

Variant: *NM_000257.4(MYH7):c.1208G>A (p.Arg403Gln)*

CA010365 [↗](#)

14087 (ClinVar) [↗](#)

Gene: MYH7 ([HGNC:4625](#))

Condition: hypertrophic cardiomyopathy ([MONDO:0005045](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: ae1c8298-2afe-4242-9a38-eea990986d41

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HGVS expressions

NM_000257.4(MYH7):c.1208G>A (p.Arg403Gln)

NM_000257.4:c.1208G>A

NC_000014.9:g.23429278C>T

CM000676.2:g.23429278C>T

NC_000014.8:g.23898487C>T

CM000676.1:g.23898487C>T

NC_000014.7:g.22968327C>T

NG_007884.1:g.11384G>A

ENST00000355349.4:c.1208G>A

ENST00000355349.3:c.1208G>A

NM_000257.3:c.1208G>A

Pathogenic

Met criteria codes **7**

PS3

PP1_Strong

PS4

PP3

PM1

PM5

PM2

Evidence Links **10**

Expert Panel

Cardiomyopathy VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** *ClinGen Cardiomyopathy Expert*

Panel Specifications to the ACMG/AMP Variant

Interpretation Guidelines for MYH7 Version 2.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Cardiomyopathy VCEP

The c.1208G>A (p.Arg403Gln) variant in MYH7 has been reported in >30 individuals with hypertrophic cardiomyopathy and segregated with disease in >30 affected family members (PS4 and PP1_Strong; PMID:1638703; PMID:1975517; PMID:7789380; PMID:12975413; PMID:24268868; PMID:10725281; PMID:20800588; PMID:12707239; PMID:27532257; AGCMC Sydney ClinVar SCV000692503.1; Invitae ClinVar SCV000253815.4; Partners LMM ClinVar SCV000059359.5; SHaRe consortium, PMID: 30297972). Mouse model indicates that this variant disrupts the function of MYH7 and leads to a phenotype consistent with HCM (PS3: PMID:8614836). This variant was absent from large population studies (PM2; <http://exac.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; PMID:27532257). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (PP3). A different pathogenic missense variant has been

previously identified at this codon which may indicate that this residue is critical to the function of the protein (PM5; c.1207C>T (p.Arg403Trp) - Variation ID 14102). 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): PS3; PS4; PP1_Strong; PM1; PM2; PM5; PP3

Met criteria codes

PS3			In vivo mouse model with R403Q. Homozygous mice died 7 days after birth, heterozygous mice survived 1 year but had cardiac histopathology and dysfunction resembling HCM. In vivo mouse model with R403Q. Homozygous mice died 7 days after birth, heterozygous mice survived 1 year but had cardiac histopathology and dysfunction resembling HCM. PubMed:8614836 
PP1_Strong			>30 segregations (including ClinVar SCV000692503.1; ClinVar SCV000059359.5) Variant segregated with disease in 6 affected family members PubMed:12975413  Variant segregated with disease in 20 affected family members PubMed:1975517  Variant segregation with disease in 11 affected family members PubMed:1638703 
PS4			>25 probands with HCM (including data from: ClinVar SCV000692503.1; ClinVar SCV000253815.4; ClinVar SCV000059359.5; SHaRe data) Variant identified in 1 proband with HCM PubMed:10725281  Variant identified in 2 probands with HCM PubMed:12975413  Variant identified in 1 proband with HCM PubMed:1975517  Variant identified in 4 probands with HCM PubMed:27532257  The variant was identified in 2 probands with HCM PubMed:7789380  Variant identified in 1 proband with HCM PubMed:12707239  Variant identified in 1 proband with HCM PubMed:24268868  Variant identified in 1 proband with HCM PubMed:20800588  1 proband with HCM was identified PubMed:1638703 
PP3			Tools predict damaging
PM1			Variants in head region of the protein (aa 181-937) are statistically more likely to be disease-associated Variants in head region of the protein (aa 181-937) are statistically more likely to be disease-associated PubMed:27532257 
PM5			c.1207C>T (p.Arg403Trp) - Variation ID 14102 - Pathogenic by ClinGen Expert Panel
PM2			Absent from ExAC

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