

Variant: *NM\_000257.3(MYH7):c.5329G>A (p.Ala1777Thr)*

Version: 2.0

[CA015952](#)

[177697 \(ClinVar\)](#)

**Gene:** MYH7 ([HGNC:4625](#))

**Condition:** hypertrophic cardiomyopathy ([MONDO:0005045](#))

**Inheritance Mode:** Autosomal dominant inheritance

**UUID:** a16a1f02-844a-4b61-bd74-71c8230a85de

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### *HGVS expressions*

**NM\_000257.3:c.5329G>A**

NM\_000257.3(MYH7):c.5329G>A (p.Ala1777Thr)

NC\_000014.9:g.23415225C>T

CM000676.2:g.23415225C>T

NC\_000014.8:g.23884434C>T

CM000676.1:g.23884434C>T

NC\_000014.7:g.22954274C>T

NG\_007884.1:g.25437G>A

ENST00000355349.4:c.5329G>A

ENST00000355349.3:c.5329G>A

NM\_000257.4:c.5329G>A

Uncertain Significance

Not Met criteria codes **25**

PP2 PP3 PP1 PS1 PS4 PS2  
PM3 PM2 PM5 PM6 PM1  
PM4 PS3 PVS1 BA1 BP3  
BP1 BP4 BP7 BP2 BP5 BS2  
BS1 BS4 BS3

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 MYH7 Version 2.0.0*

**Criteria Specification Approval History**

**Criteria Specifications for this VCEP**
















Evidence submitted by expert panel




























#### ***Cardiomyopathy VCEP***

The NM\_000257.4(MYH7):c.5329G>A (p.Ala1777Thr) variant has been identified in at least 14 individuals with HCM, 2 of whom had an additional variant in another gene that may contribute to their disease, 1 individual with RCM with another pathogenic MYH7 variant, and 5 individuals with DCM including 2 that also had disease-causing variants (Richard 2003 PMID:12707239; Bos 2014 PMID:24793961; Homburger 2016 PMID:27247418; Walsh 2017 PMID: 27532257; Ho 2018 PMID:30297972; Ambry pers. comm.; GeneDx pers. comm.; LMM pers. comm.; OMGL pers. comm). This variant has also been identified in 1 individual with LVNC requiring transplant who also had 2 pathogenic MYBPC3 variants, 1 individual with Brugada syndrome, and 2 individuals with myopathy - 1 with myofibrillar myopathy and 1 with distal and axial myopathy (Hertz 2014 PMID:25467552; Evilä 2016 PMID:26627873; Chanson 2016 PMID:26969127; Liu 2020

PMID:31918855). This variant has been observed to segregate with DCM in 1 relative of a proband with DCM as well as not segregate with HCM in an affected sibling of a proband with HCM (OMGL per. comm.). Because of the variability in phenotypes observed in individuals with this variant and because PS4 is only applicable when the variant is absent or rare in large population studies, the PS4 criterion was not applied (Kelly 2018 PMID:29300372). Additionally, the segregation data is currently insufficient to establish segregation or non-segregation with disease and therefore neither PP1 nor BS4 were applied. This variant has been identified in 0.008% (FAF 95% CI; 17/129,190) of European chromosomes in gnomAD v.2.1.1 (<http://gnomad.broadinstitute.org>) and is above the threshold of 0.004%, therefore PM2 cannot be applied. Computational prediction tools and conservation do not provide evidence for or against an impact to the protein. In summary, due to conflicting evidence, this variant is classified as uncertain significance for cardiomyopathy in an autosomal dominant manner. MYH7-specific ACMG/AMP criteria applied (Kelly 2018 PMID:29300372): None.

#### Not Met criteria codes

<b>PP2</b>		No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PP3</b>	 	In silico tools are mixed on predicted impact and REVEL is below threshold.
<b>PP1</b>	 	1 non-segregation from OMGL lab (internal data), variant did not segregate to affected sister of proband
<b>PS1</b>	 	No other variants affecting the same AA reported.
<b>PS4</b>	 	Variant has been identified in: 6 individuals with HCM in the literature (Richard 2003 PMID:12707239; Bos 2014 PMID:24793961; Homburger 2016 PMID:27247418; Walsh 2017 PMID: 27532257; Ho 2018 PMID:30297972). 8 individuals with HCM from internal data (2 with other disease-causing variants; splice and nonsense in MYBPC3), 1 RCM with another MYH7 missense considered path by this VCEP), & 5 DCM (2 have TTN LP variants)(Ambry pers. comm.; GeneDx pers. comm.; LMM pers. comm.; OMGL pers. comm) it was also seen in 1 LVNC requiring transplant with 2 pathogenic MYBPC3 variants, 1 Brugada syndrome, 1 myofibrillar myopathy, 1 patient with distal & axial myopathy, (Hertz 2014 PMID:25467552; Evilä 2016 PMID:26627873; Chanson 2016 PMID:26969127; Liu 2020 PMID:31918855). Literature search complete: ClinVar, Google, HGMD INTERNAL DATA: Ambry 1 HCM, 1 GI symptoms, heart disease, renal issues; HCM proband with MYBPC3 c.3330+1G>T VLP GeneDx 3 HCM, 3 DCM; 1 of the HCM probands has no clinical information provided to support the HCM diagnosis. All 3 of the DCM probands have other variants reported (one has a TTN LPath; another has VUS on RYR2, RBM20 and LDB3 and the third one has a family history of HCM and DCM and VUS on MYH7, DSP and TPM1) Invitae 3 HCM, 1 DCM, 1 LQTS; 1 DCM proband also has Likely Pathogenic variant in TTN (NM_001267550.2:c.52847G>A (p.Trp17616*)), 1 HCM proband has Path MYBPC3 p.Gln404* variant LMM 1 RCM that had another MYH7 variant (p.Arg453Cys - pathogenic by this EP) OMGL 1 HCM (+2 HCM in Walsh paper) and 1 non-segregation with HCM (not detected in affected sister of one HCM proband), 1 DCM and 1 segregation with DCM
<b>PS2</b>	 	Updated 2021: data not available to assess this criteria
<b>PM3</b>		No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PM2</b>		Variant seen in 0.008% (FAF 95% CI; 17/129,190) of European chromosomes in gnomAD v.2.1.1
<b>PM5</b>	 	No other variants affecting the same AA reported.

<b>PM6</b>			Updated 2021: data not available to assess this criteria
<b>PM1</b>			Variant is located outside of the head domain
<b>PM4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PS3</b>			This variant is reported in a PhD thesis which performed a number of functional studies, however the results have not been subsequently reported in the published literature. Author William Wallefeld, University of Western Australia, primary supervisor Dr Nigel Liang. Results not sufficient to apply this criteria.
<b>PVS1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BA1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP3</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP7</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP2</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP5</b>			Updated 2021: no reports found to support this criteria
<b>BS2</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS4</b>			1 non-segregation from OMGL lab (internal data), variant did not segregate to affected sister of proband
<b>BS3</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

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