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

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/7/2021
Gender:	Female
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	DNA

Stickler Syndrome Interp

Positive

INDICATION FOR TESTING
Confirm Diagnosis

RESULT
One pathogenic variant was detected in the COL2A1 gene.

PATHOGENIC VARIANT
Gene: COL2A1 (NM_001844.4)
Nucleic Acid Change: c.2710C>T; Heterozygous
Amino Acid Alteration: p.Arg904Cys
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.2710C>T; p.Arg904Cys, 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 several skeletal 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 diagnosis of a COL2A1-related disorder. Clinical correlation is recommended.

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 limitations of this test.

Evidence for variant classification:
The COL2A1 c.2710C>T; p.Arg904Cys variant (rs121912882), also known in traditional nomenclature as Arg704Cys, is reported in the literature in multiple individuals and families affected with Stickler syndrome type I or a related skeletal dysplasia (Ballo 1998, Barat-Houari 2016, Goyal 2016, Guo 2017, Hoornaert 2006, Nagendran 2012, Tomcikova 2018, Wang 2016, Yang 2018). In one family, the variant was observed to segregate with disease (Ballo 1998), while in another family the variant was found in the proband but neither parent, suggesting a de novo origin (Guo 2016). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. The arginine at codon 904 is highly conserved, it occurs in the collagen triple helix domain, and computational analyses (SIFT, PolyPhen-2) predict that this

variant is deleterious. Arginine-to-cysteine substitutions in the COL2A1 triple helix domain have been reported in association with a spectrum of skeletal phenotypes and can interfere with collagen stability, trafficking, or fibril formation (Hoornaert 2006). Based on available information, the p.Arg904Cys variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members may consider testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

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

REFERENCES
Ballo R et al. Stickler-like syndrome due to a dominant negative mutation in the COL2A1 gene. Am J Med Genet. 1998 Oct 30;80(1):6-11.

Barat-Houari M et al. The expanding spectrum of COL2A1 gene variants IN 136 patients with a skeletal dysplasia phenotype. Eur J Hum Genet. 2016 Jul;24(7):992-1000.

Goyal M et al. Stickler Syndrome Type 1 with Short Stature and Atypical Ocular Manifestations. Case Rep Pediatr. 2016;2016:3198597.

Guo L et al. Novel and recurrent COL11A1 and COL2A1 mutations in the Marshall-Stickler syndrome spectrum. Hum Genome Var. 2017 Oct 5;4:17040.

Hoornaert KP et al. The phenotypic spectrum in patients with arginine to cysteine mutations in the COL2A1 gene. J Med Genet. 2006 May;43(5):406-13.

Nagendran S et al. Somatic mosaicism and the phenotypic expression of COL2A1 mutations. Am J Med Genet A. 2012 May;158A(5):1204-7.

Tomcikova D et al. Marshall and stickler syndrome in one family. Cesk Slov Oftalmol. Winter 2018;74(3):108-111.

Wang X et al. Mutation survey and genotype-phenotype analysis of COL2A1 and COL11A1 genes in 16 Chinese patients with Stickler syndrome. Mol Vis. 2016 Jun 23;22:697-704.

Yang L et al. Pathogenic gene screening in 91 Chinese patients with short stature of unknown etiology with a targeted next-generation sequencing panel. BMC Med Genet. 2018 Dec 12;19(1):212.

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

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	21-068-111041	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Stickler Syndrome Interp	21-068-111041	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