ARUP LABORATORIES | www.aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: (801) 583-2787, toll free: (800) 522-2787
Julio C. Delgado, MD, MS, Director of Laboratories

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/9/2011
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Noonan Spectrum Disorders Panel, Sequencing

ARUP test code 2010772

Noonan Disorders Sequencing Specimen: Whole Blood

Noonan Disorders Sequencing Interp: Positive

INDICATION FOR TESTING
Short stature and facial features suggestive of Noonan syndrome.

RESULT
One pathogenic variant was detected in the PTPN11 gene.

PATHOGENIC VARIANT
Gene: PTPN11 (NM_002834.3)
Nucleic Acid Change: c.188A>G; Heterozygous
Amino Acid Alteration: p.Tyr63Cys
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.188A>G; p.Tyr63Cys, was detected in the PTPN11 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic PTPN11 variants are inherited in an autosomal dominant manner, and are associated with Noonan syndrome 1 (MIM: 163950), metachondromatosis (MIM: 156250), and LEOPARD syndrome 1 (MIM: 151100).

No additional pathogenic variants were identified in the other targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The PTPN11 c.188A>G, p.Tyr63Cys variant (rs121918459) has been reported in multiple patients diagnosed with Noonan syndrome (Tartaglia 2001, Jongmans 2011, Martinelli 2012, Hashida 2013, Lepri 2014, Okamoto 2015). This variant is located in a structurally important region of the catalytic N-terminal SH2 domain of PTPN11 (Hof 1998), and several additional variants in neighboring codons have also been identified in Noonan patients (Jongmans 2011, Tartaglia 2002, Tartaglia 2006). Functional characterization of the p.Tyr63Cys variant protein indicates over-activation of p38alpha MAP kinase and phosphoERK1/2 upon growth factor signaling (Martinelli 2012, Hashida 2013), consistent with the established disease mechanisms of Noonan syndrome. The variant is listed as pathogenic in ClinVar by multiple clinical laboratories (Variation ID: 13333). Based on the above information, the p.Tyr63Cys variant is classified as pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of

medical screening and management. At risk family members should be offered testing for the identified pathogenic PTPN11 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Benign variants are not included in this report, but are available upon request.

REFERENCES
Hashida N et al. MAPK activation in mature cataract associated with Noonan syndrome. BMC Ophthalmol. 2013;13:70.

Hof P et al. Crystal structure of the tyrosine phosphatase SHP-2. Cell. 1998;92(4):441-450.

Jongmans M et al. Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation. Eur J Hum Genet. 2011;19(8):870-4.

Lepri et al. Diagnosis of Noonan syndrome and related disorders using target next generation sequencing. BMC Med Genet. 2014;15:14

Martinelli S et al. Counteracting effects operating on Src homology 2 domain-containing protein-tyrosine phosphatase 2 (SHP2) function drive selection of the recurrent Y62D and Y63C substitutions in Noonan syndrome. J Biol Chem. 2012;287(32):27066-77.

Okamoto N et al. Targeted next-generation sequencing in the diagnosis of neurodevelopmental disorders. Clin Genet. 2015;88(3):288-92.

Tartaglia M et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet. 2001;29(4):465-8.

Tartaglia M et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet. 2011;70(6):1555-1563.

Tartaglia M et al. Diversity and functional consequences of germline and somatic PTPN11 mutations in human disease. Am J Hum Genet. 2006;78(2):279-290.

This result has been reviewed and approved by Rong Mao, MD, FACMG.

BACKGROUND INFORMATION: Noonan Spectrum Disorders Panel, Sequencing

CHARACTERISTICS: Group of disorders caused by variants in genes involved in the Ras/mitogen activated protein kinase (MAPK) pathway. Common symptoms include short stature, heart defect, developmental delay, coagulation defects, lymphatic dysplasia and undescended testes. Disorders tested include Noonan syndrome (NS), cardiofaciocutaneous (CFC) syndrome, Costello syndrome (CS), LEOPARD syndrome, Legius syndrome, and Noonan-like syndrome with loose anagen hair.

EPIDEMIOLOGY: Prevalence is 1 in 1,000 to 1 in 2,500 for NS.

CAUSE: Pathogenic germline variants in genes involved in the MAPK pathway.

INHERITANCE: Autosomal dominant for all analyzed genes.

CLINICAL SENSITIVITY: Approximately 99 percent for CFC, 80-90 percent for CS, 95 percent for LEOPARD syndrome and 75 percent for NS.

GENES TESTED: BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RASA2, RIT1, SHOC2, SOS1, SOS2, SPRED1

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of a MAPK pathway disorder. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Noonan Disorders Sequencing Specimen	18-344-107410	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Noonan Disorders Sequencing Interp	18-344-107410	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical