OMNIHEALTH DIAGNOSTICS

Cardio-pulmonary NGS Panel

Patient		Specimen		Ordering Physician	
First Name:	John	Specimen Type:	Buccal Swab	Physician:	Test Doctor
Last name:	Doe	Collection Date:	04-01-2023	Institution:	Test Facility
Date of Birth:	09-31-9999	Received Date:	04-11-2023	Reported Date:	04-18-2023
Gender:	Male	Panel Coverage :	96.48%	Ref Accession:	N/A
Accession ID:	CP04172023	Average Read Depth:	211x		

Test Result:

+Positive : For Pathogenic Variant on COL5A1 gene.

Gene & Transcript	Variant	Inheritance	Disorder or PhoneType	Criteria	Classification
COL5A1 NM_000093.5	c.3341G>C p.Gly1114Ala	Autosomal Dominant / Heterozygous	Ehlers-Danlos syndrome, classic type	PM2, PM1, PP2, PP3	Pathogenic

Location	Allele State	Allelic Read Depths
Exon 42	Heterozygous	Ref(G): 27, Alt(C): 28, VAF: 50.91%

Genomic Position	Variant Frequency
Chr9:NC_000009.11:g.137698117G>C	Not identified in large population studies

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Patient

Name : John Doe | Date of Birth: 09-31-9999 | Accession : CP04172023

Gene info

COL5A1 NM_000093.5

Variant Info

The missense variant NM_000093.5(COL5A1):c.3341G>C (p.Gly1114Ala) has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. Although the variant is present at 0.0000% in gnomAD All, it has the flag "AC0" and may not represent the true population frequency. The p.Gly1114Ala variant is novel (not in any individuals) in 1kG All. There is a small physicochemical difference between glycine and alanine, which is not likely to impact secondary protein structure as these residues share similar properties. The gene COL5A1 has a low rate of benign missense variation as indicated by a high missense variants Z-Score of 2.07. The gene COL5A1 contains 25 pathogenic missense variants, indicating that missense variants are a common mechanism of disease in this gene. 2 variants within 6 amino acid positions of the variant p.Gly1114Ala have been shown to be pathogenic, while none have been shown to be benign. The p.Gly1114Ala missense variant is predicted to be damaging by both SIFT and PolyPhen2. The nucleotide c.3341 in COL5A1 is predicted conserved by GERP++ and PhyloP across 100 vertebrates. For these reasons, this variant has been classified as Pathogenic.

Variant interpretation

The Variant is found at Chr9:NC_000009.11:g.137698117G>C location with a missense variant c.3341G>C p.Gly1114Ala change on the patient's COL5A1

Inheritance

Autosomal Dominant /
Heterozygous

ACMG-Classification

Pathogenic
(PM2, PM1, PP2, PP3)

Gene & Disorder or Phenotype

COL5A1-Ehlers-Danlos syndrome, classic type

What's next

Correlate the findings with clinical symptoms, biochemical profile and family history whilst closely monitoring the subject with periodical visits.Genetic counseling is recommended.

OMNIHEALTH DIAGNOSTICS, LLC
CLIA: 45D2089485 | Address: 1840 N Greenville Ave, Suite 176, Richardson, TX 75081
Lab Director: Dr. Akhtar Afshan Ali | Phone: 972.887.3444 | Fax: 972.887.3443

Gene info 	COL5A1 NM_000093.5
Variant Info 	The missense variant NM_000093.5(COL5A1):c.3341G>C (p.Gly1114Ala) has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. Although the variant is present at 0.0000% in gnomAD All, it has the flag "AC0" and may not represent the true population frequency. The p.Gly1114Ala variant is novel (not in any individuals) in 1kG All. There is a small physicochemical difference between glycine and alanine, which is not likely to impact secondary protein structure as these residues share similar properties. The gene COL5A1 has a low rate of benign missense variation as indicated by a high missense variants Z-Score of 2.07. The gene COL5A1 contains 25 pathogenic missense variants, indicating that missense variants are a common mechanism of disease in this gene. 2 variants within 6 amino acid positions of the variant p.Gly1114Ala have been shown to be pathogenic, while none have been shown to be benign. The p.Gly1114Ala missense variant is predicted to be damaging by both SIFT and PolyPhen2. The nucleotide c.3341 in COL5A1 is predicted conserved by GERP++ and PhyloP across 100 vertebrates. For these reasons, this variant has been classified as Pathogenic.
Variant interpretation 	The Variant is found at Chr9:NC_000009.11:g.137698117G>C location with a missense variant c.3341G>C p.Gly1114Ala change on the patient's COL5A1
Inheritance 	Autosomal Dominant / Heterozygous
ACMG-Classification	Pathogenic (PM2, PM1, PP2, PP3)
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What's n 	Correlate the findings with clinical symptoms, biochemical profile and family history whilst closely monitoring the subject with periodical visits.Genetic counseling is recommended.

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Test Methodology

Test Methodology

Cardiomyopathy-Pulmonary Disease Risk Factor Screening 236 gene panel screening performed at Elite Clinical Lab LLC utilizes Next Generation Sequencing (NGS) technology using targeted gene enrichment chemistry on the IIlumina® MiniSeq platform. Genomic DNA extracted from Buccal swabs (Dry and Wet) are tagemented and enriched for regions of interest using probes specific for each region specified in the BED (Browser Extensible Data) file. Positive (www.coriell.org) and Negative controls are included with each machine run to ensure the accuracy of amplicon preparation alongside targeted sequencing on coding regions and intronic/exonic boundaries of interest and precise finding of the variant on the positive control and negative control respectively. Sequences obtained are then aligned against a human reference genome and variants such as SNVs (Small Nucleotide Variants) and Indels (Insertions and Deletions) are noted. For a detailed list of regions covered and comprehensive statistics by Elite Clinical Lab LLC Cardiomyopathy-Pulmonary screen, please contact us on Email: 12345@omnihealthdx.com

Computational analysis and variant calling is performed by Elite (www.elitelabs.com). Briefly, reads from the sequence output were aligned to the human reference genome (GRCh37) using the Burrows-Wheeler Aligner (BWA). Variants to the reference were called using the Genomic Analysis Tool Kit (GATK). The variants were annotated and filtered using the Elite Clinical Lab LLC analysis work flow implementing the ACMG guidelines for interpretation of sequence variants. This includes comparison against the gnomAD population catalog of variants in 123,136 exomes, the 1000 Genomes Project Consortium's publication of 2,500 genomes, the NCBI-ClinVar database of clinical assertions on variant's pathogenicity and multiple lines of computational evidence on conservation and functional impact. The following databases and insilico algorithms are used to annotate and evaluate the impact of the variant in the context of human disease: 1000 genomes, gnomAD, ClinVar, OMIM, dbSNP, NCIB Ref Seq Genes, ExAC Gene Constraints, VS-SIFT, VS PolyPhen2, PhyloP, GERP+, GeneSplicer, Max Ent Scan, NNSplice, PWM Splice Predictor. Analysis was reported using the HGVS nomenclature (www.hgvs.org/mutnomen)as implemented by custom transcript annotation algorithm. Only variants with an end ACMG classification of "Pathogenic" or "Likely Pathogenic" are reported and VUS/Benign/Likely Benign variants are not reported. Classification of pathogenicity is consistently updated by the National Institutes of Health and the information found within this report is consistent with the current knowledge base as the knowledge base changes, so may clinical interpretation of variants. All reports are reviewed prior to release by either Elite Clinical Lab LLC's Technical Supervisor or the General Supervisor.

Genes Evaluated

ABCC9, ACTA2, ACTC1, ACTN2, ACVRL1, ADAMTS2, AKAP9, ALDH18A1, ALMS1, ALPK3, ANK2, ANKRD1, APOB, ATP6V0A2, ATP6V1E1, ATP7A, B3GAT3, B4GALT7, BAG3, BGN, BMPR2, BRAF, CACNA1C, CACNA2D1, B3GALT6, CACNB2, CALM1, CALM2, CALM3,CASQ2, CAV1,CAV3, CBS, CHRM2, CHST14, COL11A1, COL11A2, COL12A1, COL1A1, COL1A2, COL2A1, COL3A1, COL5A1, COL5A2, COL9A1, COL9A2, COL9A3, CRYAB, CSRP3, CTNNA3, DES, DMD, DOLK, DSC2, DSE, DSG2, DSP, DTNA, EFEMP2, EIF2AK4, ELN, EMD, ENG, EYA4, FBLN5, FBN1, FBN2, FHL1, FKBP14, FKRP, FKTN, FLNA, F9, FLNC, GAA, GATA4, GATA5, GATA6, GATAD1, GDF2, GJA5, KCNJ8, KCNK3, KCNQ1, KRAS, LAMA4, LAMP2, LDB3, LDLR, LDLRAP1, LMNA, LOX, LRRC10, LTBP4, MAP2K1, MAP2K2, MAT2A, MED12, MFAP5, MIB1, MURC, MYBPC3, MYH11, MYH6, MYH7, MYL2, MYL3, MYL4, MYLK, MYLK2, MYOZ2, MYPN, NEBL, NEXN,, NKX2-5, NOTCH1, NRAS, PCSK9, PDLIM3, PKP2, PLN, PLOD1, PPA2, PRDM16, PRDM5, PRKAG2, PRKG1, PTPN11, PYCR1, RAF1, RANGRF, RASA1, RBM20, RIN2, RIT1, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SGCD, SHOC2, SKI, SLC2A10, SLC39A13, SMAD2, SMAD3, SMAD4, SMAD9, SNTA1, SOS1, TAZ, TBX20, TCAP, TECRL, TGFB3, TGFB2, TGFBR1, TGFBR2, TMEM11, TMPO, TNNC1, TNNT2, TNXB, TOR1AIP1, TPM1, TRD, TRPM4, TTN, TXNRD2, VCL, ZNF469, CCDC39, CCDC40, CFTR, CHAT, CHRNA1, CHRNB1, CHRNE, COLQ, CSF2RA, CSF2RB, DKC1, CHRND, DNAAF1, DNAAF2, DNAH1, DNAH1I, DNAH5, DNAI1, DNAI2, DNAL1, EDN3, ELMOD2, FLCN, FOXF1, GAS8, GLRA1,

HPS1, HPS4, ITGA3, MECP2, NAF1, NF1, NKX2-1, NME8, PARN, PHOX2B, PIH1D3, RAPSN, RET, RSPH3, RSPH4A, RSPH9, RTEL1, SCNA4, SCNN1A, SCNN1B, SERPINA1, SFTPA1, SFTPA2, SFTPB, SFTPC, SLC34A2, SLC6A5, SLC7A7, SMPD1, STAT3, TERC, TERT, TINF2, TSC1, TSC2, ZEB2

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Test Limitations

Some variations in these genomic regions may not be reported such as: large genomic rearrangements greater than 50 bp in length, rare (low frequency) mutations, or structural (non-coding) variations ad pseudogenes. These regions are excluded from tertiary analysis and reporting, and include:

chr 1: 237919587-237919687_RYR2:Exon(254724593)
chr 1 : 47372052-47372166 MYBPC3:Exon(254724862)
chr 7 : 7123440-7123516 ACADVL:Exon(254723728)
chr 17 : 78075354-78075424_GAA:5'UTRExon(254724327}
chr 8 : 29078026-29078259_DSG2:5'UTRExon(254724285)
chr 9 : 47249302-47249347_FKRP:5'UTRExon(254725371)
chr 3 : 38691021 38691164_SCN5A:5'UTRExon(254724130)
chr X : 135229558-135229787_FHL1:5'UTRExon(254724192)
chr16:2097989:2098066:TSC2:5'UTRExon(254723602)
chr9:135779797:135779841:TSC1:Exon(254722795)

Rare diagnostics errors may occur if these mutations occur within the priming sequencing regions. Presence of a pathogenic/likely pathogenic variant does not guarantee that an individual will develop Cardiomyopathy-Pulmonary disease, nor is the absence of such variants a guarantee that an individual will not develop a 'Cardiomyopathy-Pulmonary Disease'. The results of this screen are meant strictly to guide a physician in the management of their patient's health. Any Likely pathogenic or Pathogenic variants detected in the report should be clinically correlated (As per Physicians Advice) and confirmed via the orthogonal testing platforms (Sanger Sequencing or PCR based tests).

Regulatory Disclosures

Genetics based hereditary Cardiomyopathy-Pulmonary Risk Factor screening is intended as a tool to guide physicians in the management of their patients and should NOT be treated as a diagnostic tool for NGS-based hereditary Cardiomyopathy-Pulmonary screening is considered a high-complexity laboratory-developed test (LDT) by CMS under the Clinical Laboratory Improvement Amendment (CLIA) and is not FDA-cleared. The test and performance metrics were validated in house by Elite Clinical Lab LLC technical personnel (or designated scientific advisors) and approved by their Laboratory Director The results are intended for use only by the ordering physician and/or designated healthcare provider. The ordering provider is responsible for 1) ascertaining the medical necessity of the ordered test, 2) resulting diagnoses, 3) management of the disease and/or decisions based on the data provided. Results rely on collection personnel following specified collection and shipment protocols.

REFERENCES

Richards, Sue, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine 17.5 (2015): 405.Exome Aggregation Consortium et al. Analysis of Protein-Coding Genetic Variation in 60,706 Humans. Nature 536.7616 (2016): 285–291. PMC. Web. 13 May 2018. The 1000 Genomes Project Consortium. A Global Reference for Human Genetic Variation. Nature 526.7571 (2015): 68–74. PMC. Web. 13 May 2018.