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_000257.3(MYH7):c.5726G>C (p.Arg1909Pro)

Version: 1.2

CA016422

43085 (ClinVar)

Gene: MYH7 (HGNC:4625)
Condition: dilated cardiomyopathy (MONDO:0005021)
Inheritance Mode: Autosomal dominant inheritance
UUID: e0f90a49-fd56-4a6e-97a3-d0cc9611d193
Approved on: 2021-03-22
Published on: 2021-10-13

HGVS expressions

NM_000257.3:c.5726G>C
NM_000257.3(MYH7):c.5726G>C (p.Arg1909Pro)
ENST00000355349.4:c.5726G>C
ENST00000355349.3:c.5726G>C
NM_000257.4:c.5726G>C
NC_000014.9:g.23413823C>G
CM000676.2:g.23413823C>G
NC_000014.8:g.23883032C>G
CM000676.1:g.23883032C>G
NC_000014.7:g.22952872C>G
NG_007884.1:g.26839G>C

Likely Pathogenic

The Expert Panel has overridden the computationally generated classification - "*Uncertain Significance - Insufficient Evidence*"

Met criteria codes 3

PP3 PM6 PM2

Not Met criteria codes 10

BS3 BS4 BS1 BP4 PS4 PS1 PS2 PS3 BA1 PP1

Evidence Links 0

Expert Panel

Cardiomyopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cardiomyopathy VCEP

The c.5726G>C (p.Arg1909Pro) variant in MYH7 has been reported as a de novo occurrence in 1 individual with dilated cardiomyopathy and myopathy features (PM6; Partners LMM ClinVar SCV000059632.5). Additionally, this variant reportedly segregated with DCM and in 2 affected relatives (Partners LMM ClinVar SCV000059632.5); however this data is currently insufficient to establish co-segregation and apply PP1. This variant was absent from large population studies (PM2; https://gnomad.broadinstitute.org, v2.1.1). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (PP3). This variant was previously classified as likely pathogenic for DCM by this expert panel (EP) based on clinical judgement; however, upon re-evaluation, the EP has deemed that uncertain significance was more appropriate based on the available evidence. In summary, this variant is classified as uncertain significance for dilated cardiomyopathy in an autosomal dominant manner. MYH7-specific ACMG/AMP criteria applied (Kelly 2018 PMID:29300372): PM6, PM2, PP3.

Met criteria codes

PP3	✔	Alamut tools (SIFT, MutationTaster, and PolyPhen2) are supportive of damaging, while AlignGVGD is tolerated. Sarcomere polyphen calls Path. Amino acid is conserved across 100 vertebrates in UCSC with good alignments. REVEL score also is strongly supportive of damaging.
PM6	✔	LMM: Assumed de novo occurrence in case with DCM and myopathy (SCV000059632)
PM2	✔	Absent with >30x coverage

Not Met criteria codes

BS3	✖	No functional data
BS4	✖	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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	SUMMARY: This variant has been reported as a de novo occurrence in 1 individual with dilated cardiomyopathy and myopathy features (PM6; Partners LMM ClinVar SCV000059632.5). Additionally, this variant reportedly segregated with disease in 2 affected family members (Partners LMM ClinVar SCV000059632.5). LMM: 1 de novo occurrence (parentage not confirmed) in 1 individuals with DCM and myopathy with additional segregation in 2 affected family members with XXX. Has NOT been observed by any other labs (Invitae, OMGL, Ingles, Ambry, ARUP, CHEO, GeneDx) Google Scholar search found Wang 2018 (PMID: 29687901) which lists this variant, but only cites occurrence in Dalin 2017 (PMID: 27886618), which appears to only reference the DCM case submitted by the VCEP in 2016 and does not contribute any new additional probands. No additional literature listed in HGMD.
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 functional data
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP1	✖	LMM: Variant segregated with disease in 2 affected family members (ClinVar SCV000059632) - currently insufficient for PP1

Curation History

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