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.2845G>A (p.Glu949Lys)

Version: 1.0

CA013144

14093 (ClinVar)

Gene: MYH7 (HGNC:4625)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1d9bb12c-bae2-4030-a50c-cddb240c95e8
Approved on: 2021/3/22
Published on: 2021/8/25

HGVS expressions

NM_000257.4:c.2845G>A
NM_000257.4(MYH7):c.2845G>A (p.Glu949Lys)
NC_000014.9:g.23423984C>T
CM000676.2:g.23423984C>T
NC_000014.8:g.23893193C>T
CM000676.1:g.23893193C>T
NC_000014.7:g.22963033C>T
NG_007884.1:g.16678G>A
ENST00000355349.4:c.2845G>A
ENST00000355349.3:c.2845G>A
NM_000257.3:c.2845G>A

Likely Pathogenic

Met criteria codes 4

PS4_Moderate PP3 PM2 PM6

Not Met criteria codes 16

PS3 PS1 PS2 PP1 PM5 PM1 PM4 BA1 BS1 BS4 BS3 PVS1 BP4 BP7 BP2 BP5

Evidence Links 0

Expert Panel

Cardiomyopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cardiomyopathy VCEP

The c.2845G>A (p.Glu949Lys) variant in MYH7 has been reported in 12 individuals with HCM (PS4_Moderate; Watkins 1992 PMID:1552912; Walsh 2017 PMID:27532257; Zigova 2018 PMID:28815794; CHEO pers comm.). This variant segregated with disease in 1 affected relative with HCM (Watkins 1992 PMID:1552912); however, this data is currently insufficient to establish co-segregation with disease and apply PP1. Additionally, this variant has been reported as a de novo occurence in 1 child with RCM (PM6; Kapoor 2017 http://repository.ias.ac.in/114592/1/JPractCardiovascSci33143-8313497_230534.pdf). This variant was absent from large population studies (PM2; http://gnomad.broadinstitute.org). Computational prediction tools and conservation analysis suggest that this variant may impact

the protein (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. MYH7-specific ACMG/AMP criteria applied (Kelly 2018 PMID:29300372): PS4_Moderate; PM6; PM2; PP3

Met criteria codes

PS4_Moderate	✔	1 LMM/Walsh HCM proband + 1 CHEO HCM proband + 9 Zigova 2018 HCM probands + 1 Watkins 1992 HCM proband; considered PS4, but minor concern regarding Slovakian founder effects for the 9 Zigova probands, so stayed at moderate.
PP3	✔	BayesDel deleterious (0.46)
PM2	✔	absent in gnomAD with ~100X coverage and ~251000 total alleles sequenced per surrounding region
PM6	✔	Detected in 11 yo boy with RCM. Clinical and genetic analysis of parents was negative. Unclear if paternity confirmed. No PMID for lit. (and note prior paper, also without PMID, indicated 10 unaffected family members without variant--assume this includes the parents) Kapoor M, Das S, Biswas A, Seth S, Bhargava B, Rao VR. Epidemiology of cardiomyopathy – A Clinical and Genetic Study of Restrictive Cardiomyopathy: The EPOCH-R Study. J Pract Cardiovasc Sci 2017;3:143-9. http://repository.ias.ac.in/114592/1/JPractCardiovascSci33143-8313497_230534.pdf

Not Met criteria codes

PS3	✖	No knock-in mammalian model available
PS1	✖	No such variants reported
PS2	✖	no such cases
PP1	✖	only 1 meiosis from Watkins 1992
PM5	✖	E949V is VUS (PM2 only)
PM1	✖	not in head domain (aa181-937)
PM4	✖	missense change
BA1	✖	variant is rare
BS1	✖	variant is rare
BS4	✖	No failure to segregate with disease reported reported.

BS3		✖	No knock-in mammalian model available
PVS1		✖	missense change
BP4		✖	BayesDel deleterious (0.46)
BP7		✖	missense change
BP2		✖	No such cases.
BP5		✖	no such cases

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.