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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/7/1986
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Noonan Spectrum Disorders Panel, Sequencing, Fetal

ARUP test code 2010769

Maternal Contamination Study Fetal Spec	Fetal Cells Single fetal genotype present; no maternal cells present. Fetal and maternal samples were tested using STR markers to rule out maternal cell contamination.
Maternal Contam Study, Maternal Spec	Whole Blood For quality assurance purposes, ARUP Laboratories will confirm the above result at no charge following delivery. Order Confirmation of Fetal Testing and include a copy of the original fetal report (or the mother's name and date of birth) with the test submission. Please contact an ARUP genetic counselor at (800) 242-2787 extension 2141 prior to specimen submission.
Noonan Disorders Seq. Specimen, Fetal	Cultured Amnio
Noonan Disorders Seq. Interp, Fetal	Positive INDICATION FOR TESTING Abnormal ultrasound - cystic hygroma. RESULT One pathogenic variant was detected in the RIT1 gene. PATHOGENIC VARIANT Gene: RIT1 (NM_006912.6) Nucleic Acid Change: c.246T>G; Heterozygous Amino Acid Alteration: p.Phe82Leu Inheritance: Autosomal Dominant INTERPRETATION One copy of a pathogenic variant, c.246T>G; p.Phe82Leu, was detected in the RIT1 gene by massively parallel sequencing and confirmed by Sanger sequencing in this prenatal sample. Pathogenic germline RIT1 variants are inherited in an autosomal dominant manner and are associated with Noonan syndrome 8 (MIM: 615355). This molecular result is consistent with a diagnosis of Noonan syndrome. No additional pathogenic variants were identified in the 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.

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

Evidence for variant classification:
The RIT1 c.246T>G; p.Phe82Leu variant (rs730881014), is reported in the literature in multiple individuals affected with Noonan syndrome, including several cases in which the variant was de novo (Aoki 2013, Bertola 2014, Cave 2016, Joyce 2016, Kiel 2014, Kouz 2016, Yaoita 2016). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 181522), and is absent from general population databases (1000 Genomes Project, Exome Variant Server, and Genome Aggregation Database), indicating it is not a common polymorphism. Additionally, other variants at this codon (c.246T>A; p.Phe82Leu and p.Phe82Val/Ile/Ser) have been reported in individuals with Noonan syndrome and are considered pathogenic (Aoki 2013, Cave 2016, Kouz 2016, Yaoita 2016). The phenylalanine at codon 82 is highly conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Functional analyses of the p.Phe82Leu variant protein show increased RIT1 activity (Aoki 2013, Berger 2014, Yaoita 2016), and codon 82 lies within the functionally conserved switch II domain where many pathogenic variants in RIT1 are located (Aoki 2016). Based on available information, the c.246T>G; p.Phe82Leu variant is considered pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members, including the parents, should be offered testing for the identified pathogenic RIT1 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not reported.

REFERENCES
Aoki Y et al. Gain-of-function mutations in RIT1 cause Noonan syndrome, a RAS/MAPK pathway syndrome. Am J Hum Genet. 2013 Jul 11;93(1):173-80.
Aoki Y et al. Recent advances in RASopathies. J Hum Genet. 2016 Jan;61(1):33-9.
Berger AH et al. Oncogenic RIT1 mutations in lung adenocarcinoma. Oncogene. 2014 Aug 28;33(35):4418-23.
Bertola DR et al. Further evidence of the importance of RIT1 in Noonan syndrome. Am J Med Genet A. 2014 Nov;164A(11):2952-7.
Cave H et al. Mutations in RIT1 cause Noonan syndrome with possible juvenile myelomonocytic leukemia but are not involved in acute lymphoblastic leukemia. Eur J Hum Genet. 2016 Aug;24(8):1124-31.
Joyce S et al. The lymphatic phenotype in Noonan and Cardiofaciocutaneous syndrome. Eur J Hum Genet. 2016 May;24(5):690-6.
Kiel C and Serrano L. Structure-energy-based predictions and network modelling of RASopathy and cancer missense mutations. Mol Syst Biol. 2014 May 6;10:727.
Kouz K et al. Genotype and phenotype in patients with Noonan syndrome and a RIT1 mutation. Genet Med. 2016 Dec;18(12):1226-1234.
Yaoita M et al. Spectrum of mutations and genotype-phenotype analysis in Noonan syndrome patients with RIT1 mutations. Hum Genet. 2016 Feb;135(2):209-22.

This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: Noonan Spectrum Disorders Panel, Sequencing, Fetal

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.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Maternal Contamination Study Fetal Spec	21-321-401332	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Maternal Contam Study, Maternal Spec	21-321-401332	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Noonan Disorders Seq. Specimen, Fetal	21-321-401332	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Noonan Disorders Seq. Interp, Fetal	21-321-401332	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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