Veritas a LetsGetChecked company | my Cardio

Name
Date of birth
Sex
Provider
Sample type

Sample ID
Sample collected
Sample received
Report date

POSITIVE RESULT

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

ADDITIONAL FINDINGS

No additional variants of clinical significance were detected.

INTERPRETATION

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.

Pathogenic and likely pathogenic variants in myCardio genes are associated with increased risk for cardiovascular disease for both women and men. The disease risk differs from gene to gene. For some of the genes on this panel an exact disease risk may not currently be known. Furthermore, an elevated risk for non-cardiovascular related conditions may be revealed, depending on the gene variant(s) identified. If a variant is detected in more than one gene, it may be difficult to assess the overall disease risk. Medical management recommendations will depend on the gene in which the variant(s) was identified.

Genetic test results should be interpreted by a certified genetic counsellor or other qualified medical professional, in the context of the patient's clinical and family history, for accurate assessment of the personal risk. Any changes in medical management or screening based on these results should only be done through consultation with the referring physician. For patients with a personal or family history of cardiovascular disease, additional genetic testing may be indicated.

REFERENCES

12707239; 27532257; 20378854; 25611685; 23642604; 27000522

METHODS AND LIMITATIONS

Veritas' myCardio test is a next-generation sequencing (NGS) assay for detecting variants in 100 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). Sequencing data is processed using bioinformatics pipeline with both Bayesian and Heuristic-based statistical variant callers and developed for this intended use. Mapping and analysis are based on the human genome build UCSC hg19 reference sequence.

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 less than 10X coverage are excluded from reporting unless confirmed by an alternate technology.

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 when necessary. VUSs are not confirmed with a secondary methodology. If VUS classification is upgraded to likely pathogenic or pathogenic in the future, then secondary testing would be recommended for confirmation of the variant at that time.

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.

NGS based tests may not be able to detect some variants and there may be other genes associated with hereditary cardiovascular conditions that are not covered by this panel.

References

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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

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

GENES TESTED

ABCC9, ABCG5, ABCG8, ACTA2, ACTC1, ACTN2, APOB, APOE, BAG3, BRAF, CACNA1C, CALM1, CALM2, CALM3, CASQ2, CAV3, CBL, COL3A1, COX15, CRYAB, CSRP3, DES, DSC2, DSG2, DSP, EFEMP2, ELN, EMD, FBN1, FBN2, FHL1, FKTN, FLNA, FLNC, FXN, GAA, GLA, HRAS, JPH2, JUP, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, KRAS, LAMP2, LDB3, LDLR, LDLRAP1, LIPA, LMNA, LOX, MAP2K1, MAP2K2, MYBPC3, MYH11, MYH7, MYL2, MYL3, MYLK, NEXN, NF1, NOTCH1, NRAS, PCSK9, PKP2, PLN, PPP1CB, PRKAG2, PRKG1, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SHOC2, SKI, SLC2A10, SLC25A4, SMAD3, SMAD4, SOS1, SOS2, TAZ, TCAP, TGFB2, TGFB3, TGFBR1, TGFBR2, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TTN, TTR, VCL

Note: The number in parentheses indicates the percentage of the coding region sequenced at a coverage greater than 20x in those genes in which such coverage cannot be achieved in the whole coding region for technical reasons.

VALIDATION

Technical Director: Medical Director: Approved by:

DISCLAIMER

Findings included in this report are based on current understanding and knowledge of genetic disease, variant classification may evolve over time as more information becomes available. For any clinical questions or to contact our genetic counselors, please contact us by email at genetic.counseling@veritasint.com or visit https://www.veritasint.com/en/contact for local contact details.

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