Veritas
The Genome Company

myCardio Gene Panel Test

Name	Veritas myCardio Demo	Sample Type	Saliva
DOB	May 05 1950	Sample Collected	Nov 12 2018
Sex	Female	Sample Received	Nov 19 2018
Provider	Veritas Doctor	Batch ID	mCardio1234
Date of Report	Dec 14 2018	Customer ID	98765432

POSITIVE RESULT

MYBPC3 c.1504C>T (p.Arg502Trp), NM_000256, heterozygous, pathogenic

ADDITIONAL FINDINGS

MYH7 c.5329G>A (p.Ala1777Thr), NM_000257, heterozygous, VUS

A variant of uncertain significance (VUS) is a genetic change whose meaning is not yet established. This is usually due to insufficient data or conflicting evidence in the medical literature. In the absence of further information, the interpretation of the variant is inconclusive. Clinical correlation and variant studies in affected family members are recommended to clarify the clinical significance of the VUS.

CLINICAL NOTE

Please note that this individual carries a well-established, pathogenic variant in *MYBPC3*, which is known to cause hypertrophic cardiomyopathy (HCM). An additional variant of uncertain significance has been identified in the *MYH7* gene. Variants in this gene are associated with a range of cardiomyopathies including HCM and DCM and this variant's interpretation is listed below. This individual was reportedly diagnosed with HCM at the age of 10 years, which is earlier than the typical onset of disease in carriers of the *MYBPC3* p.Arg502Trp variant. Given the reported family history of mild LVH (maternal side) and adult onset HCM (paternal side), it is possible that this individual's early onset HCM is caused by a combination of the two variants. Parental testing is recommended to further clarify the significance of the p.Ala1777Thr variant.

***MYH7* c.5329G>A (p.Ala1777Thr)**

- 3 individuals with hypertrophic cardiomyopathy (PMID:27532257; PMID:12707239)
- 4/66738 European chromosomes (http://exac.broadinstitute.org)
- Computational prediction tools and conservation analysis suggest that this variant may impact the protein

INTERPRETATION

Variant Information

***MYBPC3* c.1504C>T (p.Arg502Trp)** is a well-established pathogenic variant associated with autosomal dominant hypertrophic cardiomyopathy (HCM). This variant is the most common HCM variant known to date. It has been identified in nearly 2% (>100) of individuals tested (Walsh 2017) and segregated with the disease in 16 individuals from at least 12 families (Saltzman 2010, Alfares 2015, Camuglia 2013, Cann 2017). Other nucleotide changes affecting the same amino acid at position 502 (p.Arg502Gln, p.Arg502Leu and p.Arg502Gly) have also been reported in affected individuals. This variant has been identified in 13/126700 European (non-Finnish) chromosomes by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org; dbSNP rs375882485) and is present in ClinVar (ID: 42540, accessed 3/2/18). In summary, the p.Arg502Trp variant meets criteria (ACMG, Richards 2015) to be classified as a pathogenic variant for autosomal dominant HCM.

REFERENCES

12707239; 27532257; 20378854; 25611685; 23642604; 27000522

METHODS AND LIMITATIONS

Veritas' myCardio test is a next-generation sequencing (NGS) assay for detecting variants in 90 genes. The test is performed on saliva or whole blood. Extracted genomic DNA is processed by a capture-based assay and sequenced on a next-generation sequencer (Illumina). For sample tracking and quality assurance, each sample is also assessed with the Infinium QC Array-24 microarray (Illumina). Sequencing is performed in Veritas Genetics' CLIA licensed and CAP accredited laboratory. Sequencing data are aligned to the hg19 (build 37.1) human reference genome. Data analysis is performed with Veritas Genetics' custom bioinformatics pipeline, which uses both Bayesian and Heuristic-based statistical variant callers.

Single nucleotide variants and small insertions/deletions are detected. Promoter regions are not analyzed.

Only inherited (germline) variants are detected, and not somatic variants, mosaicism, or heteroplasmy. Copy number variants, inversions and complex structural rearrangements such as translocations are not detected.

Regions with high sequence homology (as defined in PMID: 27228465) or other technical limitations of Next Generation Sequencing are not analyzed, see gene list for reference. Positions with <10X coverage are excluded from reporting unless confirmed by an alternate technology.

Analytic sensitivity is 99.9%, 95% CI [99.7%, 100%] for SNVs and 93.6%, 95% CI [88.2%, 97.0%] for small insertions/deletions. Analytical positive predictive value is 99.1%, 95% CI [98.8%, 99.4%] for SNVs and 94.9%, 95% CI [89.8%, 97.9%] for small insertions/deletions.

Variants are classified as pathogenic, likely pathogenic, uncertain significance (VUS), likely benign, or benign based on the American College of Medical Genetics and Genomics (ACMG) guidelines (PMID: 25741868). Pathogenic, likely pathogenic variants, and VUSs are included in the report, whereas benign and likely benign variants are not reported. Intronic variants of uncertain significance are not reported beyond 2 base pairs from the coding region, but likely pathogenic or pathogenic variants up to 10 base pairs from the coding region are always reported (15 base pairs for genes where splice variants are a common cause of disease). Pathogenic and likely pathogenic variants detected by NGS are confirmed with Sanger sequencing. VUSs are not confirmed with a secondary methodology. If a VUS is upgraded to a likely pathogenic or pathogenic classification in the future, then secondary testing would be recommended at that time for confirmation of the variant.

No clinical test is perfect. Current technology may not be able to detect some variants, and there may be other genes associated with cardiovascular conditions that are not covered by this panel.

References

Zook JM. et al. Extensive sequencing of seven human genomes to characterize benchmark reference materials. Sci Data 2016;3:160025 doi: 10.1038/sdata.2016.25. PMID: 27271295

Mandelker D et al. Navigating highly homologous genes in a molecular diagnostic setting: a resource for clinical next-generation sequencing. Genet Med 2016;18:1282-1289. PMID: 27228465

Landrum MJ et al. ClinVar: public archive of interpretations of clinically relevant variants. Nuc Acids Res 2016;44(1):D862–D868. doi: 10.1093/nar/gkv1222. PMID 26582918

Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation

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METHODS AND LIMITATIONS

of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-424. PMID 25741868

Stenson PD et al. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet 2017;136:665-677. PMID: 28349240

GENES TESTED

ABCC9, ACTA2, ACTC1, ACTN2, APOB, BAG3, BRAF, CACNA1C, CALM1, CALM2, CALM3, CASQ2, CAV3, CBL, COL3A1, COX15, CRYAB, CSRP3, DES, DSC2, DSG2, DSP, EFEMP2, EMD, FBN1, FBN2, FHL1, FKTN, FLNC (97.5%), FXN, GAA, GLA, HRAS, JPH2, JUP, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, KRAS, LAMP2, LDB3, LDLR, LDLRAP1, LMNA, LOX, MAP2K1, MAP2K2, MYBPC3, MYH11, MYH7 (93.8%), MYL2, MYL3, MYLK, NEXN, NF1, NRAS, PCSK9, PKP2, PLN, PPP1CB, PRKAG2, PRKG1, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SHOC2, SLC25A4, SMAD3, SOS1, SOS2, TAZ, TCAP, TGFB2, TGFB3, TGFBR1 (94.0%), TGFBR2, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TTN (97.8%), TTR, VCL

AUTHORIZED SIGNATURES

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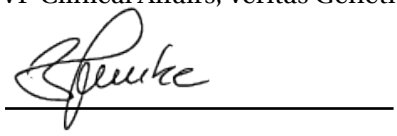

DISCLAIMER

This test was developed and its performance characteristics determined by Veritas Genetics. The analytical validation of this test meets CLIA and CAP requirements. The test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The Veritas Genetics laboratory is regulated under CLIA as qualified to perform high-complexity testing. If you have any questions about this report or wish to speak with one of Veritas Genetics' genetic counselors, please call 888-507-6619