Variant: NM_001276345.2(TNNT2):c.851+1G>A

Version: 1.0

CA005196

43673 (ClinVar)

Gene: TNNT2 (HGNC:7139)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1d86a007-768b-4b8c-be66-f13fd8f5d403
Approved on: 2025-11-14
Published on: 2025-11-14

HGVS expressions

NM_001276345.2:c.851+1G>A
NM_001276345.2(TNNT2):c.851+1G>A
NC_000001.11:g.201359622C>T
CM000663.2:g.201359622C>T
NC_000001.10:g.201328750C>T
CM000663.1:g.201328750C>T
NC_000001.9:g.199595373C>T
NG_007556.1:g.23056G>A
ENST00000455702.7:c.836+1G>A
ENST00000367318.10:c.821+1G>A
ENST00000367322.6:c.809+1G>A
ENST00000412633.3:c.812+1G>A
ENST00000422165.6:c.842+1G>A
ENST00000438742.6:c.800+1G>A
ENST00000651504.1:n.1312+1G>A
ENST00000656932.1:c.851+1G>A
ENST00000658476.1:c.886+1G>A
ENST00000660295.1:c.821+1G>A
ENST00000662159.1:c.*210+1G>A
ENST00000663843.1:c.*751+1G>A
ENST00000666449.1:c.*96+1G>A
ENST00000236918.11:c.851+1G>A
ENST00000360372.8:c.722+1G>A
ENST00000367315.6:c.830+1G>A
ENST00000367317.8:c.803+1G>A
ENST00000367318.9:c.821+1G>A
ENST00000367320.6:c.722+1G>A
ENST00000367322.5:c.812+1G>A
ENST00000421663.6:c.635+1G>A
ENST00000438742.5:c.803+1G>A
ENST00000458432.6:c.635+1G>A
ENST00000460780.5:n.1970+1G>A
ENST00000476888.5:n.268+1G>A
ENST00000491504.5:n.2060+1G>A
ENST00000509001.5:c.821+1G>A
NM_000364.3:c.842+1G>A
NM_001001430.2:c.821+1G>A

NM_001001431.2:c.812+1G>A
NM_001001432.2:c.803+1G>A
NM_001276345.1:c.851+1G>A
NM_001276346.1:c.722+1G>A
NM_001276347.1:c.821+1G>A
NM_000364.4:c.842+1G>A
NM_001001430.3:c.821+1G>A
NM_001001431.3:c.812+1G>A
NM_001001432.3:c.803+1G>A
NM_001276346.2:c.722+1G>A
NM_001276347.2:c.821+1G>A

Likely Pathogenic

Met criteria codes 3

PS3_Moderate PM2_Supporting PP1_Strong

Not Met criteria codes 7

PM6 BA1 BS1 BP2 PVS1 PS2 PS4

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 TNNT2 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Cardiomyopathy VCEP

NM_001276345.2(TNNT2):c.851+1G>A. This variant has been reported in individuals with HCM and other cardiomyopathies (LMM data, Thierfelder 1994 PMID: 8205619, Watkins 1995 PMID: 7898523, Varnava 2001 PMID: 11560853) and is absent from large population studies (PM2_supporting; gnomAdD v2.1). It is not statistically increased in individuals with cardiomyopathy compared to controls [OR lower 95% CI <5]. Therefore, the PS4 criterion has not been applied. The variant segregated with HCM in at least 13 affected relatives from one family (PP1_Strong; Thierfelder 1994 PMID: 8205619, Watkins 1995 PMID: 7898523). This variant occurs within the canonical splice site (+/- 1,2) and is predicted to cause altered splicing leading to an abnormal or absent protein. This alteration is shown to affect the second to last exon, therefore, likely to escape nonsense mediated decay (NMD) and result in a truncated protein. In vitro and in vivo functional studies provide some evidence that this variant affected protein function (PS3_Moderate; Thierfelder 1994 PMID: 8205619, Watkins 1996 PMID: 8958207, Tardiff 1998 PMID: 9637714, Mukherjea 1999 PMID: 10529204, Szczesna 2000 PMID: 10617660, Gafurov 2004 PMID: 15568820, Becker 2011 PMID: 21245263). In summary, this variant meets criteria to be classified as likely pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner based on PM2_Supporting, PP1_Strong and PS3_Moderate.

Met criteria codes

PS3_Moderate	✔	In vitro and in vivo functional studies provide some evidence that this variant affected protein function (PS3_Moderate; Thierfelder 1994 PMID: 8205619, Watkins 1996 PMID: 8958207, Tardiff 1998 PMID: 9637714, Mukherjea 1999 PMID: 10529204, Szczesna 2000 PMID: 10617660, Gafurov 2004 PMID: 15568820, Becker 2011 PMID: 21245263)
PM2_Supporting	✔	Absent in gnomad (2.1 and 4.1)

PP1_Strong		✔	The variant segregated with HCM in at least 13 affected relatives from one family (Thierfelder 1994 PMID: 8205619, Watkins 1995 PMID: 7898523)

Not Met criteria codes

PM6		✖	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
BS1		✖	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
PVS1		✖	Splicing impact, out of frame exon but LOF is not dx mechanism
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	This variant has been reported in individuals with HCM and other cardiomyopathies (LMM data, Thierfelder 1994 PMID: 8205619, Watkins 1995 PMID: 7898523, Varnava 2001 PMID: 11560853) and i sabsent from large population studies (gnomAdD v2.1). It is not statistically increased in individuals with cardiomyopathy compared to controls [OR lower 95% CI <5]. Therefore, the PS4 criterion has not been applied and the PM2_Supporting criterion has been applied (PM2_Supporting).

Curation History

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