Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

Patient: PROD, OINGS val

DOB	5/17/2021
Gender:	Female
Patient Identifiers:	30520
Visit Number (FIN):	30826
Collection Date:	5/18/2021 10:11

Osteogenesis Imperfecta and Low Bone Density Panel, Sequencing

ARUP test code 3001607

Osteogenesis Imperfecta Specimen	Whole Blood

Osteogenesis Imperfecta Interp	Positive

INDICATION FOR TESTING
Confirm diagnosis.

RESULT
One pathogenic variant was detected in the COL1A1 gene.

PATHOGENIC VARIANT
Gene: COL1A1 (NM_000088.3)
Nucleic Acid Change: c.1094G>C, Heterozygous
Amino Acid Alteration: p.Gly365Ala
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.1094G>C; p.Gly365Ala, was detected in the COL1A1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic COL1A1 variants are inherited in an autosomal dominant manner, and are associated with osteogenesis imperfecta (OI, MIM:166210).

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. 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 COL1A1 c.1094G>C, p.Gly365Ala variant (rs66494876) is reported in the literature in at least one individual affected with OI (Marini 2007). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. The glycine at codon 365 is highly conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. This codon is located in a triple helix repeat domain, and glycine substitutions are the most frequent pathogenic alterations in this region (Ben Amor 2011). Additionally, other variants at this codon have been reported in individuals with osteogenesis imperfecta (Li 2019, Marini 2007). Based on available information, this variant is considered to be 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

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

(Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

REFERENCES
Ben Amor I et al. Genotype-phenotype correlations in autosomal dominant osteogenesis imperfecta. J Osteoporos. 2011; 2011:540178.

Li L et al. Genotypic and phenotypic characterization of Chinese patients with osteogenesis imperfecta. Hum Mutat. 2019 May;40(5):588-600.

Marini JC et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. Hum Mutat. 2007 Mar;28(3):209-21.

This result has been reviewed and approved by Yuan Ji, Ph.D.

BACKGROUND INFORMATION: Osteogenesis Imperfecta and Low Bone Density Panel, Sequencing

CHARACTERISTICS: Although osteoporosis is present in 10 percent of the US population, monogenetic causes of osteoporosis, such as osteogenesis imperfecta (OI), are rare. OI is defined by a continuum of phenotypes ranging from individuals with perinatal lethal OI, severe skeletal deformities, dentinogenesis imperfecta (DI) and severe short stature to individuals with normal stature, dentition and lifespan but mild predisposition to fractures. This panel targets monogenic forms of OI and low bone density; it excludes genes causative for hypophosphatemic rickets and osteopetrosis.
EPIDEMIOLOGY: 6 to 7 per 100,000 for OI.
CAUSE: Varies depending on causative gene; pathogenic germline variants in COL1A1 and COL1A2 are causative for 90 percent of OI.

INHERITANCE: Varies depending on causative gene; autosomal dominant for COL1A1 and COL1A2.

CLINICAL SENSITIVITY: Greater than 90 percent for OI and unknown for other monogenic causes of low bone density.

GENES TESTED: ALPL, ANO5, BMP1, CASR, CLCN5, COL1A1, COL1A2, CREB3L1, CRTAP, CYP27B1, FKBP10, GORAB, IFITM5, LRP5*, P3H1, P4HB, PLOD2, PLS3, PPIB, SEC24D, SERPINF1, SERPINH1, SLC34A3, SP7, SPARC, TMEM38B, WNT1.

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

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. 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 a monogenic form of OI or low bone density. This test only detects variants

within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants, large deletions/duplications/inversions 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 has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

The following region is not sequenced due to technical limitations of the assay:
LRP5 (NM_002335) exon 1

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
Osteogenesis Imperfecta Specimen	21-138-105100	5/18/2021 10:11:00 AM	5/18/2021 10:11:45 AM	5/18/2021 10:17:00 AM
Osteogenesis Imperfecta Interp	21-138-105100	5/18/2021 10:11:00 AM	5/18/2021 10:11:45 AM	5/18/2021 10:17:00 AM

END OF CHART

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