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

Stickler Syndrome Panel, Sequencing

ARUP test code 3001613

Stickler Syndrome Specimen	Whole Blood

Stickler Syndrome Interp

Positive

RESULT
One pathogenic variant was detected in the COL2A1 gene.

PATHOGENIC VARIANT
Gene: COL2A1 (NM_001844.5)
Nucleic Acid Change: c.3121G>A; Heterozygous
Amino Acid Alteration: p.Gly1041Ser
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.3121G>A; p.Gly1041Ser, was detected in the COL2A1 gene by massively parallel sequencing. Pathogenic germline COL2A1 variants are inherited in an autosomal dominant manner, and are associated with several skeletal and ocular disorders including Stickler syndrome type I (MIM: 108300), achondrogenesis type II/hypochondrogenesis (MIM 200610), Kniest dysplasia (MIM 156550), Legg-Calve-Perthes disease (MIM: 150600), spondyloepiphyseal dysplasia congenita (MIM 183900), and spondyloperipheral dysplasia (MIM 271700). This result is consistent with a type II collagenopathy. Clinical correlation is recommended.

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 COL2A1 c.3121G>A; p.Gly1041Ser variant has been reported in the literature in several individuals diagnosed with skeletal dysplasia and is reported to occur de novo (Huang 2018, Meredith 2007, Scocchia 2019, Yamamoto 2020). The variant is reported as pathogenic in the ClinVar database (Variation ID: 1224342) but is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The glycine at codon 1041 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.993). Additionally, 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). 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 COL2A1 variant

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

(Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. 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
Barat-Houari M et al. Mutation Update for COL2A1 Gene Variants Associated with Type II Collagenopathies. Hum Mutat. 2016 Jan;37(1):7-15. PMID: 26443184.
Huang Z et al. Genetic Evaluation of 114 Chinese Short Stature Children in the Next Generation Era: a Single Center Study. Cell Physiol Biochem. 2018;49(1):295-305. PMID: 30138938.
Meredith SP et al. Significant ocular findings are a feature of heritable bone dysplasias resulting from defects in type II collagen. Br J Ophthalmol. 2007 Sep;91(9):1148-51. PubMed: 17347327.
Scocchia A et al. Clinical whole genome sequencing as a first-tier test at a resource-limited dysmorphology clinic in Mexico. NPJ Genom Med. 2019 Feb 14;4:5. PMID: 30792901.
Yamamoto K et al. Parental somatogonadal COL2A1 mosaicism contributes to intrafamilial recurrence in a family with type 2 collagenopathy. Am J Med Genet A. 2020 Mar;182(3):454-460. PMID: 31854518.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Stickler Syndrome Panel, Sequencing

CHARACTERISTICS: Stickler syndrome and related disorders are a group of connective tissue disorders characterized by ocular abnormalities, hearing loss, and skeletal or joint problems.
INCIDENCE: Approximately 1/7500 to 1/9000 newborns
CAUSE: Pathogenic germline variants in certain genes associated with collagen formation.
INHERITANCE: Most cases are autosomal dominant; there are rare autosomal recessive causes.
PENETRANCE: 100 percent
CLINICAL SENSITIVITY: Variable, dependent on phenotype
GENES TESTED: COL11A1, COL11A2, COL2A1, COL9A1, COL9A2, COL9A3, VCAN
METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) is used for data analysis.
ANALYTICAL SENSITIVITY/SPECIFICITY: 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 diagnosis of Stickler syndrome or a related disorder. 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. 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 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 are not analyzed.

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
Stickler Syndrome Specimen	22-311-111125	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Stickler Syndrome Interp	22-311-111125	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