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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	Unknown
Gender:	Unknown
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

RESULT
One pathogenic variant was detected in the COL1A1 gene.

PATHOGENIC VARIANT
Gene: COL1A1 (NM_000088.4)
Nucleic Acid Change: c.2596G>A; Heterozygous
Amino Acid Alteration: p.Gly866Ser
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.2596G>A; p.Gly866Ser, was detected in the COL1A1 gene by massively parallel sequencing. Pathogenic germline COL1A1 variants are inherited in an autosomal dominant manner, and are associated with osteogenesis imperfecta type I (MIM: 166200), osteogenesis imperfecta type II (MIM: 166210), osteogenesis imperfecta type III (MIM: 259420) and osteogenesis imperfecta type IV (MIM: 166220). This result is consistent with a diagnosis of osteogenesis imperfecta.

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 COL1A1 c.2596G>A; p.Gly866Ser variant (rs67445413) is reported in several individuals with osteogenesis imperfecta, including the variant occurring de novo in several individuals (Higuchi 2021, Lindahl 2015, Yin 2018, Zhytnik 2019). This variant is reported in the ClinVar database (Variation ID: 425612) and is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The glycine at codon 866 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.979). This codon is located in a Gly-X-Y triple helix repeat domain, and glycine substitutions are the most frequent pathogenic alterations in this region (Ben Amor 2011). Based on available information, this variant is classified as 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 COL1A1 variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS

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

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
Ben Amor I et al. Genotype-phenotype correlations in autosomal dominant osteogenesis imperfecta. J Osteoporos. 2011; 2011:540178. PMID: 21912751.
Higuchi Y et al. Genetic analysis in Japanese patients with osteogenesis imperfecta: Genotype and phenotype spectra in 96 probands. Mol Genet Genomic Med. 2021 Jun;9(6):e1675. PMID: 33939306.
Lindahl K et al. Genetic epidemiology, prevalence, and genotype-phenotype correlations in the Swedish population with osteogenesis imperfecta. Eur J Hum Genet. 2015 Aug;23(8):1042-50. PMID: 25944380.
Yin X et al. Identification of a de novo fetal variant in osteogenesis imperfecta by targeted sequencing-based noninvasive prenatal testing. J Hum Genet. 2018 Nov;63(11):1129-1137. PMID: 30131598.
Zhytnik L et al. De novo and inherited pathogenic variants in collagen-related osteogenesis imperfecta. Mol Genet Genomic Med. 2019 Mar;7(3):e559. PMID: 30675999.

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Skeletal dysplasias are a heterogeneous group of more than 400 disorders characterized by abnormal growth of cartilage or bone. Clinical features may include shortening, bowing, fracturing, thinning, thickening, or under mineralization of the bones; abnormal ribs; small chest circumference; and extra fingers or toes. Some disorders may be detectable prenatally, while others are not identified until birth or later childhood.

EPIDEMIOLOGY: Collective incidence of 1 in 5000

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

INHERITANCE: Contingent on etiology; autosomal recessive, autosomal dominant, and X-linked inheritance, depending on the causative gene

CLINICAL SENSITIVITY: Dependent on the specific skeletal dysplasia; 99 percent for achondroplasia and thanatophoric dysplasia; greater than 95 percent for COL1A1/2 osteogenesis imperfecta; greater than 90 percent for achondrogenesis type 1B, diastrophic dysplasia, and campomelic dysplasia.

GENES TESTED: AGPS, ALPL, ARSL, CANT1, CCN6, CILK1, COL1A1, COL1A2,* COL2A1, COL10A1, COL11A1, COL11A2, COMP, CRTAP, DDR2, DLL3, DYM,* DYNC2H1, EBP, EVC,* EVC2, FGFR1,* FGFR2, FGFR3, FKBP10, FLNA, FLNB, GDF5, GNPAT, HSPG2, IFT80, INPPL1, LBR, LIFR, NEK1,* NPR2, P3H1, PCNT, PEX7, POR,* PPIB, PTH1R, RUNX2, SERPINH1, SLC26A2, SLC35D1, SMARCAL1, SOX9, TRIP11, TRPV4, TTC21B, WDR19, WDR35
*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

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. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large

deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: 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. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

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. Variants in the chr17:70,119,704-70,119,743 region of SOX9 exon 3 may not be detected. 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, including deletions/duplications in the upstream regulatory region of SOX9. 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. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. 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) mutations, 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.

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:
COL1A2(NM_000089) 3; EVC (NM_153717) 1; EVC(NM_001306090) 1; EVC(NM_001306092) 1;
FGFR1(NM_001354367) 18; FGFR1(NM_001354369) 18;
FGFR1(NM_001354370) 17; DYM(NM_001353212) 14; DYM(NM_001353213) 14; DYM(NM_001353214) 14; DYM(NM_001353215) 14;
DYM(NM_001374428) 15; DYM(NM_001374429) 14; DYM(NM_001374430) 14 18; DYM(NM_001374431) 14; DYM(NM_001374432) 13;
DYM(NM_001374433) 17; DYM(NM_001374441) 9; NEK1(NM_001374422) 17; NEK1(NM_001374423) 16; POR (NM_001382655) 3

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
Skeletal Dysplasia Panel Specimen	22-311-111117	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Skeletal Dysplasia Panel Interp	22-311-111117	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

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