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.3134G>T (p.Arg1045Leu)

Version: 1.0

CA013375

42948 (ClinVar)

Gene: MYH7 (HGNC:4625)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 40ccb7f9-d0a7-4e61-9756-8fef5c463031
Approved on: 2021-08-25
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HGVS expressions

NM_000257.4:c.3134G>T
NM_000257.4(MYH7):c.3134G>T (p.Arg1045Leu)
NC_000014.9:g.23422291C>A
CM000676.2:g.23422291C>A
NC_000014.8:g.23891500C>A
CM000676.1:g.23891500C>A
NC_000014.7:g.22961340C>A
NG_007884.1:g.18371G>T
ENST00000355349.4:c.3134G>T
ENST00000355349.3:c.3134G>T
NM_000257.3:c.3134G>T

Likely Pathogenic

Met criteria codes 4

PP1_Moderate PM2 PP3 PS4_Moderate

Not Met criteria codes 20

PM3 PM5 PM6 PM1 PM4 BA1 PVS1 BS1 BS4 BS3 BS2 BP3 BP4 BP7 BP2 BP5 PS3 PS1 PS2 PP4

Evidence Links 0

Expert Panel

Cardiomyopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cardiomyopathy VCEP

The c.3134G>T (p.Arg1045Leu) variant in MYH7 has been reported in at least 15 individuals with HCM (PS4_Moderate; Cann 2017 PMID:27000522; Sheikh 2018 PMID:29764897, Walsh 2017 PMID:27532257; GeneDx pers. comm., Invitae pers. comm., LMM pers. comm., OMGL pers. comm.), 4 of whom also had additional variants in other HCM-associated genes (GeneDx pers. comm., Invitae pers. comm., LMM pers. comm.). Because of the additional variants observed in multiple cases, PS4 was downgraded to Moderate. This variant also segregated with HCM in 6 affected relatives from 3 families (PP1_Moderate; Cann 2017 PMID:27000522; GeneDx pers. comm., LMM pers. comm., OMGL pers. comm.). This variant has also been identified in 0.001% (FAF 95% CI, 4/113744) of European chromosomes in gnomAD

v2.1.1 (https://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; PP1_Moderate; PM2; PP3.

Met criteria codes

PP1_Moderate	✔	Total number of segregations: 5 (internal data log)
PM2	✔	Popmax FAF in gnomAD is < 0.004%
PP3	✔	In silico analysis programs (SIFT, PolyPhen-2, Mutation Taster) predict this variant to have an impact on the protein function
PS4_Moderate	✔	Total number of probands: 13 (11 from internal data log + 2 from PMID 27000522, 29764897)

Not Met criteria codes

PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	A different missense substitution at this codon (p.Arg1045Cys) has been previously reported by our laboratory and other laboratories in ClinVar as likely pathogenic. approved by expert panel
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	not in head domain 181-937 aa
PM4	✖	variant is missense
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	variant is missense
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3	✖	variant is missense
BP4	✖	In silico analysis programs (SIFT, PolyPhen-2, Mutation Taster) predict this variant to have an impact on the protein function
BP7	✖	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
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	n/a
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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