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Variant: NM_001018005.2(TPM1):c.842T>C (p.Met281Thr)

Version: 1.0

CA018416

31885 (ClinVar)

Gene: TPM1 (HGNC:7168)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6debff91-5fa6-43cd-ba3f-4f21edf1ee18
Approved on: 2025/11/13
Published on: 2025/11/13

HGVS expressions

NM_001018005.2(TPM1):c.842T>C (p.Met281Thr)
NM_001018005.2:c.842T>C
NC_000015.10:g.63064133T>C
CM000677.2:g.63064133T>C
NC_000015.9:g.63356332T>C
CM000677.1:g.63356332T>C
NC_000015.8:g.61143385T>C
NG_007557.1:g.26495T>C
ENST00000558868.6:n.1555+1488T>C
ENST00000559831.6:c.*191+1488T>C
ENST00000560131.2:n.2408T>C
ENST00000560615.6:c.394+1488T>C
ENST00000561395.6:c.*261T>C
ENST00000651622.2:c.734T>C
ENST00000705544.1:c.529T>C
ENST00000317516.12:c.664+1488T>C
ENST00000334895.10:c.664+1488T>C
ENST00000357980.9:c.898+1488T>C
ENST00000403994.9:c.842T>C
ENST00000404484.9:c.664+1488T>C
ENST00000558910.3:c.734T>C
ENST00000559281.6:c.734T>C
ENST00000559397.6:c.772+1488T>C
ENST00000560970.6:c.842T>C
ENST00000561266.6:c.842T>C
ENST00000644204.1:n.794+1488T>C
ENST00000651344.1:n.1288+1488T>C
ENST00000651577.1:c.394+1488T>C
ENST00000651590.1:c.664+1488T>C
ENST00000651622.1:c.174T>C
ENST00000651704.1:c.394+1488T>C
ENST00000267996.11:c.772+1488T>C
ENST00000288398.10:c.842T>C
ENST00000317516.11:c.664+1488T>C
ENST00000334895.9:c.664+1488T>C
ENST00000357980.8:c.898+1488T>C
ENST00000358278.7:c.772+1488T>C

ENST00000403994.7:c.842T>C
ENST00000404484.8:c.664+1488T>C
ENST00000558072.5:n.291+1488T>C
ENST00000558264.5:c.*191+1488T>C
ENST00000558347.5:c.*180+1488T>C
ENST00000558544.5:c.*380+1488T>C
ENST00000558910.2:c.87T>C
ENST00000559108.1:n.240+1488T>C
ENST00000559281.5:c.734T>C
ENST00000559397.5:c.772+1488T>C
ENST00000559556.5:c.772+1488T>C
ENST00000560131.1:n.330T>C
ENST00000560445.1:c.187-1828T>C
ENST00000560970.5:c.784T>C
ENST00000560975.5:n.2621+1488T>C
ENST00000561266.5:c.658T>C
ENST00000561395.5:c.468T>C
NM_000366.5:c.842T>C
NM_001018004.1:c.772+1488T>C
NM_001018005.1:c.842T>C
NM_001018006.1:c.772+1488T>C
NM_001018007.1:c.772+1488T>C
NM_001018008.1:c.664+1488T>C
NM_001018020.1:c.772+1488T>C
NM_001301244.1:c.842T>C
NM_001301289.1:c.664+1488T>C
NM_001330344.1:c.664+1488T>C
NM_001330346.1:c.734T>C
NM_001330351.1:c.664+1488T>C
NM_001365776.1:c.772+1488T>C
NM_001365777.1:c.772+1488T>C
NM_001365778.1:c.898+1488T>C
NM_001365779.1:c.842T>C
NM_001365780.1:c.664+1488T>C
NM_001365781.1:c.734T>C
NM_001365782.1:c.734T>C
NM_000366.6:c.842T>C
NM_001018004.2:c.772+1488T>C
NM_001018006.2:c.772+1488T>C
NM_001018007.2:c.772+1488T>C
NM_001018008.2:c.664+1488T>C
NM_001018020.2:c.772+1488T>C
NM_001301244.2:c.842T>C
NM_001301289.2:c.664+1488T>C
NM_001330344.2:c.664+1488T>C
NM_001330346.2:c.734T>C
NM_001330351.2:c.664+1488T>C
NM_001365781.2:c.734T>C

Met criteria codes 4

Expert Panel

Uncertain Significance

PP2 PP3 PM2_Supporting PS4_Supporting

Not Met criteria codes 15

PP1 PM6 PM1 PM5 PM4 BA1 PVS1 BS1 BS4 BS3 BP4 BP5 PS1 PS2 PS3

Evidence Links 0

Cardiomyopathy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TPM1 Version 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cardiomyopathy VCEP

NM_001018005.2(TPM1):c.842T>C (p.Met281Thr) - This variant has been reported in individuals with HCM (PMIDs: 12860912, 18533079, 21835320, 25524337, 27532257) and is statistically increased in individuals with cardiomyopathy compared to controls [OR lower 95% CI >5]. Therefore, the PS4_Supporting criterion has been applied. This variant is present in gnomAD (v2.1.1), but did meet the threshold for PM2_Supporting. This variant lies in a gene where variants are statistically more likely to be disease-associated (PP2; PMID: 30696458). Computational prediction tools suggest that this variant may impact the protein (REVEL score >0.7; PP3). In summary, this variant is classified as Uncertain Significance for HCM in an autosomal dominant manner based on PS4_Supporting, PM2_Supporting, PP2, and PP3.

Met criteria codes

PP2	✔	New guidelines: PP2_supporting applies for this TPM1 in context of HCM. This variant lies in a gene where variants are statistically more likely to be disease-associated (PP2; PMID: 30696458).
PP3	✔	1/11/23: REVEL: 0.706 REVEL:0.846 Computational prediction tools and conservation analyses suggest that this variant may impact the protein, though this information is not predictive enough to determine pathogenicity (PP3).
PM2_Supporting	✔	gnomAD v2.1.1: European non-Finnish AC=1, AN=113,468. Not detected in any other population.
PS4_Supporting	✔	Disease specific rules: Case-control odds ratio (OR) calculations (Lower 95% CI of OR ≥5 SUPPORTING; ≥10 MODERATE; ≥20 STRONG) OR calculated based on counts in the literature and ClinVar Case data Literature: 4 cases (not including LMM-counted under ClinVar) ClinVar: entries from 7 centres (including LMM). Count as minimum 7 occurrences? Estimated case count= min 11 Estimated no cases tested=minimum ~15,000 Control data Variant found in African population in gnomAD v3.1 (AC=2 AN=41,464). The Total gnomAD population used as denominator for case vs control analysis, as this was considered to reflect the ancestries represented in the case population. However, this might mean we are underestimating the frequency of this variant in controls. gnomAD (Total data from v3.1) number with variant=2 , number without variant= 76,116 OR:27.91 95% CI [6.19-125.93] Note: On initial review, using gnomAD v2.1.1 data only. PS4_supporting was applied. This variant has been reported in individuals with HCM (PMIDs: 12860912, 18533079, 21835320, 25524337, 27532257) and is statistically increased in individuals with cardiomyopathy compared to controls [OR lower 95% CI >5]. Therefore, PS4_Supporting criteria has been applied.

Not Met criteria codes

PP1	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM6	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	gnomAD v2.1.1: FAF < 0.1% BA1 threshold.
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	gnomAD v2.1.1: FAF < 0.02% BS1 threshold.
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001018005.2(TPM1):c.842T>C (p....	Uncertain Significance	Hypertrophic Cardiomyopathy	2025-11-13	1.0	ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TPM1 Version 1.0.0	TPM1

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