The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

# *Variant: NM_000256.3(MYBPC3):c.2573G>A (p.Ser858Asn)*

Version: 1.0

*CA012667*

*164070 (ClinVar)*

**Gene**: MYBPC3 (HGNC:4607)
**Condition**: hypertrophic cardiomyopathy (MONDO:0005045)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 3a6aea26-e296-4bd1-8eb3-ea6bf17777ab
**Approved on**: 2025-11-14
**Published on**: 2025-11-14

## *HGVS expressions*

**NM_000256.3:c.2573G>A**
NM_000256.3(MYBPC3):c.2573G>A (p.Ser858Asn)
NC_000011.10:g.47337420C>T
CM000673.2:g.47337420C>T
NC_000011.9:g.47358971C>T
CM000673.1:g.47358971C>T
NC_000011.8:g.47315547C>T
NG_007667.1:g.20283G>A
ENST00000545968.6:c.2573G>A
ENST00000256993.8:c.2573G>A
ENST00000399249.6:c.2573G>A
ENST00000544791.1:c.*78G>A
ENST00000545968.5:c.2573G>A

**Uncertain Significance**

**Met criteria codes** 2

PS4_Supporting PP3

**Not Met criteria codes** 13

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

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.2573G>A (p.Ser858Asn). This variant has been in individuals with HCM (ClinVar Variation ID: 164070) and has also been identified in 2 out of 124800 (0.005% FAF 95% CI) of European chromosomes in gnomAD (https://gnomad.broadinstitute.org/; v.2.1). This 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 based on PS4_Supporting, and PP3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PS4_Supporting** | ✔ | Walsh 2017 : 4 LMM 2 OMGL 6/6179 cases vs 2/124800 NFE gnomad 2.1 6 in 6179 case genotypes vs 2 in 62400 control genotypes gives an odds ratio of 30.32 (95%CI=6.12-150.28) Lower bound CI: Strong 95%CI=6.12 (threshold for strong ≥20) Moderate 95%CI=6.12 (threshold for moderate ≥10) Supporting 95%CI=6.12 (threshold for supporting ≥5) The lower bound 95%CI is greater than 5 (95%CI=6.12). Therefore PS4 is set to PS4_Supporting. Decipher 3/14976 alleles, similar OR Note that in gnomad 4.1 18/1174272 NFE PS4_moderate |
| **PP3** | ✔ | Computational prediction tools and conservation analyses suggest that this variant may impact the protein (PP3; REVEL score ≥0.70) |

**Not Met criteria codes**

| | | |
|---|---|---|
| **BA1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS3** | ✖ | no studies |
| **BP4** | ✖ | Computational prediction tools and conservation analyses suggest that this variant may impact the protein (PP3; REVEL score ≥0.70) |
| **BP2** | ✖ | 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 |
| **PS2** | ✖ | no denovo |
| **PS3** | ✖ | no studies |
| **PP2** | ✖ | n/a for MYBPC3 |
| **PM6** | ✖ | no de novo |
| **PM2** | ✖ | This variant has been identified in been identified in 2 out of 124800 (0.005% FAF 95% CI) of European chromosomes (> 0.004%) |

| | | | |
|---|---|---|---|
| **PM1** | | ✖ | not in codons 485-502 & 1248- 1266 |
| **PM5** | | ✖ | variants at same codon do not meet criteria for LP/P |

## Curation History

Showing 1 to 1 of 1 rows