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

Physician: Doctor, Example

## Patient: Patient, Example

| | |
|---|---|
| **DOB** | 12/9/2003 |
| **Gender:** | Male |
| **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 | Negative |

INDICATION FOR TESTING
Suspected Noonan syndrome presenting with short stature, scoliosis, learning difficulties and congenital heart disease.

RESULT
No pathogenic variants were detected in any of the genes tested.

INTERPRETATION
No pathogenic variants were identified by massively parallel sequencing of the coding regions and exon-intron boundaries of the genes tested. This result decreases the likelihood of, but does not exclude, a diagnosis of a Noonan spectrum disorder. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

RECOMMENDATIONS
This test does not detect all variants associated with Noonan spectrum disorders. Medical screening and management should rely on clinical findings and family history. Genetic consultation is recommended.

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

This result has been reviewed and approved by Rong Mao, M.D.

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

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 | 18-344-107425 | 00/00/0000 00:00 | 00/00/0000 00:00 | 00/00/0000 00:00 |
| Noonan Disorders Sequencing Interp | 18-344-107425 | 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