Variant: NM_000256.3(MYBPC3):c.1505G>A (p.Arg502Gln)

Version: 1.0

CA010508

42541 (ClinVar)

Gene: MYBPC3 (HGNC:4607)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 75e6fc83-0e92-4632-a645-2cd4543aeaa4
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HGVS expressions

NM_000256.3:c.1505G>A
NM_000256.3(MYBPC3):c.1505G>A (p.Arg502Gln)
NC_000011.10:g.47342697C>T
CM000673.2:g.47342697C>T
NC_000011.9:g.47364248C>T
CM000673.1:g.47364248C>T
NC_000011.8:g.47320824C>T
NG_007667.1:g.15006G>A
ENST00000545968.6:c.1505G>A
ENST00000256993.8:c.1505G>A
ENST00000399249.6:c.1505G>A
ENST00000544791.1:c.1505G>A
ENST00000545968.5:c.1505G>A

Pathogenic

Met criteria codes 4

PP1_Strong PM2_Supporting PS4 PM5

Not Met criteria codes 2

PS1 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

NM_000256.3(MYBPC3):c.1505G>A (p.Arg502Gln) - This variant has been reported in numerous individuals with HCM (statistically increased in individuals with cardiomyopathy compared to controls [OR lower 95% CI >20]), and shown to segregate with disease in numerous individuals across multiple families (PMIDs: 9562578, 16566405, 16858239, 18403758, 18533079, 18803133, 18957093, 20433692, 21239446, 22112859, 22857948, 23074333, 24093860, 27532257, 27561770, 27930701, LMM data, OMGL data). Therefore, the PS4 and PP1_Strong criteria have been applied. This variant is absent from gnomAD v2.1.1 (PM2_Supporting;

http://gnomad.broadinstitute.org). Another variant involving this codon (p.Arg502Trp) has been identified in individuals with HCM and is classified as pathogenic by this VCEP (PM5). This variant lies in a region of the protein where variants are statistically more likely to be disease-associated with HCM (PMID: 30696458), but this cannot be combined with PM5. Computational prediction tools are inconclusive about the potential impact of this variant (REVEL score <0.7). In summary, this variant is classified as Pathogenic for HCM in an autosomal dominant manner based on PS4, PP1_Strong, PM5, and PM2_Supporting.

Met criteria codes

PP1_Strong	✔	This variant segregated with HCM in numerous affected individuals across multiple families (LMM data, OMGL data, PMIDs: 9562578, 18403758, 20433692, 22112859, 27561770). PP1_Strong Nimura et al PMID:9562578 (8 meoisis?); OMGL (1 meosis); PMID:18403758(1); PMID:27561770 (3); PMID:20433692(16?)
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting; http://gnomad.broadinstitute.org).
PS4	✔	This variant has been reported in numerous individuals with HCM (statistically increased in individuals with cardiomyopathy compared to controls [OR lower 95% CI >20]) LMM data, OMGL data, PMIDs: 9562578, 16566405, 16858239, 18403758, 18533079, 18803133, 18957093, 20433692, 21239446, 22857948, 23074333, 24093860, 27532257, 27930701
PM5	✔	p.Arg502Trp is pathogenic

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	Computational prediction tools are inconclusive about the potential impact of this variant (REVEL score <0.7).

Curation History

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