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_000257.4(MYH7):c.2606G>A (p.Arg869His)

Version: 1.0

CA012723

177667 (ClinVar)

Gene: MYH7 (HGNC:4625)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 10a62d23-9dad-468c-a363-8c26ffef1bb5
Approved on: 2021-09-28
Published on: 2021-10-01

HGVS expressions

NM_000257.4:c.2606G>A
NM_000257.4(MYH7):c.2606G>A (p.Arg869His)
NC_000014.9:g.23424842C>T
CM000676.2:g.23424842C>T
NC_000014.8:g.23894051C>T
CM000676.1:g.23894051C>T
NC_000014.7:g.22963891C>T
NG_007884.1:g.15820G>A
ENST00000355349.4:c.2606G>A
ENST00000355349.3:c.2606G>A
NM_000257.3:c.2606G>A

Likely Pathogenic

Met criteria codes 4

PS4 PM1 PP1_Moderate PM2_Supporting

Not Met criteria codes 20

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

Evidence Links 0

Expert Panel

Cardiomyopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cardiomyopathy VCEP

The NM_000257.4(MYH7):c.2606G>A (p.Arg869His) variant has been identified in >30 individuals with HCM, including at least 2 individuals with an additional variant in another gene that may contribute to their disease (PS4; Van Driest 2004 PMID: 15358028; Girolami 2006 PMID: 16858239; Cecchi 2006 PMID: 17180650; Olivotto 2008 PMID: 18533079; Girolami 2010 PMID: 20359594; Olivotto 2011 PMID: 21835430; Witjas-Paalberends 2013 PMID: 23674513; Marsiglia 2013 PMID: 24093860; Bos 2014 PMID: 24793961; Coppini 2014 PMID: 25524337; Adalsteinsdottir 2014 PMID: 25078086; Homburger 2016 PMID: 27247418; Viswanathan 2017 PMID: 29121657; Walsh 2017 PMID: 2753225; Ho 2018 PMID: 30297972; Ambry pers. comm.; Centenary Institute Sydney pers. comm.; CHEO pers. comm.; GeneDx pers.

comm.; Invitae pers. comm.; LMM pers. comm.; OMGL pers. comm.). This variant also segregated in 6 affected relatives with HCM from at least two families (PP1_Moderate; Girolami 2010 PMID: 20359594; GeneDx pers. comm.). Additionally, this variant has also been reported in 1 individual with DCM with an additional variant in another gene that may contribute to their disease, 1 individual with LVH and suspected HCM, 1 individual with LVNC, 1 individual with septal hypertrophy with AV conduction defect, and 4 individuals with unspecified heart disease (Ambry pers. comm.; GenDx pers. comm.). This variant was identified in 0.002% (FAF 95% CI; 2/16254) of African chromosomes by gnomAD v2.1.1 (https://gnomad.broadinstitute.org), but has also been identified in a greater number of African chromosomes in gnomAD v.3.1. Therefore, the PM2 criterion was downgraded to PM2_supporting. This variant lies in the head region of the protein (aa 181-937) and missense variants in this region are statistically more likely to be associated with HCM (PM1; Walsh 2017 PMID:27532257). Computational prediction tools and conservation analyses do not provide strong support for or against an impact to the protein. In summary, this variant meets criteria to be classified as likely pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. ACMG/AMP Criteria applied: PS4, PP1_Moderate, PM2_Supporting, PM1.

Met criteria codes

PS4	✔	This variant was observed in > 15 individuals with HCM
PM1	✔	This variant is located within the head region (codons 181-937) of the Myosin-7 protein (NM_000257.2; NP_000248.2), where MYH7 pathogenic variants are significantly clustered (PMID 29300372).
PP1_Moderate	✔	This variant was found to segregate with disease in 6 individuals from 2 different families (PMID 20359594, internal laboratories data from the ClinGen CMP working group).
PM2_Supporting	✔	Variant was identified in 6/251440 (0.002%) of alleles tested from presumed healthy individuals in the Genome Aggregation Database (gnomAD), including 0.01% of African alleles (Popmax filtering allele frequency: 0.002%), but has also been identified in a greater number of African chromosomes in gnomAD v.3.1. Therefore, the PM2 criterion was downgraded to PM2_supporting.

Not Met criteria codes

BP3	✖	Missense variant
BP1	✖	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
BP7	✖	missense variant
BP2	✖	not observed
BP5	✖	not applicable here
PS3	✖	no experimental data available

PS1	✖	n/a
PS2	✖	no de novo cases
PP3	✖	In silico analysis programs (SIFT, PolyPhen-2, Mutation Taster) gave conflicting results with regards to a possible impact on the protein function and/or structure.
PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	CHEO has previously reported p.Arg869Cys as likely pathogenic in Nov 2019. As per our CHEO internal rules, we apply PM5 if variant classified by us as LP or P within the last year. Not met because only applies to P variants. variant in same codon is LP at best
PM6	✖	no de novo cases
PM4	✖	Missense variant
PVS1	✖	missense variant
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
BS4	✖	n/a
BS3	✖	no experimental data available
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows