

Variant: NM_000258.3(MYL3):c.460C>T (p.Arg154Cys)

Version: 1.0

CA013849 [↗](#)

43124 (ClinVar) [↗](#)

Gene: MYL3 (HGNC:4634)

Condition: hypertrophic cardiomyopathy (MONDO:0005045)

Inheritance Mode: Autosomal dominant inheritance

UID: 4ca2eb66-cce1-41af-ad2e-46d4ffe0abfe

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HGVS expressions

NM_000258.3:c.460C>T

NM_000258.3(MYL3):c.460C>T (p.Arg154Cys)

NC_000003.12:g.46859496G>A

CM000665.2:g.46859496G>A

NC_000003.11:g.46900986G>A

CM000665.1:g.46900986G>A

NC_000003.10:g.46875990G>A

NG_007555.2:g.27674C>T

ENST00000431168.2:c.460C>T

ENST00000292327.6:c.460C>T

ENST00000653454.1:c.460C>T

ENST00000654597.1:c.460C>T

ENST00000655244.1:n.682C>T

ENST00000662933.1:c.460C>T

ENST00000664891.1:n.418C>T

ENST00000292327.4:c.460C>T

ENST00000395869.5:c.460C>T

NM_000258.2:c.460C>T

Uncertain Significance

Met criteria codes **2**

PP3 PS4_Supporting

Not Met criteria codes **16**

PP1 PP2 BS1 BS4 BS3 BP5
BP4 BP2 PM1 PM5 PS1
PS2 PS3 BA1 PM6 PM2

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 MYL3 Version 1.0.0

[↗](#) **Criteria Specification Approval History**





[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel


















Cardiomyopathy VCEP












NM_000258.3(MYL3):c.460C>T (p.Arg154Cys). This variant has been reported in individuals with HCM and other cardiomyopathies (ClinVar Variation ID 43124) and has also been identified in 4 out of 282804 (0.025% FAF 95% CI) of pan-ethnic chromosomes in gnomAD (<https://gnomad.broadinstitute.org/>; v2.1). The variant is statistically increased in individuals with HCM compared to controls (OR, lower 95% CI>5), therefore, the PS4 criterion has been applied at supporting strength (PS4_Supporting) and the PM2_Supporting criterion has not been applied. Computational prediction tools and conservation analyses suggest that this variant may impact the protein (PP3; REVEL score ≥ 0.70). In summary, due to insufficient evidence, this variant is classified as uncertain significance for hypertrophic cardiomyopathy in an autosomal dominant manner. MYL2-specific ACMG/AMP criteria applied: PS4_Supporting, PP3.

Met criteria codes

PP3			Computational prediction tools and conservation analyses suggest that this variant may impact the protein (PP3; REVEL score ≥ 0.70)
PS4_Supporting			Walsh 2017: 1/1535 Oxford, 2/2650 LMM (african american, asian, unspecified, decided to use global gnomad) gnoMAD: 2/129136 NFE 4/282804 global 3 in 4185 case genotypes vs 4 in 141402 control genotypes gives an odds ratio of 25.36 (95%CI=5.67-113.34) Lower bound CI: Strong 95%CI=5.67 (threshold for strong ≥ 20) Moderate 95%CI=5.67 (threshold for moderate ≥ 10) Supporting 95%CI=5.67 (threshold for supporting ≥ 5) The lower bound 95%CI is greater than 5 (95%CI=5.67). Therefore PS4 is set to PS4_Supporting

Not Met criteria codes

PP1			1 seg LMM , not counting code
PP2			n/a for MYL3
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No studies
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			n/a for MYL3
PM5			2 other variants in this codon are VUS

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			AF = 0.008%, 95% CI =0.02% (gnomad 4 not met, just above 0.004%)

Curation History [↗](#)

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