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

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/6/2020
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication

ARUP test code 2012015

Skeletal Dysplasia Panel Specimen: Whole Blood

Skeletal Dysplasia Panel Interp: **Positive** *

INDICATION FOR TESTING
Abnormal ribs/small chest, bowed/fractured bones, shortening of arms and legs, hypoplastic lungs.

RESULT
One likely pathogenic variant was detected in the COL2A1 gene. One variant of uncertain significance was detected in the DYNC2H1 gene.

LIKELY PATHOGENIC VARIANT
Gene: COL2A1 (NM_001844.4)
Nucleic Acid Change: c.3464G>A; Heterozygous
Amino Acid Alteration: p.Gly1155Asp
Inheritance: Autosomal Dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: DYNC2H1 (NM_001080463.1)
Nucleic Acid Change: c.476T>C; Heterozygous
Amino Acid Alteration: p.Leu159Ser
Inheritance: Autosomal Recessive

INTERPRETATION
One copy of a likely pathogenic variant, c.3464G>A; p.Gly1155Asp, was detected in the COL2A1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic germline COL2A1 variants are inherited in an autosomal dominant manner and are associated with a variety of phenotypes, including Stickler syndrome type I (MIM 108300), spondyloepiphyseal dysplasia congenita (MIM 183900), achondrogenesis type II (MIM 200610), Kniest dysplasia (MIM 156550), and spondyloperipheral dysplasia (MIM 271700). This result is consistent with a diagnosis of a COL2A1-related disorder.

In addition, one copy of a variant of uncertain clinical significance, c.476T>C; p.Leu159Ser, was detected in the DYNC2H1 gene by massively parallel sequencing. Pathogenic variants in DYNC2H1 are associated with autosomal recessive short-rib thoracic dysplasia 3 with or without polydactyly (MIM: 613091). Therefore, if the DYNC2H1 variant is later determined to be pathogenic, this patient would be at least a carrier of short-rib thoracic dysplasia 3. However, our analysis cannot detect variants in deep intronic or regulatory regions; therefore, the presence of additional pathogenic variants in these regions cannot be excluded.

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

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and the limitations of this test.

Evidence for variant classification:
The COL2A1 c.3464G>A; p.Gly1155Asp variant, to our knowledge, is not reported in the medical literature or gene-specific databases. This variant is also absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. The glycine at codon 1155 is highly conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. This variant disrupts the repeating Gly-X-Y sequence motif of the collagen triple helix and is predicted to impair collagen function (Barat-Houari 2016). Indeed, another variant at this residue (p.Gly1155Val) has been reported in an individual affected with congenital spondyloepiphyseal dysplasia (Terhal 2012). Based on available information, the p.Gly1155Asp variant is considered to be likely pathogenic.

The DYNC2H1 c.476T>C; p.Leu159Ser variant (rs201510850), to our knowledge, is not reported in the medical literature but is reported in the Leiden open variation database (copied from Exome Variant Server, see link). This variant is found in the African population with an allele frequency of 0.22% (49/22318 alleles) in the Genome Aggregation Database. The leucine at codon 159 is moderately conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is tolerated. Due to limited information, the clinical significance of the p.Leu159Ser variant is uncertain at this time.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Due to the complex nature of this result, genetic consultation is recommended. At-risk family members should be offered testing for the identified likely pathogenic COL2A1 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Because parental somatic or germline mosaicism for the identified COL2A1 likely pathogenic variant cannot be excluded, this individual's parents should be offered prenatal diagnosis in future pregnancies (Familial Mutation, Targeted Sequencing, Fetal; ARUP test code 2001980). Surveillance of the literature for new information concerning the uncertain DYNC2H1 variant is recommended.

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not included in this report.

REFERENCES
Barat-Houari M et al. Mutation Update for COL2A1 Gene Variants Associated with Type II Collagenopathies. Hum Mutat. 2016 Jan;37(1):7-15.

Link to Leiden open variation database:
http://databases.lovd.nl/whole_genome/variants/0001138966#00004984

Terhal PA et al. Mutation-based growth charts for SEDC and other COL2A1 related dysplasias. Am J Med Genet C Semin Med Genet. 2012 Aug 15;160C(3):205-16.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication

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

CHARACTERISTICS: Skeletal dysplasias (SD) are a heterogeneous group of >350 disorders characterized by abnormal growth of cartilage or bone. Some may be detectable prenatally while others are not identified until birth or later childhood. Symptoms may include: shortening, bowing, fracturing, thinning, thickening, or under-mineralization of the bones, abnormal ribs, small chest circumference and extra fingers or toes.

EPIDEMIOLOGY: Incidence is 1 in 5000 births.

CAUSE: Pathogenic germline variants in genes associated with cartilage and bone growth.

INHERITANCE: Autosomal recessive, autosomal dominant, X-linked recessive and X-linked dominant dependent on the causative gene.

CLINICAL SENSITIVITY: Dependent on the specific SD; 99 percent for achondroplasia and thanatophoric dysplasia; >90 percent for achondrogenesis type 1B, diastrophic dysplasia and campomelic dysplasia.

GENES TESTED: AGPS, ALPL, ARSE, CANT1**, COL1A1, COL1A2, COL2A1, COMP**, CRTAP, DDR2**, DLL3, DYNC2H1, EBP, EVC*, EVC2, FGFR1, FGFR2, FGFR3, FKBP10, FLNA, FLNB, GDF5**, GNPAT, HSPG2**, ICK, IFT80, LBR, LIFR, NEK1, P3H1, PCNT**, PEX7, POR, PPIB, PTH1R**, RUNX2, SERPINH1, SLC26A2, SLC35D1, SOX9, TRIP11, TRPV4**, TTC21B, WDR19, WDR35

* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
** - Deletion/duplication detection is not available for this gene.

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. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. 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 diagnosis of a skeletal dysplasia. 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 and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. 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.

The following regions are not sequenced due to technical limitations of the assay:
EVC(NM_153717) exon(s) 1

Single exon deletions/duplications will not be called for the

following exons:
ARSE(NM_000047) 9;ARSE(NM_001282631) 1;COL1A1(NM_000088) 5;COL1A2(NM_000089) 20,22;EVC(NM_001306092) 12;PEX7(NM_000288) 1

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Skeletal Dysplasia Panel Specimen	20-069-400342	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Skeletal Dysplasia Panel Interp	20-069-400342	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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