

Variant: *NM_000256.3(MYBPC3):c.1484G>A (p.Arg495Gln)*

Version: 1.0

[CA010464](#)

[164113 \(ClinVar\)](#)

Gene: MYBPC3 ([HGNC:4607](#))

Condition: hypertrophic cardiomyopathy ([MONDO:0005045](#))

Inheritance Mode: Autosomal dominant inheritance

UID: 632dba69-eba4-43bd-aeb8-8e6a23dab49b

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HGVS expressions

NM_000256.3:c.1484G>A

NM_000256.3(MYBPC3):c.1484G>A (p.Arg495Gln)

NC_000011.10:g.47342718C>T

CM000673.2:g.47342718C>T

NC_000011.9:g.47364269C>T

CM000673.1:g.47364269C>T

NC_000011.8:g.47320845C>T

NG_007667.1:g.14985G>A

ENST00000545968.6:c.1484G>A

ENST00000256993.8:c.1484G>A

ENST00000399249.6:c.1484G>A

ENST00000544791.1:c.1484G>A

ENST00000545968.5:c.1484G>A

Likely Pathogenic

Met criteria codes **3**

PS4_Moderate **PP1_Strong** **PM1**

Not Met criteria codes **9**

BS1 **BS3** **BP4** **BA1** **PS1** **PS3**
PM2 **PP2** **PP3**

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

















The **NM_000256.3(MYBPC3):c.1484G>A (p.Arg495Gln)**. This variant has been reported in individuals with HCM and other cardiomyopathies (ClinVar Variation ID: 164113) and has also been identified in 5 out of 112974 (0.009% FAF 95% CI) of European chromosomes in gnomAD (<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 not been applied. This variant segregated with disease in >7 affected individuals with HCM from at least 4 families (PP1_Strong; Maron 2011

PMID: 21185001, Agarwal 2015 PMID: 26271555, Mattos 2016 Year PMID: 27737317, Ross 2017 PMID: 28615295). 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 do not provide strong support for or against an impact to the protein (REVEL score <0.7). In summary, this variant meets criteria to be classified as likely pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner based on PS4_Moderate, PP1_Strong and PM1.

Met criteria codes

PS4_Moderate			Walsh (OGML+ LMM) : 14/6179 cases, gnomad 2.1 (NFE) : 5/112974 alleles OR calculations: 14 in 6179 case genotypes vs 5 in 56487 control genotypes gives an odds ratio of 25.65 (95%CI=9.24-71.24) Lower bound CI: Strong 95%CI=9.24 (threshold for strong ≥ 20) Moderate 95%CI=9.24 (threshold for moderate ≥ 10) Supporting 95%CI=9.24 (threshold for supporting ≥ 5) The lower bound 95%CI is greater than 5 (95%CI=9.24). Therefore PS4 is set to PS4_Supporting. Given that this is just shy of 10, and gnomad 4.1.0 will get this to Moderate, will upgrade to PS4_moderate (this was what was denoted in the pilot variant excel sheet summary as well)
PP1_Strong			see below
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).

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			no functional studies
BP4			Computational prediction tools and conservation analyses do not provide strong support for or against an impact to the protein.
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			no functional studies
PM2			Variant is present in gnomAD v2.1.1 but does not meet threshold for PM2_Supporting.
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			Computational prediction tools and conservation analyses do not provide strong support for or against an impact to the protein.

Curation History [↗](#)

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