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Julio Delgado, MD, MS, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/3/2009
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Noonan Syndrome (PTPN11) Sequencing

ARUP test code 0051805

PTPN11 FGS Specimen	Whole Blood

Noonan Syndrome (PTPN11) Sequencing

Positive *

TEST PERFORMED - 0051805
TEST DESCRIPTION - Noonan Syndrome (PTPN11) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the PTPN11 gene.

DNA VARIANT
Classification: Pathogenic
Gene: PTPN11
Nucleic Acid Change: c.1529A>G; Heterozygous
Amino Acid Alteration: p.Gln510Arg

INTERPRETATION
One copy of the pathogenic variant, c.1529A>G; p.Gln510Arg, was detected in the PTPN11 gene by sequencing. This result is consistent with a diagnosis for Noonan or LEOPARD syndrome. Future offspring of this individual will have a 50 percent chance to inherit the causative variant.

Evidence for variant classification: The PTPN11 c.1529A>G; p.Gln510Arg variant (rs121918470), is reported in the literature in multiple individuals affected with Noonan syndrome or LEOPARD syndrome (Atik 2016, Bertola 2005, Carcavilla 2013). Additionally, in testing performed at ARUP Laboratories, this variant has been observed in at least one other individual with symptoms of a RASopathy. This variant is found on a single chromosome (1/251492 alleles) in the Genome Aggregation Database, indicating it is not a common polymorphism. The glutamine at codon 510 is highly conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Additionally, other amino acid substitutions at this codon (Glu, His, and Pro) have been reported in individuals with Noonan syndrome or LEOPARD syndrome and are considered pathogenic (Chen 2019, Gezdirici 2017, Keren 2004, Wakabayashi 2011). Based on available information, the p.Gln510Arg variant is considered to be pathogenic.

RECOMMENDATIONS
Medical genetic consultation, including a discussion of medical screening and management, is indicated. The 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 Sequence: GenBank # NM_002834.3 (PTPN11)
Nucleotide numbering begins at the "A" of the ATG initiation codon.

REFERENCES
Atik T et al. Mutation Spectrum and Phenotypic Features in Noonan Syndrome with PTPN11 Mutations: Definition of Two Novel Mutations. Indian J Pediatr. 2016 Jun;83(6):517-21.
Bertola DR et al. Neurofibromatosis-Noonan syndrome: molecular evidence of the concurrence of both disorders in a patient. Am J Med Genet A. 2005 Jul 30;136(3):242-5.
Carcavilla A et al. LEOPARD syndrome: a variant of Noonan syndrome strongly associated with hypertrophic cardiomyopathy. Rev Esp Cardiol (Engl Ed). 2013 May;66(5):350-6.
Chen H et al. Clinical and mutation profile of pediatric patients with RASopathy-associated hypertrophic cardiomyopathy: results from a Chinese cohort. Orphanet J Rare Dis. 2019 Feb 7;14(1):29.
Gezdirici A et al. How necessary is to analyze PTPN11 gene in fetuses with first trimester cystic hygroma and normal karyotype? J Matern Fetal Neonatal Med. 2017 Apr;30(8):938-941.
Keren B et al. PTPN11 mutations in patients with LEOPARD syndrome: a French multicentric experience. J Med Genet. 2004 Nov;41(11):e117.
Wakabayashi Y et al. Implantable cardioverter defibrillator for progressive hypertrophic cardiomyopathy in a patient with LEOPARD syndrome and a novel PTPN11 mutation Gln510His. Am J Med Genet A. 2011 Oct;155A(10):2529-33.

This result has been reviewed and approved by Yuan Ji, Ph.D.

BACKGROUND INFORMATION: Noonan Syndrome (PTPN11) Sequencing

CHARACTERISTICS OF NOONAN SYNDROME (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.
CHARACTERISTICS OF LEOPARD SYNDROME: Lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness.
INCIDENCE: 1 in 1000 to 1 in 2500 for NS; rare for LEOPARD syndrome.
INHERITANCE: Autosomal dominant.
PENETRANCE: Unknown.
CAUSE OF NS: Deleterious mutations in PTPN11, SOS1, RAF1, KRAS and other unidentified genes.
CAUSE OF LEOPARD SYNDROME: Mutations in PTPN11 exons 7 and 12 as well as other unidentified genes.
GENE TESTED: PTPN11.
CLINICAL SENSITIVITY; 50 percent of NS is due to PTPN11 mutations; unknown for LEOPARD syndrome.
METHODOLOGY: Bidirectional sequencing of the entire PTPN11 coding region and intron-exon boundaries.
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, will not be detected. This assay is not designed to detect somatic variants associated with malignancy. Interpretation of this test result may be impacted if the patient has had an allogeneic stem cell transplantation.

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

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
PTPN11 FGS Specimen	19-242-133214	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Noonan Syndrome (PTPN11) Sequencing	19-242-133214	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