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Variant: NM_000257.4(MYH7):c.715G>A (p.Asp239Asn)

Version: 1.0

CA016679

43100 (ClinVar)

Gene: MYH7 (HGNC:4625)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8c8707d1-9b0c-4e28-94c8-cc7321eb8840
Approved on: 2021/3/22
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HGVS expressions

NM_000257.4:c.715G>A
NM_000257.4(MYH7):c.715G>A (p.Asp239Asn)
NC_000014.9:g.23431602C>T
CM000676.2:g.23431602C>T
NC_000014.8:g.23900811C>T
CM000676.1:g.23900811C>T
NC_000014.7:g.22970651C>T
NG_007884.1:g.9060G>A
ENST00000355349.4:c.715G>A
ENST00000355349.3:c.715G>A
NM_000257.3:c.715G>A

Likely Pathogenic

Met criteria codes 4

PP1_Moderate PS4_Moderate PM2 PM1

Not Met criteria codes 11

BS1 BS4 BS3 BP4 BA1 PM5 PM6 PS3 PS1 PS2 PP3

Evidence Links 0

Expert Panel

Cardiomyopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cardiomyopathy VCEP

The c.715G>A (p.Asp239Asn) variant in MYH7 has been identified in at least 13 individuals with HCM (PS4_Moderate; Iascone 2007 PMID:17438619; Kaski 2009 PMID:20031618; Garcia-Pavia 2011 PMID:21896538; Murphy 2016 PMID:26914223; Homburger 2016 PMID:27247418; Walsh 2017 PMID:27532257; Ingles 2017 PMID:28408708) and segregated with HCM in 5 affected individuals from 4 families (PP1_Moderate; Iascone 2007 PMID:17438619; Garcia-Pavia 2011 PMID:21896538; LMM ClinVar SCV000059647.6 and pers comm). This variant has been identified in 0.003% (1/34592) of Latino chromosomes but is absent from all other populations in gnomAD v2.1.1 (PM2; http://gnomad.broadinstitute.org). 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 disease-associated (PM1; Walsh 2017 PMID:27532257). Computational prediction tools and

conservation analysis were mixed about the potential impact of this variant. 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; PM1

Met criteria codes

PP1_Moderate	✔	This variant segregated with disease in 5 affected individuals with HCM in 4 families (PP1_Moderate; Iascone 2007 PMID:17438619; Garcia-Pavia 2011 PMID:21896538; LMM ClinVar SCV000059647.6 and pers comm). 2 segregations with HCM from 1 family from Garcia-Pavia 2011 PMID:21896538 1 segregation from Iascone 2007 (PMID:17438619) 2 segregations with HCM in 2 families from LMM internal
PS4_Moderate	✔	The c.715G>A (p.Asp239Asn) variant in MYH7 has been identified in at least 13 individuals with HCM (PS4_Moderate; Iascone 2007 PMID:17438619; Kaski 2009 PMID:20031618; Garcia-Pavia 2011 PMID:21896538; Murphy 2016 PMID:26914223; Homburger 2016 PMID:27247418; Walsh 2017 PMID:27532257; Ingles 2017 PMID:28408708). Iascone 2007 (PMID:17438619) described in ClinVar evidence blurbs, but is only a mutation report: "Aminoacid charge change—aminoacid conserved during evolution—not found in 100 alleles (healthy blood donors) —found in one patient [with HCM]: age at onset 5 years, myectomy at 7 years; the mother is affected and she carried the same mutation. He has another novel mutation in MYBPC3." LMM Internal (overlap with Walsh paper and potentially SHaRe - Homburger paper): Seen it in 5 probands with HCM (14 yrs F; 50 yrs M; 45 yrs F; 26 yrs M; 45 yrs M) Variant segregated with HCM in two affected relatives from 2 families (19yrs M, 24 yrs F). No other variants identified.
PM2	✔	This variant has been identified in 0.003% (1/34592) of Latino chromosomes in gnomAD v2.1.1 (http://gnomad.broadinstitute.org).
PM1	✔	The variant is located in a mutational hot-spot, in the the head domain (amino acids 181-937).

Not Met criteria codes

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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	NM_000257.4(MYH7):c.717C>G (p.Asp239Glu): Listed in ClinVar as VUS with no assertion criteria HGMD has entry with single article (PMID:27247418) - Single case in SHaRe registry, so likely HCM

PM6		✖	No de novo evidence
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No de novo evidence
PP3		✖	Tools are mixed, include REVEL, SIFT (per Alamut is Tolerated with score of 0.44), and others below.

Curation History

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