YOUR LAB

Your Lab
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Additional Information

Test Performed: **Hereditary Disorder Panel**

Report Date Feb 12, 2021
Status -

Patient		Client		Specimen	
Patient Name	Michael Doe	Client	General Hospital	Accession ID	1613158CARD
Date of Birth		Client ID	ABC123	Specimen	blood
Age	51	Physician	Dr. E Smith	Collection	Feb 2, 2021
Sex	Male	Pathologist	Dr. R Jones	Accession	Feb 12, 2021
Ethnicity	African American				
Symptoms	Not Applicable				
Indication	hereditary disorder				

Result: Positive

1
Pathogenic

Report Summary

Pathogenic PKP2 frameshift variant was detected.

Variant Summary

Gene / Variant	Genotype	Assessment	Mode of Inheritance	Phenotype
PKP2 c.2065_2070delCACACCinsG p.H689fs*8 g.32955434_32955439delGGTGTGinsC	Heterozygous	Pathogenic	dominant	Arrhythmogenic right ventricular cardiomyopathy

Individual Variant Interpretations

Gene ***PKP2***
Exon 10
Amino Acid p.H689fs*8
Nucleotide NM_001005242.3:
g.32955434_32955439delGGTGTGinsC
c.2065_2070delCACACCinsG
Assessment Pathogenic
Genotype Heterozygous

Interpretation
The PKP2 gene codes for the plakophilin-2 protein, which has a structural role in desmosomes and is primarily located in the myocardium [Genetics Home Reference]. The desmosomes containing the PKP2 protein provide structural and functional coherence to neighboring cells [6, 13]. PKP2 pathogenic variants can disturb intercellular connections, which can cause arrhythmia [9]. Arrhythmogenic cardiomyopathy, originally described as arrhythmogenic right ventricular cardiomyopathy (ARVC) [13], is a disease caused by multiple factors [6]. Pathogenic variants of PKP2 cause arrhythmogenic right ventricular dysplasia 9 (ARVC9) [OMIM: 609040], an autosomal dominant disorder that is characterized by arrhythmia, syncope and abnormal ECG [8, 9]. Specific information for ARVC9 is not available, but the onset of ARVC is usually in adulthood, although it can have childhood onset. The prevalence of ARVC is estimated to be between 1/1000 and 1/2500 [4, 9; Genetics Home Reference], and 34%-74% of all ARVC cases are attributed to PKP2 variants [9].

Evidence for Pathogenicity

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 7583.95; 95% confidence interval = (471.12, 122085.47); FET 2-tail p-value < 0.0001; affected individual count = 104] (Strong) [5, 12, 19, 2, 4, 7, 15, 14, 11, 20, 3, 16, 10, 18, 1]
- PM2 - Absent from controls (or at extremely low frequency if recessive) in gnomAD [In these sources of population frequency data, this variant's frequency is 0% or <= 0.001%] (Moderate)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Genes Tested

Test information such as gene name and hot spot region can be included in this section.

Methods and Limitations

EXAMPLE Statement including sample type (FFPE, etc), method of extraction, amplification reactions, panel targeted regions, sequencing technology, etc. Additionally, a description of the data analysis software(s), genome of reference and the sensitivity of the methods should be described.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (7.1.20201218), Ingenuity Knowledge Base (B-release), CADD (v1.6), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2020-04-06), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2021-01-29 01:43:35.0), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (B-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Nov 20 02:39), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 33), CentoMD (5.3), OMIM (July 06, 2020), gnomAD (2.1.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2020-09-15), DGV (2016-05-15), COSMIC (v92), HGMD (2020.4), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 153, GRCh38 153), SIFT4G (2016-02-23)

Selected Citations

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3. Bhonsale A, James CA, Tichnell C, Murray B, Madhavan S, Philips B, Russell SD, Abraham T, Tandri H, Judge DP, Calkins H (2013) Risk stratification in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. Circ Arrhythm Electrophysiol. 2013 Jun;6(3):569-78. Epub 2013 May 13 (PMID: 23671136)

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