severe feeding difficulty and failure to thrive.

Neurofibromatosis type 1 shares some features with Noonan syndrome, and is caused by heterozygous mutations in the *NF1* gene. These shared features include short stature, learning disabilities, and café au lait patches. Multiple studies report patients found to have a pathogenic mutation in *NF1* with a Noonan-like phenotype (5, 6)

Our Noonan Syndrome Panel includes sequence and deletion/duplication analysis the 13 genes listed below.

Noonan Syndrome Panel genes			
BRAF	MAP2K1	PTPN11	SOS1
CBL	MAP2K2	RAF1	
KRAS	NF1	RIT1	
HRAS	NRAS	SHOC2	

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Noonan Syndrome Panel (13 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2000
CPT codes:	81406
	81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555

References:

1. Allanson JE, Roberts AE. Noonan Syndrome. In: Pagon RA, Adam MP, Ardinger HH et al., eds. GeneReviews(R). Seattle (WA): University of Washington, Seattle University of Washington, Seattle. All rights reserved., 1993.
2. Tartaglia M, Mehler EL, Goldberg R et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 2001: 29: 465-468.
3. Martinelli S, De Luca A, Stellacci E et al. Heterozygous germline mutations in the CBL tumor-suppressor gene cause a Noonan syndrome-like phenotype. Am J Hum Genet 2010: 87: 250-257.
4. Cordeddu V, Di Schiavi E, Pennacchio LA et al. Mutation of SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose anagen hair. Nat Genet 2009: 41: 1022-1026.
5. Stevenson DA, Viskochil DH, Rope AF et al. Clinical and molecular aspects of an informative family with neurofibromatosis type 1 and Noonan phenotype. Clin Genet 2006: 69: 246-253.
6. Nyström AM, Ekvall S, Allanson J et al. Noonan syndrome and neurofibromatosis type I in a family with a novel mutation in NF1. Clin Genet 2009: 76: 524-534.

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