MAYO CLINIC

1-800-533-1710

Noonan Syndrome and Related Panel

NSRGG

PATIENT NAME				ORDER NUMBER
ABNORMAL, NSRGG				**M229000167**
PATIENT ID SA00154612	DATE OF BIRTH 01/01/1980	AGE 42 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 9/28/2022, 11:00 AM	RECEIVED 9/29/2022, 8:28 AM	REPORTED 9/30/2022, 11:06 AM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location. 7028846 MCL RochesterCampus Rochester MN 55901				CLIENT ORDER NUMBER SA00154612 CLIENT MRN SA00154612

TEST DESCRIPTION

Evaluation of 20 genes associated with Noonan syndrome and related conditions

SPECIMEN

DNA (ul)

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
PTP11 (NM_002834.3)	C.922A>G p.Asn308Asp (p.N308D) Chr12(GRCh37):g.112915523A>G	Heterozygous	Pathogenic

The following heterozygous PATHOGENIC variant was detected: PTPN11 (NM_002834.3), Chr12 (GRCh37):g.112915523A>G, c.922A>G, p.Asn308Asp (p.N308D)

No additional reportable variants were detected within all other tested genes. See the Method section for a complete list of genes evaluated by this assay.

INTERPRETATION

PTPN11 c.922A>G (p.Asn308Asp): The heterozygous c.922A>G (p.Asn308Asp) variant in the PPTN11 gene (MIM: 176876) is classified as pathogenic. The PTPN11 gene encodes SHP2, a member of the protein tyrosine phosphate family of signaling molecules that regulate a variety of cellular processes including cell growth and differentiation. Pathogenic variants in this gene have been associated with autosomal dominant Noonan syndrome, autosomal dominant Noonan syndrome with multiple lentigines (NSML), and in some cases of autosomal dominant Noonan syndrome with overlapping features of cardiofaciocutaneous (CFC) syndrome. The p.Asn308Asp variant identified in this individual is the most common pathogenic variant observed in Noonan syndrome, accounting for approximately 25% of cases (1). The p.Asn308Asp variant has been demonstrated to cause a gain of function of the SHP2 protein, and crystal structure studies indicate that this variant likely results in the open form of SHP2 being more favorable than the closed form, thus resulting in increased activity of the SHP2 protein (2, 3). The p.Asn308Asp variant has been observed in patients with a broad range of Noonan-related sequelae, including pulmonary valve stenosis and other congenital heart defects, hypertrophic cardiomyopathy, and various malignancies (4, 5). Taken together, this result is supportive of a diagnosis of Noonan syndrome or related condition for this individual. Clinical correlation is recommended.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the

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laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:
1. Tartaglia M, Gelb BD. Noonan syndrome and related disorders: genetics and pathogenesis. Annu Rev Genomics Hum Genet. 2005;6:45-68. doi:10.1146/annurev.genom.6.080604.162305 (PMID: 16124853)
2. Fragale A, Tartaglia M, Wu J, Gelb BD. Noonan syndrome-associated SHP2/PTPN11 mutants cause EGF-dependent prolonged GAB1 binding and sustained ERK2/MAPK1 activation. Hum Mutat. 2004;23(3):267-277. doi:10.1002/humu.20005 (PMID: 14974085)
3. Qiu W, Wang X, Romanov V, et al. Structural insights into Noonan/LEOPARD syndrome-related mutants of protein-tyrosine phosphatase SHP2 (PTPN11). BMC Struct Biol. 2014;14:10. Published 2014 Mar 14. doi:10.1186/1472-6807-14-10 (PMID: 24628801)
4. Sznajer Y, Keren B, Baumann C, et al. The spectrum of cardiac anomalies in Noonan syndrome as a result of mutations in the PTPN11 gene. Pediatrics. 2007;119(6):e1325-e1331. doi:10.1542/peds.2006-0211 (PMID: 17515436)
5. Jongmans MC, van der Burgt I, Hoogerbrugge PM, et al. Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation. Eur J Hum Genet. 2011;19(8):870-874. doi:10.1038/ejhg.2011.37 (PMID: 21407260)

METHOD

Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS, and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the presence of deletions and duplications in the genes analyzed. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID NSRGG) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ACTB, ACTG1, BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, MRAS, NRAS, PPP1CB, PTPN11, RAF1, RIT1, RRAS2, SHOC2, SOS1, SOS2, SPRED1

DISCLAIMER

Clinical Correlations
An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

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To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

Technical Limitations
Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Noonan Syndrome and Related Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID NSRGG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

TEST CLASSIFICATION
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

Linnea M. Baudhuin, Ph.D.

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