ARUP LABORATORIES | 800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Jonathan R. Genzen, MD, PhD, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/1/2018
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

SHOX Deficiency Disorders, Sequencing and Deletion/Duplication

ARUP test code 3004603

SHOX Specimen: Whole Blood

SHOX Interp: Negative

RESULT
No pathogenic variants were detected in the SHOX gene.

INTERPRETATION
No pathogenic variants were detected in the SHOX gene. This result decreases the likelihood of, but does not exclude, a diagnosis of a SHOX deficiency disorder. Please refer to the background information included in this report for the methodology and limitations of this test.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. If this individual has a family history, determination of a causative familial variant in an affected family member is necessary for optimal interpretation of this negative result. Further testing may be warranted if there is a familial variant that is not detectable by this assay. Genetic consultation is recommended.

COMMENTS
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

This result has been reviewed and approved by [redacted]

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.

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

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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
SHOX Specimen	23-073-401248	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SHOX Interp	23-073-401248	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