Patient ID	Patient Name		Birth Date	Sex	Age
SA00154752	ABNORMAL, OIBFG		1987-11-25	F	34
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00154752	SA00154752	CLIENT,CLIENT			
Account Information		**Collected**			
C7028846 DLMP Rochester		07 Oct 2022 08:00			

OI and Bone Fragility Gene Panel

Interpretation

MCR

COL1A1 c.174C>A (p.Cys58*): The heterozygous c.174C>A (p.Cys58*) variant in the COL1A1 gene (MIM: 120150) is classified as pathogenic. The COL1A1 gene encodes the alpha 1 chain of type I collagen, which is one of the major types of collagen in skin, tendon, and bone. Pathogenic variants in COL1A1 are associated with several different autosomal dominant disorders, including osteogenesis imperfecta (OI), Caffey disease, arthrochalasia Ehlers-Danlos syndrome (also known as aEDS or EDS type VIIA), and COL1A1-related classical EDS. In some cases, individuals with a pathogenic COL1A1 variant may have a mixed osteogenesis imperfecta/Ehlers-Danlos syndrome phenotype (OIEDS1). The p.Cys58* variant has been previously reported in association with OI (1–3). This variant results in premature truncation of the alpha 1 chain, which is predicted to lead to a quantitative (loss-of-function) defect of type 1 collagen. Quantitative defects of COL1A1 typically result in a classic non-deforming OI phenotype (previously OI type I), but clinical assessment is required to confirm an OI subtype. Taken together, this result is supportive of a diagnosis of osteogenesis imperfecta (OI) for this individual. Clinical correlation is recommended.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1–800–533–1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:

1. Li L, Mao B, Li S, et al. Genotypic and phenotypic characterization of Chinese patients with osteogenesis imperfecta. Hum Mutat. 2019;40(5):588–600. doi:10.1002/humu.23718 (PMID: 30715774)
2. Demir S, Yal??ntepe S, Atl? E?, et al. Targeted High-Throughput Sequencing Analysis Results of Osteogenesis Imperfecta Patients from Different Regions of Turkey. Genet Test Mol Biomarkers. 2021;25(1):59–67. doi:10.1089/gtmb.2020.0169 (PMID: 33470886)
3. Chen P, Tan Z, Shek HT, et al. Phenotypic Spectrum and Molecular Basis in a Chinese Cohort of Osteogenesis Imperfecta With Mutations in Type I Collagen. Front Genet. 2022;13:816078. Published 2022 Jan 28. doi:10.3389/fgene.2022.816078 (PMID: 35154279)

Result Summary

MCR

Pathogenic Variant Detected

Result

MCR

The following heterozygous PATHOGENIC variant was detected:
COL1A1 (NM_000088.3), Chr17(GRCh37):g.48277238G>T, c.174C>A, p.Cys58* (p.C58*)

No additional reportable pathogenic variants, likely pathogenic variants, or variants of uncertain significance were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by the assay.

Test Description

MCR

Evaluation of 25 genes associated with osteogenesis imperfecta (OI) and other hereditary conditions associated with bone fragility.

Specimen

MCR

WB Whole Blood

Method

MCR

Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS, and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292

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presence of deletions and duplications in the genes analyzed. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID OIBFG) for details regarding genes with regions not routinely covered.

Genes Analyzed

MCR

ALPL, ANO5, BMP1, COL1A1, COL1A2, CREB3L1, CRTAP, FKBP10, IFITM5, LRP5, MBTPS2, P3H1, P4HB, PLOD2, PLS3, PPIB, SEC24D, SERPINF1, SERPINH1, SP7, SPARC, TAPT1, TMEM38B, WNT1, and XYLT2

Disclaimer

1 MCR

Clinical Correlations
An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1–800–533–1710.

Technical Limitations
Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the OI and Bone Fragility Gene Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID OIBFG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

Released By

MCR

Linnea M. Baudhuin, Ph.D.

Received: 10 Oct 2022 13:37 **Reported:** 10 Oct 2022 19:10

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MAYO CLINIC LABORATORIES

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Laboratory Notes

[1] This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

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