Variant: NM_005159.5(ACTC1):c.301G>A (p.Glu101Lys)

Version: 1.0

CA019743

18331 (ClinVar)

Gene: ACTC1 (HGNC:70)
Condition: hypertrophic cardiomyopathy (MONDO:0005045)
Inheritance Mode: Autosomal dominant inheritance
UUID: 482b7c62-0e79-4ac7-8fa0-01ff2199a237
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HGVS expressions

NM_005159.5:c.301G>A
NM_005159.5(ACTC1):c.301G>A (p.Glu101Lys)
NC_000015.10:g.34793398C>T
CM000677.2:g.34793398C>T
NC_000015.9:g.35085599C>T
CM000677.1:g.35085599C>T
NC_000015.8:g.32872891C>T
NG_007553.1:g.7329G>A
ENST00000560563.2:n.407G>A
ENST00000290378.6:c.301G>A
ENST00000647798.1:n.448G>A
ENST00000648556.1:n.458G>A
ENST00000650163.1:n.381G>A
ENST00000290378.4:c.301G>A
NM_005159.4:c.301G>A
NR_120329.1:n.299+15967C>T

Pathogenic

Met criteria codes 5

PS3_Moderate PP1_Strong PS4_Moderate PP3 PM2_Supporting

Not Met criteria codes 14

PVS1 PM6 PM5 PM4 BA1 BS1 BS4 BS3 BP5 BP7 BP4 BP2 PS1 PS2

Evidence Links 1

Expert Panel

Cardiomyopathy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ACTC1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cardiomyopathy VCEP

NM_005159.5(ACTC1): c.301G>A (p.Glu101Lys). This variant has been reported in individuals with HCM and other cardiomyopathies (Olson 2000 PMID: 10966831, Arad 2005 PMID: 16267253, Bookwalter 2006 PMID: 16611632, Monserrat 2007 PMID: 17611253, Monserrat 2007 PMID: 18801786, Klassen 2008 PMID: 18506004, Debold 2010 PMID: 19799913, Walsh 2017 PMID:) and has also been identified in 1 out of 113768 (0.004% FAF 95% CI) of European chromosomes in gnomAD (https://gnomad.broadinstitute.org/; v.2.1). The variant is statistically increased in individuals with hypertrophic cardiomyopathy (HCM) compared to controls (OR lower 95% CI>10), therefore, the PS4 criterion has been applied at moderate strength (PS4_Moderate) and the PM2_Supporting criterion has been applied (PM2_Supporting). This variant segregated with disease in numerous affected individuals with HCM from multiple families (PP1_Strong; Monserrat 2007 PMID: 16267253, Olson 2000 PMID: 10966831). A mouse knock-in model for this variant indicates that this variant disrupts the function of ACTC1 and leads to a phenotype consistent with HCM (PS3_Moderate; Song 2011 PMID:21622575). Computational prediction tools and conservation analyses suggest that this variant may impact the protein (PP3; REVEL score ≥0.70). In summary, this variant meets criteria to be classified as pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. ACTC1-specific ACMG/AMP criteria applied: PP1_Strong, PS4_Moderate, PS3_Moderate, PM2_Supporting, PP3.

Met criteria codes

PS3_Moderate	✔	Based on PMID:21622575. Transgenic mouse model. Expressed variant at 50% of total heart actin: high death rate in males and females. Hearts of male survivors at 21 weeks had enlarged atria, increased interstitial fibrosis and sarcomere disarray. MRI showed hypertrophy, predominantly at the apex of the heart. End-diastolic volume and end-diastolic pressure were increased, and relaxation rates were reduced compared with non-transgenic littermates. End-systolic pressures and volumes were unaltered. ECG abnormalities were present, and the contractile response to B-adrenergic stimulation was much reduced. Older mice (29-week-old females and 38-week-old males) developed dilated cardiomyopathy with increased end-systolic volume and continuing increased end-diastolic pressure and slower contraction and relaxation rates. ECG showed atrial flutter and frequent atrial ectopic beats at rest in some mice. Authors propose that this ACTC variant causes higher myofibrillar Ca2+ sensitivity that is responsible for the sudden cardiac death, apical hypertrophy, and subsequent development of heart failure in humans and mice. PubMed:21622575
PP1_Strong	✔	Data from PMID:10966831; PMID:16267253
PS4_Moderate	✔	Case-control odds ratio (OR) calculations (Lower 95% CI of OR ≥5 SUPPORTING; ≥10 MODERATE; ≥20 STRONG) Control data used: gnomAD(EUR-NF combined data from v2.1.1 and v3.1.1(non-v2): number with variant =2, number without variant =82,852. 1. OR calculated using single study case data (PMID: 27532257) Cases: number with variant=5, number without variant=4180 OR:49.55 95% CI [9.61-255.48]. 2. OR calculated based on counts in the literature and ClinVar PMID: 27532257 Variant detected in 5/4180 HCM probands. PMID: 10966831 Variant detected in 1/368 HCM probands. PMID: 16267253 Variant detected in 2/15 HCM probands. PMID: 18506004 Variant detected in 2/63 LNVC probands. PMID: 17611253 Variant detected in 5/247 HCM, LVNC probands. ClinVar entries from 7 centers (count as minimum 7 occurrences?) Estimated case count= min 22 Estimated cases=~10,000 OR:91.14 95% CI [21.43-387.63] Based on the above data, curator feels that PS4_Mod is appropriate.
PP3	✔	REVEL score: 0.873 (Prediction: Pathogenic)
PM2_Supporting	✔	Detected in 1 individual (European non-Finnish AC=1, AN=113,768) in gnomAD v2.1.1. Detected in 1 individual (European non-Finnish AC=1, AN=51,940) in gnomAD v3.1.1(non-v2). 2.1 observed MAF 0.0008%. Upper 95&CI: 0.004% Upper 95% CI of MAF is less or euqal to 0.004% PM2 threshold.

Not Met criteria codes

PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	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
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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