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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1752
Sex:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

SHOX Deficiency Disorders, Sequencing and Deletion/Duplication

ARUP test code 3004603

SHOX Specimen	Whole Blood
SHOX Interp	Positive

RESULT
One pathogenic variant was detected in the SHOX gene.

PATHOGENIC VARIANT
Gene: SHOX (NM_000451.3)
Nucleic Acid Change: SHOX full gene deletion; heterozygous

INTERPRETATION
One pathogenic variant, a SHOX full gene deletion, has been identified in the SHOX gene by multiplex ligation-dependent probe amplification (MLPA) analysis. This molecular result is consistent with a diagnosis of a SHOX deficiency disorder; however, clinical manifestations are variable. Full or partial deletions of the SHOX gene, as well as its surrounding regions, on a single chromosome result in haploinsufficiency of SHOX, and are causative for SHOX deficiency disorders such as Leri-Weill dyschondrosteosis (LWD) or idiopathic/isolated short stature (ISS). In addition, this result decreases the likelihood of, but does not exclude, a diagnosis of Langer mesomelic dysplasia (LMD), which is associated with biallelic SHOX inactivation. This individuals offspring have a 50 percent chance of inheriting the pathogenic deletion regardless of sex.

No disease-causing variants were identified in the SHOX gene by massive parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The SHOX full gene deletion and deletions in this region have been described in individuals with idiopathic short stature or Leri-Weill dyschondrosteosis (Chen, 2009). This deletion involves a portion of the PPP2R3B as well as the entire SHOX gene including upstream and downstream enhancer regions. However, the exact breakpoints of this deletion were not determined. Based on available information, this deletion is considered pathogenic.

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 deletion (Deletion/Duplication Analysis by MLPA, ARUP test code 3003144). If clinically indicated, this individuals reproductive partner should be offered SHOX testing (ARUP test code #######), as biallelic SHOX inactivation is associated with Langer mesomelic

dysplasia (LMD).

COMMENTS
Likely benign and benign variants are not reported.

REFERENCES
Chen J, et al. Enhancer deletions of the SHOX gene as a frequent cause of short stature: the essential role of a 250 kb downstream regulatory domain. J Med Genet. 2009;46(12):834-839. PMID: 19578035

BACKGROUND INFORMATION: SHOX Deficiency Disorders, Sequencing and Deletion/Duplication

CHARACTERISTICS: Pathogenic variants in the SHOX gene result in a spectrum of disorders due to haploinsufficiency of the SHOX gene. Clinical features often include short stature, mesomelia (shortening of the lower portion of arm and leg), and abnormal alignment of the radius, ulna, and carpal bones at the wrist (Madelung deformity). Variable expressivity results in some individuals only affected with isolated short stature (ISS), while others have short stature and additional findings resulting in syndrome disorders (e.g., Leri-Weill dyschondrosteosis [LWD] or Langer mesomelic dysplasia [LMD]).

EPIDEMIOLOGY: Prevalence of SHOX deficiency disorders is estimated to be at least 1 in 1,000 individuals.

CAUSE: A single pathogenic variant in the SHOX gene causes ISS or LWD. Biallelic pathogenic variants in the SHOX gene cause LMD.

INHERITANCE: SHOX is located in the pseudoautosomal region 1 (PAR1) on the X and Y chromosomes and escapes X-inactivation. Thus, inheritance is pseudoautosomal dominant for ISS and LWD, and pseudoautosomal recessive for LMD.

PENETRANCE: High, with variable expressivity

CLINICAL SENSITIVITY: At least 90 percent in individuals with SHOX deficiency disorders. Approximately 10 percent of individuals with LWD do not have a demonstrable SHOX pathogenic variant.

GENE TESTED: SHOX (NM_000451)
Exon 6b (NM_006883) is not covered by sequencing.

METHODOLOGY: Probe hybridization-based 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 to confirm reported variants that do not meet acceptable quality metrics. Multiplex ligation-dependent probe amplification (MLPA) of the SHOX gene.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. The analytical sensitivity for MLPA is greater than 99 percent.

LIMITATIONS: A negative result does not exclude a SHOX deficiency disorder. This test only detects variants within the coding regions and intron-exon boundaries of the SHOX gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications

may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

SNVs and indels will not be called in the following regions due to technical limitations of the assay: SHOX (NM_006883) exon 6, also known as exon 6b.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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
SHOX Specimen	22-136-101134	5/16/2022 8:37:00 AM	5/16/2022 8:37:57 AM	5/16/2022 8:52:00 AM
SHOX Interp	22-136-101134	5/16/2022 8:37:00 AM	5/16/2022 8:37:57 AM	5/16/2022 8:52:00 AM

END OF CHART

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