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

Physician: Doctor, Example

Patient: Patient, Example

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

Distal Arthrogryposis Panel, Sequencing

ARUP test code 3003917

Distal Arthrogryposis Specimen	Whole Blood
Distal Arthrogryposis Interp	Positive

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

RESULT
One pathogenic variant was detected in the MYH3 gene.

PATHOGENIC VARIANT
Gene: MYH3 (NM_002470.3)
Nucleic Acid Change: c.2015G>A; Heterozygous
Amino Acid Alteration: p.Arg672His
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.2015G>A; p.Arg672His, was detected in the MYH3 gene by massively parallel sequencing. Pathogenic MYH3 variants are inherited in an autosomal dominant manner, and are associated with distal arthrogryposis (MIM: 193700). This result is consistent with a diagnosis of distal arthrogryposis. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The MYH3 c.2015G>A; p.Arg672His variant is one of the most common pathogenic variants reported in patients with distal arthrogryposis, Freeman-Sheldon syndrome type (Toydemir 2006). Clinical manifestations are highly variable.

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 MYH3 variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Toydemir R et al. Mutations in embryonic myosin heavy chain (MYH3) cause Freeman-Sheldon syndrome and Sheldon-Hall syndrome. Nat Genet. 2006 38(5):561-5.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Distal Arthrogryposis Panel, Sequencing

CHARACTERISTICS: Distal arthrogryposes (DA) are a subset of arthrogryposis disorders that involve contractures of the distal parts of the limbs. The contractures are congenital but typically do not have primary neurologic and/or muscle disease; the shared findings among DA include a consistent pattern of hand and foot involvement, limited involvement of the proximal joints, and variable expressivity. There are multiple types of DA caused by different genes (genetic heterogeneity).

PREVALENCE: Approximately 1 in 3,000.

CAUSE: Pathogenic germline variants in genes associated with decreased fetal movement leading to contractures.

INHERITANCE: Autosomal dominant and autosomal recessive.

GENES TESTED: ECEL1, FBN2, MYBPC1, MYH3, MYH8*, NALCN*, PIEZO2*, TNNI2, TNNT3, TPM2

*One or more exons are not covered by sequencing for the indicated gene; see Limitations section below.

METHODOLOGY: 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.

ANALYTICAL SENSITIVITY/SPECIFICITY: 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 heritable form of arthrogryposis. 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 massively 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 mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
MYH8 (NM_002472) exon 5
NALCN (NM_001350748) exon 19
PIEZO2 (NM_022068) exon 4

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
Distal Arthrogryposis Specimen	22-301-101332	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Distal Arthrogryposis Interp	22-301-101332	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