Variant: NM_000257.4(MYH7):c.4066G>A (p.Glu1356Lys)

Version: 1.0

CA014400

164294 (ClinVar)

Gene: MYH7 (HGNC:4625)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8112b9be-baa4-485d-a686-c223e112af4e
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HGVS expressions

NM_000257.4:c.4066G>A
NM_000257.4(MYH7):c.4066G>A (p.Glu1356Lys)
NC_000014.9:g.23418313C>T
CM000676.2:g.23418313C>T
NC_000014.8:g.23887522C>T
CM000676.1:g.23887522C>T
NC_000014.7:g.22957362C>T
NG_007884.1:g.22349G>A
ENST00000355349.4:c.4066G>A
ENST00000355349.3:c.4066G>A
NM_000257.3:c.4066G>A

Pathogenic

Met criteria codes 4
PM2 PP1_Strong PS4 PP3

Not Met criteria codes 7
PM5 PM6 PM1 BS3 PS3 PS1 PS2

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.4066G>A (p.Glu1356Lys) variant has been identified in at least 40 individuals with HCM, including 1 with features of RCM (PS4; Brito 2005 PMID: 16335287; Van Driest 2004 PMID: 15358028; Perrot 2005 PMID: 15856146; Theis 2009 PMID: 19808356; Brito 2012 PMID: 22857948; Zou 2013 PMID: 23283745; Lopes 2013 PMID: 23396983; Núñez 2013 PMID: 23782526; Captur 2014 PMID: 24704860; Homburger 2016 PMID: 27247418; Walsh 2017 PMID: 27532257; Mademont-Soler 2017 PMID: 28771489; Lu 2018 PMID: 30165862; Ambry pers. comm.; GeneDx pers. comm.; Invitae pers. comm.; LMM pers. comm.; OMGL pers. comm.). This variant segregates with HCM in at least 10 relatives from 5 families (PP1_Strong; LMM pers. comm.; OMGL pers. comm.; Stanford Inherited Heart Center pers. comm.). This variant was also reported to segregate with disease in a family with HCM, although details were not provided (Brito 2012 PMID: 22857948). This variant was absent from large population studies (PM2; gnomAD v2.1.1, http://gnomad.broadinstitute.org). In vitro functional studies provide some evidence that this variant alters protein function; however, this data is currently insufficient to establish

functional impact and apply PS3 (Armel 2010 PMID: 19913502; Wolny 2013 PMID: 24047955). 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 (Kelly 2018 PMID:29300372): PS4, PP1_Strong, PM2, PP3.

Met criteria codes

PM2	✔	Absent from gnomAD v.2.1.1 with sufficient coverage.
PP1_Strong	✔	This variant segregates with HCM in at least 10 relatives from 5 families (PP1_Strong; LMM pers. comm.; OMGL pers. comm.; Stanford Inherited Heart Center pers. comm.). This variant was also reported to segregate with disease in a family with HCM, although details were not provided (Brito 2012 PMID: 22857948). 4 segregations in 1 family at Stanford (proband was in SHaRe) per Colleen Caleshu in original MYH7 pilot assessment. HCM proband and affected 1st cousin once-removed had variant with 3 linking relatives all affected/with clinical features of HCM (with with HCM and had myectomy, 1 with LVH, and 3 reported as having arrhythmias, pacemaker, and lightheadedness. Not counting the last one since phenotype is less specific, so conservatively 3 segregations.
PS4	✔	This variant has been identified in at least 40 individuals with HCM, including 1 with features of RCM (PS4; Brito 2005 PMID: 16335287; Van Driest 2004 PMID: 15358028; Perrot 2005 PMID: 15856146; Theis 2009 PMID: 19808356; Brito 2012 PMID: 22857948; Zou 2013 PMID: 23283745; Lopes 2013 PMID: 23396983; Núñez 2013 PMID: 23782526; Captur 2014 PMID: 24704860; Homburger 2016 PMID: 27247418; Walsh 2017 PMID: 27532257; Mademont-Soler 2017 PMID: 28771489; Lu 2018 PMID: 30165862; Ambry pers. comm.; GeneDx pers. comm.; Invitae pers. comm.; LMM pers. comm.; OMGL pers. comm.). Brito 2005 16335287 - 1 with HCM, "de novo" but unlikely true, likely overlap with later publication Van Driest 2004 PMID: 15358028 - at least 1 with HCM Perrot 2005 PMID: 15856146 - 1 with HCM Theis 2009 PMID: 19808356 - 1 with HCM, Functional too? Millat 2010 PMID: 20800588 - Found in cohort, but no specifics provided; Functional? Brito 2012 PMID: 22857948 - 1 with HCM Zou 2013 PMID: 23283745 - 3 with HCM Lopes 2013 PMID: 23396983 - 1 with HCM Núñez 2013 PMID: 23782526 - 1 with HCM; Captur 2014 PMID: 24704860 - 1 with HCM Chanavat 2016 PMID: 26688388 - 1 in a cohort of cases, but did not provide phenotypic information about the cases only the initial test requested (which was for HCM) Homburger 2016 PMID: 27247418 - 3 in SHaRe, but likely overlap with Clinical lab data Walsh 2017 PMID: 27532257 - 5 OMGL with HCM; 1 LMM with HCM Mademont-Soler 2017 PMID: 28771489 - 1 with HCM Lu 2018 PMID: 30165862 - 1 with RCM/HCM Marschall 2019 PMID: 31737537 - Could not find reference to variant or list of variants identified Gao 2020 PMID: 32344918 - RNAseq data from NCBI Seq Read Archive from an HCM patient (likely to overlap with other published cases, so not counting). Ormondroyd 2020 PMID: 32686758 - Identified as a secondary findings, but no patient specific information available. MAK - Literature search complete. Internal data reviewed.
PP3	✔	Tools predict damaging; REVEL predicts impact

Not Met criteria codes

PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	Variant is located outside head domain

BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	Armel 2010 PMID: 19913502 - Thermodynamically destabilizes the protein and decreased the ability of the protein to form filaments. Wolny 2013 PMID: 24047955 suggested E1356K may lead to reduced sarcomere incorporation of myosin in vivo but did not observe any adverse effects on muscle contraction. However, collectively this data is insufficient to apply PS3.
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✖	Brito D et al. Sarcomeric hypertrophic cardiomyopathy: genetic profile in a Portuguese population. 2012 Sep;31(9):577-87. PMID: 22857948: Variant listed as "de novo", but doesn't appear to have been tested in parents, so not counting as de novo.

Curation History

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