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	8/15/2018
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Noonan Syndrome (PTPN11) Sequencing with Reflex to (SOS1) Sequencing

ARUP test code 2004189

NS REFLEX Specimen: Whole Blood

Noonan Syndrome Interpretation: **Positive** *

TEST PERFORMED - 2004189
TEST DESCRIPTION - Noonan Syndrome (PTPN11) Sequencing with Reflex to (SOS1) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the SOS1 gene.

DNA VARIANT
Classification: Pathogenic
Gene: SOS1
Nucleic Acid Change: c.508A>G; Heterozygous
Amino Acid Alteration: p.Lys170Glu

INTERPRETATION
One copy of a pathogenic variant, c.508A>G; p.Lys170Glu, was detected in the SOS1 gene by sequencing; no pathogenic variants were detected by sequencing the PTPN11 gene. This result is consistent with a diagnosis for Noonan syndrome. Any future offspring of this individual would have a 50 percent chance of inheriting the pathogenic variant.

Evidence for variant classification: The SOS1 c.508A>G; p.Lys170Glu variant (rs397517172), is reported in the literature in multiple individuals affected with Noonan syndrome (Denayer 2010, Ko 2008, Lepri 2011). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 40651), and is absent from general population databases (1000 Genomes Project, Exome Variant Server, and Genome Aggregation Database), indicating it is not a common polymorphism. Functional analyses of the variant protein shows increased activation of Ras and ERK, due to structural changes in the autoinhibitory HF domain (Lee 2011, Smith 2013). The lysine at codon 170 is highly conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Based on available information, the p.Lys170Glu variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. This individual's parents and at-risk family members should be offered testing for the identified variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

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

COMMENTS
Reference Sequences: GenBank # NM_002834.3 (PTPN11); NM_005633.3 (SOS1)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Benign variants are not included in this report but are available upon request.

REFERENCES
Denayer E et al. Tumor spectrum in children with Noonan syndrome and SOS1 or RAF1 mutations. Genes Chromosomes Cancer. 2010 Mar;49(3):242-52.

Ko JM et al. PTPN11, SOS1, KRAS, and RAF1 gene analysis, and genotype-phenotype correlation in Korean patients with Noonan syndrome. J Hum Genet. 2008;53(11-12):999-1006.

Lee BH et al. Spectrum of mutations in Noonan syndrome and their correlation with phenotypes. J Pediatr. 2011 Dec;159(6):1029-35.

Lepri F et al. SOS1 mutations in Noonan syndrome: molecular spectrum, structural insights on pathogenic effects, and genotype-phenotype correlations. Hum Mutat. 2011 Jul;32(7):760-72.

Smith MJ et al. NMR-based functional profiling of RASopathies and oncogenic RAS mutations. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4574-9.

This result has been reviewed and approved by Steven Steinberg, Ph.D.

BACKGROUND INFORMATION: Noonan Syndrome (PTPN11) Sequencing with Reflex to (SOS1) Sequencing

CHARACTERISTICS OF NS: Short stature, developmental delay, dysmorphic facial features, congenital heart disease, broad or webbed neck, superior pectus carinatum and inferior pectus excavatum, low-set nipples, cryptorchidism, coagulation, and lymphatic disorders.
INCIDENCE: 1 in 1000 to 1 in 2500
INHERITANCE: Autosomal dominant.
PENETRANCE: Unknown.
CAUSE OF NS: Pathogenic mutations in PTPN11, SOS1, RAF1, KRAS and other unidentified genes.
GENES TESTED: PTPN11 and SOS1.
CLINICAL SENSITIVITY: Approximately 70 percent.
METHODOLOGY: Bidirectional sequencing of the entire PTPN11 coding region and intron-exon boundaries. If no known pathogenic mutations are detected, bidirectional sequencing of the SOS1 coding region and intron-exon boundaries is performed.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations, deep intronic mutations and large deletions/duplications will not be detected. Mutations in genes, other than PTPN11 and SOS1, will not be evaluated.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
NS REFLEX Specimen	18-232-401531	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Noonan Syndrome Interpretation	18-232-401531	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