Variant: NM_000257.4(MYH7):c.4130C>T (p.Thr1377Met)

Version: 1.0

CA014494

42992 (ClinVar)

Gene: MYH7 (HGNC:4625)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: f4dea66d-87b3-467f-862c-c239472e6930
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HGVS expressions

NM_000257.4:c.4130C>T
NM_000257.4(MYH7):c.4130C>T (p.Thr1377Met)
NC_000014.9:g.23418249G>A
CM000676.2:g.23418249G>A
NC_000014.8:g.23887458G>A
CM000676.1:g.23887458G>A
NC_000014.7:g.22957298G>A
NG_007884.1:g.22413C>T
ENST00000355349.4:c.4130C>T
ENST00000355349.3:c.4130C>T
NM_000257.3:c.4130C>T

Pathogenic

Met criteria codes 4

PS4 PP3 PM2 PP1_Strong

Not Met criteria codes 17

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

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.4130C>T (p.Thr1377Met) variant in MYH7 has been reported in >30 individuals with HCM (PS4; Richard 2003 PMID: 12707239; Van Driest 2004 PMID: 15358028; Girolami 2006 PMID: 16858239; Millat 2010 PMID: 20624503; Witjas-Paalberends 2013 PMID: 23674513; Berge 2014 PMID: 24111713; Helms 2014 PMID: 25031304; Adler 2016 PMID: 26743238; Montag 2017 PMID: 29101517; Pérez-Sánchez 2018 PMID: 28687478; Wang 2018 PMID: 29343710; Ambry pers. comm.; CHEO pers. comm.; GeneDx pers. comm., Invitae pers. comm.; LMM pers. comm.; Mayo pers. comm.; OMGL pers. comm.). This variant segregated with disease in >10 affected relatives with HCM in at least 4 families (PP1_strong; Pérez-Sánchez 2018 PMID: 28687478; Wang 2018 PMID: 29343710; LMM pers. comm.). This variant was identified in 0.0009% (1/113754) of European chromosomes by gnomAD v2.1.1 (PM2; 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 pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. MYH7-specific ACMG/AMP criteria applied (PMID:29300372): PS4; PP1_Strong; PM2; PP3.

Met criteria codes

PS4	✓	>15 probands reported in the literature and by laboratories in the Internal Data Log
PP3	✓	In silico analysis programs (SIFT, PolyPhen-2, Mutation Taster) predict this variant to have an impact on the protein function.
PM2	✓	Allele frequency of 0.0004% in gnomAD (global) Seen in 1/113754 european alleles in gnomad (0.0009%)
PP1_Strong	✓	>15 segs from 7 families

Not Met criteria codes

BP3	✗	This is a missense variant.
BP4	✗	In silico analysis programs (SIFT, PolyPhen-2, Mutation Taster) predict this variant to have an impact on the protein function.
BP7	✗	This is a missense variant.
BP2	✗	n/a
PS3	✗	Functional Data not available for this variant at this time.
PS1	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✗	no reports of denovo
PM3	✗	n/a
PM5	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✗	no reports of denovo
PM1	✗	not in hotspot
PM4	✗	This is a missense variant.

BA1	✖	Allele frequency of 0.0004% in gnomAD
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	Allele frequency of 0.0004% in gnomAD
BS4	✖	No evidence of non-segregation available in the literature or the Internal Data Log
BS3	✖	Functional Data not available for this variant at this time.

Curation History

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