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Variant: NM_000256.3(MYBPC3):c.1483C>T (p.Arg495Trp)

Version: 1.0

CA010455

164114 (ClinVar)

Gene: MYBPC3 (HGNC:4607)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5d5806fe-d0fd-42ef-8a0a-6c04d6bb025c
Approved on: 2025-11-14
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HGVS expressions

NM_000256.3:c.1483C>T
NM_000256.3(MYBPC3):c.1483C>T (p.Arg495Trp)
NC_000011.10:g.47342719G>A
CM000673.2:g.47342719G>A
NC_000011.9:g.47364270G>A
CM000673.1:g.47364270G>A
NC_000011.8:g.47320846G>A
NG_007667.1:g.14984C>T
ENST00000545968.6:c.1483C>T
ENST00000256993.8:c.1483C>T
ENST00000399249.6:c.1483C>T
ENST00000544791.1:c.1483C>T
ENST00000545968.5:c.1483C>T

Likely Pathogenic

Met criteria codes 4

PP3 PM2_Supporting PM1 PS4_Moderate

Not Met criteria codes 5

PS1 PS3 BA1 BS3 BP4

Evidence Links 0

Expert Panel

Cardiomyopathy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MYBPC3 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cardiomyopathy VCEP

NM_000256.3(MYBPC3):c.1483C>T (p.Arg495Trp). This variant has been identified in individuals with HCM and other cardiomyopathies (ClinVar Variation ID 164114) and was absent from large population studies (https://gnomad.broadinstitute.org/; v.2.1). The variant is statistically increased in individuals with HCM compared to controls (OR lower 95% CI>10), therefore, the PS4 criterion has been applied at moderate strength (PS4_Moderate) and the PM2_Supporting criterion has been applied (PM2_Supporting). This variant lies in a region of the protein where variants are statistically more likely to be disease-associated (PM1_Strength; Walsh 2019 PMID: 30696458).

Computational prediction tools and conservation analyses suggest that this variant may impact the protein (PP3; REVEL score ≥0.70). In summary, this variant meets criteria to be classified as likely pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner based on PS4_Moderate, PM2_Supporting, PM1, and PP3.

Met criteria codes

PP3	✔	Computational prediction tools and conservation analyses suggest that this variant may impact the protein (PP3; REVEL score ≥0.70)
PM2_Supporting	✔	Absent in 2.1. gnomad
PM1	✔	This variant lies in a region of the protein where variants are statistically more likely to be disease-associated (PM1_Strength; Walsh 2019 PMID: 30696458).
PS4_Moderate	✔	HCMR: 3/2633 Walsh: 4/ 6179 HCM (2/2912 LMM, 2/3267 OMGL) --> LMM has now 5 cases/3200 and OMGL has at least 4 (see OMGL tab in variant excel spreadsheet) ---> Assume 10,000 tested probands between OMGL, LMM , and other labs: 9 in 10000 case genotypes vs 1 in 56495 control genotypes gives an odds ratio of 50.89 (95%CI=6.45-401.72) Lower bound CI: Strong 95%CI=6.45 (threshold for strong ≥20) Moderate 95%CI=6.45 (threshold for moderate ≥10) Supporting 95%CI=6.45 (threshold for supporting ≥5) The lower bound 95%CI is greater than 5 (95%CI=6.45). Therefore PS4 is set to PS4_Supporting LMM data with gnomad 2.1: 5 in 3200 case genotypes vs 1 in 56495 control genotypes gives an odds ratio of 88.41 (95%CI=10.33-756.96) Lower bound CI: Strong 95%CI=10.33 (threshold for strong ≥20) Moderate 95%CI=10.33 (threshold for moderate ≥10) Supporting 95%CI=10.33 (threshold for supporting ≥5) The lower bound 95%CI is greater than 10 (95%CI=10.33). Therefore PS4 is set to PS4_Moderate Plus literature and ClinVar data, this would be at least Mod. Decipher only oxford data **** Please note that with gnomad 4.1, 12/1179878 alleles PS4_moderate is met. Feel more confident about this. (ran OR with walsh data) 4 in 6179 case genotypes vs 12 in 589939 control genotypes gives an odds ratio of 31.84 (95%CI=10.27-98.76) Lower bound CI: Strong 95%CI=10.27 (threshold for strong ≥20) Moderate 95%CI=10.27 (threshold for moderate ≥10) Supporting 95%CI=10.27 (threshold for supporting ≥5) The lower bound 95%CI is greater than 10 (95%CI=10.27). Therefore PS4 is set to PS4_Moderate

Not Met criteria codes

PS1	✖	n/a
PS3	✖	no functional studies
BA1	✖	Pm2_Met
BS3	✖	no functional studies
BP4	✖	PP3 met

Curation History

Showing 1 to 1 of 1 rows