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#### **Supplemental Methods**

#### **Definition of ARVC**

ARVC was defined by fulfillment of the 2010 Task Force Criteria<sup>5</sup>.

#### Identification of genes to be curated

Genes were selected for evaluation by a PubMed and OMIM search in December 2017 to identify genes putatively causative for ARVC. This search was repeated in 2019 to identify genes newly associated with ARVC.

To identify genes for which an assertion for a role in human ARVC causation had been made we first conducted a search in the Gene resource of NCBI (<u>https://www.ncbi.nlm.nih.gov/gene</u>). We conducted the following search:

("arrhythmogenic right ventricular" OR "arrhythmogenic cardiomyopathy" OR "right ventricular dysplasia") AND "Homo sapiens"[porgn:\_\_txid9606]

Genes on the resulting list were investigated via PubMed to confirm that an assertion for ARVCcausation had indeed been made. Genes in which the relevant study reported lack of association (eg. *PLEC, SCN10A, PERP*, etc) or had been potentially implicated in a downstream pathway or model system only were discarded. Additional assertions made for the sarcomere genes were discovered during this process when investigating *MYBPC3* and *MYH7* so these genes were added to the list to be curated.

We then confirmed completeness of our list by querying OMIM

In OMIM (<u>https://www.omim.org/</u>), the following disease entities were searched:

arrhythmogenic right ventricular cardiomyopathy, arrhythmogenic right ventricular dysplasia, arrhythmogenic right ventricular dysplasia/cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, arrhythmogenic cardiomyopathy, right ventricular dysplasia, and abbreviations: ARVC, ARVD, ARVD/C, ARVC/D, ACM, AC

#### Gene curation approach

Our gene curation approach is summarized in **Figure 1**. To enhance the rigor of our evaluation of putative ARVC genes we conducted dual independent, blinded, curation. We assembled six 2-person gene curation teams. Each curation team included members with expertise in both ARVC diagnosis and clinical care and in genetic analysis. Two curation teams independently evaluated each gene and worked blinded to each other. Curation teams were excluded from primary or secondary evaluation of a gene if either member had published an assertion regarding ARVC causality of the gene. Curation team composition, expertise, and genes curated by each team are shown in **Supplementary Table I**.

Curation teams used a standard operating procedure (SOP) for gene curation per the ClinGen Gene Curation Framework, described in detail below, to preliminarily categorize gene-disease relationships into different clinical validity levels including Strong (12-18 points), Moderate (7-11 points), Limited (1-6 points), or no reported (human) evidence (0 points) (11). In this semi-quantitative scoring system genetic and experimental evidence are reviewed separately, each to saturation, and tallied for a final score.

For each gene, curation teams independently presented their results during biweekly teleconferences of the ARVC Gene Curation Expert Panel (GCEP) who discussed the evidence to determine the final clinical validity of each gene. Final classifications included the categories listed above plus options to dispute or refute the relationship of the gene with ARVC, or to consider the gene:disease relationship definitive. Definitive-evidence genes were those garnering 12-18 points with clear evidence of replication in the literature. Disputed genes were those in which evidence had arisen since the initial publication calling into question ARVC causality while for refuted genes the evidence against ARVC causality significantly outweighed any evidence supporting causality.

#### Application of the ClinGen gene curation framework

To ensure consistency in the data curated, pre-curation of each gene was performed by a PhDlevel ClinGen staff biocurator and GCEP member. Details of the ClinGen precuration approach are available at: <u>https://clinicalgenome.org/working-groups/lumping-and-splitting/</u>. Articles of interest and PMIDs (Pubmed identifier) were circulated to each curation team. Curation teams also independently reviewed the literature and shared any additional PMIDs with the corresponding team.

ARVC gene curation followed ClinGen Gene Curation Framework standard operating procedures (SOP) (https://clinicalgenome.org/docs/summary-of-updates-to-the-clingen-gene-clinical-validitycuration-sop-version-7/). Broadly speaking, this framework provides a systematic approach to evaluating the strength of evidence underpinning gene:disease associations. In this semi-quantitative scoring system points are accrued based on published genetic and experimental evidence. Genetic evidence includes assessment of clinical phenotype, variant pathogenicity, study design, type and extent of sequencing performed, and evidence of familial segregation of variants. Experimental evidence includes protein expression, in vitro assays assessing functional implications of disease-associated variants, and data from model organism and rescue studies. For both genetic and experimental evidence publications were scored until the curation team reached saturation (maximum 12 points of genetic evidence and 6 points of experimental evidence). All team members received training in the application of this framework. Furthermore, several disease-specific guidelines for scoring evidence were required that are summarized below.

#### Minor allele frequency cutoff

To curate human genetic evidence, it was necessary to define a minor allele frequency (MAF) cut-off for considering a variant potentially causative. We used two approaches to defining this value. Our first approach queried evidence from ARVC cohorts. We reasoned that the MAF of any variant of interest should be less common than the most frequent variants identified in the ARVC population. We reviewed the 15 most frequent variants detected in a cohort of ARVC probands from a combined Dutch, US, and German registry<sup>51</sup>. These were all *PKP2* variants, primarily premature terminating and splice variants. The variant with the highest allele frequency in gnomAD was c.2146-1G>C with an MAF of 0.000036. The second approach utilized a recently developed allele frequency calculator that integrates inheritance, allelic and genetic heterogeneity and penetrance<sup>52</sup>. This calculator generated an MAF of 0.000036, entirely consistent with the population-generated value. Only variants with a MAF < 0.000036 were scored during curation.

#### Phenotype in animal models

Experimental evidence scores were assigned per the ClinGen framework. A cardiomyopathic phenotype preferably with fibrofatty replacement of cardiomyocytes was considered sufficient evidence in an animal model, however, models showing ventricular arrhythmias alone were not scored.

#### Gene curation and classification process

As shown in **Figure 1**, each curation team entered data directly into an electronic gene curation interface (GCI) that records and tracks data entry. Team 1 used the GCI of record. A copy GCI (demo version) was built to allow Team 2 data to be recorded for research purposes. Preliminary clinical

validity classifications generated by each team using the automated GCI scoring included: Strong (12-18 points), Moderate (7-11 points), Limited (1-6 points), or no reported (human) evidence (0 points).

For each gene, both teams independently presented their curation results via power point presentations during biweekly teleconferences of the ARVC GCEP. The GCEP discussed the presented evidence to arrive at consensus on the final clinical validity of each gene. Final classifications included the categories listed above plus options to dispute or refute the relationship of the gene with ARVC, or to consider the gene:disease relationship definitive. Definitive-evidence genes were those garnering 12-18 points with extensive replication in the literature. Disputed genes were those in which evidence had arisen calling into question ARVC causality. Per the ClinGen framework, this evidence need not outweigh the evidence for the gene:disease relationship. In contrast, refuted genes were those in which the evidence against ARVC causality significantly outweighed any evidence supporting causality. This designation was used when the GCEP considered it had been proven to the extent possible that there is no valid evidence for ARVC causality of a gene.

Several genes (*PKP2*, *DSG2*, *DSC2*, *TMEM43*) had been previously curated for ARVC as part of the ClinGen evaluation of genes recommended by the American College of Medical Genetics and Genomics (ACMG) for return when detected as secondary findings. For these genes, an updated literature review was performed and the evidence was presented by a ClinGen curator. The evidence was then reviewed and the GCEP decided on a final classification.

#### Unique variants in ClinVar per ARVC gene

We analyzed ClinVar submissions (0-3 stars) for ARVC for all 26 genes to assess the relative frequency of variants adjudicated as P/LP for each gene and compared this frequency among different final curation classifications. ClinVar was queried on March 4, 2020.

#### Supplementary Table I: Curation teams

Curation teams	Curators	Affiliation	Genes curated
Team 1	Brittney Murray MS, CGC Cynthia A. James PhD, CGC	Division of Cardiology, Dept. of Medicine, Johns Hopkins University, Baltimore, Maryland, USA	TJP1, LMNA, CDH2, TNNI3, TNNT2, DSP
Team 2	Ronald Lekanne Deprez PhD	Dept. of Clinical Genetics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands	RYR2, CTNNA3, TTN, TGFB3, CDH2
	J. Peter van Tintelen MD, PhD	Department of Genetics, University of Utrecht, University Medical Center Utrecht, Utrecht, the Netherlands	
Team 3	Alexandros Protonotarios MD	Centre for Heart Muscle Disease, Institute of	DES, ACTC1, MYH7, MYL2,
	Petros Syrris PhD	Cardiovascular Science, University College London, London, UK	LDB3, PLN, MYBPC3
Team 4	Babken Asatryan MD, PhD	Dept. for Cardiology, Inselspital, Bern University	DSP, DES, LMNA, TTN,
	Argelia Medeiros Domingo MD, PhD	Hospital, University of Bern, Bern, Switzerland	TNNI3, TNNT2, ACTC1, MYL3, MYL2, SCN5A
Team 5	Julia Cadrin-Tourigny MD	Cardiovascular Genetics Center, Montreal Heart Institute, Université de Montréal, Montréal, Canada	JUP, PLN, RYR2, TGFB3, TJP1, TPM1, TNNC1
	Daniel P. Judge MD	Division of Cardiology, Department of Medicine Medical University of South Carolina, Charleston, South Carolina, USA	
Team 6	Rudy Celeghin PhD	University of Padua, Department of Cardiac-Thoracic-	LDB3, SCN5A, MYL3,
	Kalliopi Pilichou PhD	Vascular Sciences and Public Health, Padua, Italy	TPM1, TNNC1, JUP, CTNNA3, MYBPC3, MYH7

Gene	Team 1 score	Team 1 classification	Team 2 score	Team 2 classification	Concordant preliminary classification?
ACTC1	0	no reported evidence	0	no reported evidence	YES
CDH2	5.5	limited	6.0	limited	YES
CTNNA3	3.5	limited	3.0	limited	YES
DES	9.5	moderate	10.5	moderate	YES
DSC2	14	definitive	Prior ClinGen adjudication	definitive	YES – concordant with ClinGen review of ACMG59
DSP	14.5	definitive	15.5	definitive	YES
DSG2	18.0	definitive	Prior ClinGen adjudication	definitive	YES – concordant with ClinGen review of ACMG59
JUP	16.0	strong	15.5	strong	YES
LDB3	0.1	limited	0.1	limited	YES
LMNA	5.0	limited	6.0	limited	YES
МҮВРСЗ	1.0	limited	0.75	limited	YES
MYH7	1.75	limited	1.75	limited	YES
MYL2	0	no reported evidence	0	no reported evidence	YES
MYL3	0.25	limited	0.25	limited	YES
РКР2	18.0	definitive	Prior ClinGen adjudication	definitive	YES – concordant with ClinGen review of ACMG59
PLN	11.0	moderate	11.0	moderate	YES
RYR2	1.0	refuted	1.25	refuted	YES
SCN5A	6.0	limited	2.75	limited	YES
TGFB3	2.2	limited	1.5	limited	YES
TJP1	1.0	limited	1.0	limited	YES
TMEM43	13.1	definitive	11.6 (prior ClinGen review)	strong	YES – additional points from recent publications not initially reviewed.
TNNI3	0	no reported evidence	0	no reported evidence	YES
TNNC1	0	no reported evidence	0	no reported evidence	YES
TNNT2	0	no reported evidence	0	no reported evidence	YES
TPM1	0	no reported evidence	0	no reported evidence	YES
TTN	1.0	limited	1.5	limited	YES

Supplementary Table II: Concordance of Team 1 and Team 2 initial curation scores

	Evidence	Evidence	Evidence	Inheritance	Phenotype notes
	Genetic	experimental	total		
Limited					
SCN5A	3	3	6	AD	ARVC. Typically associated with Brugada syndrome, dilated cardiomyopathy,
					long QT syndrome
LMNA	4	1	5	AD	Typically associated with dilated cardiomyopathy with conduction disease
CDH2	3.5	2	5.5	AD	ARVC – few cases reported
CTNNA3	1.5	2	3.5	AD	ARVC – few cases reported
TGFB3	1.2	1	2.2	AD	ARVC – few cases reported, Loeys Dietz gene
TTN	0.5	0.5	1	AD	Typically associated with dilated cardiomyopathy
TJP1	1	0	1	AD	ARVC and dilated cardiomyopathy – few cases reported
MYH7	1.75	0	1.75	AD	Definitive evidence HCM gene
МҮВРС3	1	0	1	AD	Definitive evidence HCM gene
MYL3	0.25	0	0.25	AD	Definitive evidence HCM gene
Refuted					
RYR2	1.25	0	1.25	AD	Of 55 papers reviewed, cases overwhelmingly had a CPVT phenotype
Disputed					
LDB3	0	0.1	0.1	AD	ARVC phenotype, but MAF too high
No human					
evidence					
TNNI3	0	0	0	AD	Definitive evidence HCM gene
TNNT2	0	0	0	AD	Definitive evidence HCM gene
ACTC1	0	0	0	AD	Definitive evidence HCM gene
MYL2	0	0	0	AD	Definitive evidence HCM gene
TMP1	0	0	0	AD	Definitive evidence HCM gene
TNNC1	0	0	0	AD	Moderate evidence HCM gene

Supplementary Table III: Genes with limited or no contribution to ARVC pathogenesis – Final expert panel classification

AD: Autosomal dominant

The most up-to-date curation data for each gene can be accessed at <u>https://clinicalgenome.org/</u>

# **Gene Validity Curations**

### ACTC1 - arrhythmogenic right ventricular cardiomyopathy

Gene:	ACTC1 (HGNC:143)						
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	No Known Disease Relationship 🖯					
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 03/15/2019					
Replication over time	:NO	Contradictory Evidence: NO					
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP						
Evidence Summary:	ACTC1: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) HGNC: 143 MONDO_0016587 Mode of Inheritance: Autosomal dominant inheritance (HP:0000006) Expert Panel: Arrhythmogenic Right Ventricular Cardiomyopathy SOP: Gene Clinical Validity Standard Operating Procedures (SOP), Version 6 Calculated Classification (date) No reported evidence 22/02/2019 Evidence Summary: There is no evidence that ACTC1 is involved in ARVC. This gene has been investigated for pathogenic variants in three populations of patients meeting 2010 Task Force criteria for ARVC: a cohort of 14 Spanish unrelated patients (22421524), a cohort of 14 cases (27194543) and a cohort of 137 ARVC patients (29709087). No variants in ACTC1 were reported.						

		-			Gui	idelines	5		Po	oints	
		F	Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12				
			Autosomal Dominant or X- linked Disorder	Proband with predicted or proven null variant	1.5	0-2	10				
		vidence		Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7				
	Case-Level Data	Variant Evidence	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-L		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
netic						Summ LOI		Family Count			
Gei			Segregation	Candidate gene sequencin	וg			ocum			
			Evidence	Exome/genome or all genes seq in linkage region	uenced						
		1		Total Summed LOD Score	э						
	Data	Cas	se-Control Study Type	Case-Control Quality Criteria		idelines /Study		Count		oints Counted	PMIDs/Notes
	ntrol	ę	-	1. Variant Detection Methodology	0-	·6					
	Case-Control Data	Ag	gregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12				
				Total Genet	tic Evide	nce Po	ints	(Maxim	um 12)	0	
					Gui	idelines			D/	oints	
				Evidence Type	Gui	uennea	•			Jiins	PMIDs/Notes
					Default	Range	Мах	Count	Total	Counted	
				<b>Biochemical Function</b>	0.5	0 - 2					
			Function	Protein Interaction	0.5	0 - 2	2				
				Expression	0.5	0 - 2					
	<b>F</b>		ional Alteration	Patient cells	1	0 - 2					
	FU	nea	Ional Alteration	Non-patient cells	0.5	0 - 1	2				

erimental Evidence	Madala	Non-human model organism	2	0 - 4				
	Models	Cell culture model	1	0 - 2				
	Rescue	Rescue in human	2	0 - 4				
		Rescue in non-human model organism	2	0 - 4	4			
žpe		Rescue in cell culture model	1	0 - 2				
ш		Rescue in patient cells	1	0 - 2				
		Total Experimen	tal Evid	ence Po	oint	(Maximum 6)	0	

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)		
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)		
Assigned Points	0	0	0	NO		
			1-6 7-11			
CALCULATED C	CLASSIFICATION	STRONG DEFINITIVE	12-18 12-18 AND replicat			
Valid contradictory evidence (Y/N)*	NO					
	CALCULATED CLASSIFICATION (DATE)	No Known Disease Relationship	05	6/08/2020		
	EXPERT CURATION (DATE)	No Known Disease Relation ACTC1: Arrhythmogenic Right Ventricula 143 MONDO_0016587 Mode of Inheritan (HP:0000006) Expert Panel: Arrhythmo Cardiomyopathy SOP: Gene Clinical Vali (SOP), Version 6 Calculated Classificati 22/02/2019 Evidence Summary: There is in ARVC. This gene has been investigate populations of patients meeting 2010 Ta of 14 Spanish unrelated patients (22421 (27194543) and a cohort of 137 ARVC pi	ar Cardiomyopathy (ARV ce: Autosomal dominan genic Right Ventricular dity Standard Operating on (date) No reported ev s no evidence that ACTC d for pathogenic varian sk Force criteria for AR 524), a cohort of 14 cas	t inheritance Procedures vidence 1 is involved ts in three VC: a cohort ses		
	EVIDENCE SUMMARY	ACTC1 were reported.				

# CDH2 - arrhythmogenic right ventricular cardiomyopathy

Gene:	CDH2 (HGNC:1759)					
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Limited <b>B</b>				
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 07/13/2018				
Replication over time	:NO	Contradictory Evidence: NO				
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP					
Evidence Summary:	ARVC was published in 2017 (28280076) and d p.Gln229Pro. The phenotype was consistent wir phenotype that carried p.Asp407Asn. A second variant, p.Asp407Asn in a family with biventricu mouse (15662031) that that CDH2 disruption le cardiomyopathy, VT, and SCD. However, these a	<b>c</b>				

					Gui	delines			Po	oints	
		E	Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12				
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10				
		/idence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	3	2.5	2.5	Mayosi BM et al. 2017 Apr (PMID:28280076); Turkowski KL et al. 2017 Mar (PMID:28326674);
	evel Data	Variant Evidence	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-Level		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
enetic						Sumn LOI		Family Count			
ŏ			Segregation	Candidate gene sequencir	ng				1	4	
		Evidence		Exome/genome or all genes seq in linkage region	uenced	2.2	2.24		·	1	Mayosi BM et al. 2017 Apr (PMID:28280076);
				Total Summed LOD Score	Э	2.2	4				
	Data	Cas	se-Control Study Type	Case-Control Quality Criteria		delines /Study		Count		oints Counted	PMIDs/Notes
	ontrol	\$	Single Variant Analysis	1. Variant Detection Methodology	0-	0-6					
	Case-Control	Aggregate Variant Analysis         2. Power           3. Bias and confounding         0-           4. Statistical Significance         0-		6	12						
				Total Gene	tic Evide	nce Po	ints	(Maxim	um 12)	3.5	
					Gui	delines			Po	oints	
	E	vid	ence Category	Evidence Type				Count		Counted	PMIDs/Notes
				<b>Biochemical Function</b>	0.5	0 - 2					
nce			Function	Protein Interaction	0.5	0 - 2	2				
Experimental Evidence				Expression	0.5	0 - 2					
alE	-			Patient cells	1	0 - 2	~				
lent	Fu	nct	ional Alteration	Non-patient cells	0.5	0 - 1	2				
erin			Madala	Non-human model organism	2	0 - 4		1	2		Kostetskii I et al. 2005 Feb 18 (PMID:15662031);
Exp			Models	Cell culture model	1	0 - 2					

	Rescue in human	2	0 - 4					
Rescue	Rescue in non-human model organism	2	0 - 4	4			2	
	Rescue in cell culture model	1	0 - 2					
	Rescue in patient cells	1	0 - 2					
Total Experimental Evidence Points (Maximum 6) 2								

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	3.5	2	5.5	NO
		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
CALCULATED C	CLASSIFICATION	DEFINITIVE	12-18 AND replicat	ion over time
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	Limited	05	/08/2020
	EXPERT CURATION (DATE)	Limited	07	/13/2018
	EVIDENCE SUMMARY	There is moderate evidence that CDH2 i publication that associated TJP1 with AI (28280076) and described two families p.Gln229Pro. The phenotype was consis was one proband with clear ARVC pheno second publication in 2017 also identifit variant, p.Asp407Asn in a family with bi is some experimental evidence in a KO n disruption leads to dissolution of desmo cardiomyopathy, VT, and SCD. However, reported in the patients. There is emerg are associated with an ARVC phenotype mechanisms of disease, and pathogenic variants is still missing.	RVC was published in 20 : one family with five affores otype that carried p.Aspa ed in a Norwegian family ventricular ARVC phenot nouse (15662031) that the somes and area compos these are not missense ing evidence that CDH2 , but additional informat	17 ected with oond family 407Asn. A the same ype. There hat CDH2 ite, variants as mutations ion on

# CTNNA3 - arrhythmogenic right ventricular cardiomyopathy

Gene:	CTNNA3 (HGNC:2511)	
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Limited 🕄
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 08/06/2019
Replication over time	: NO	Contradictory Evidence: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	
Evidence Summary:	(HP:0000006) HGNC: 2511 MONDO:0016587 E papers were reviewed related to CTNNA3 and A gene was analyzed in 76 ARVD probands that w probands the heterozygous NM_013266.3(CTN observed in 245296 reference alleles from gno suggesting that the variant occurred de novo. U family history for ARVD. Another proband show NM_013266.3(CTNNA3):c.2296_2298del p.(Le gnomAD but was inherited from her father that variant as well but she was asymptomatic. Yeas (23136403). In another paper a missense varia found 37 times in 276338 (1 times homozygous variant. In addition the proband did carry a mis knockout of alphaT-catenin encoded by ctnna3 junctional components of the areae Composita gap junction remodelling, and increased sensiti	u766del). This variant was not found in 30971 reference alleles from only showed a mild right ventricular dilation. Her ant inherited the st two-hybrid studies with both variants showed some aberrations int was found in one of 55 Danish ARVD patients. The variant was s) reference alleles in gnomAD making it less likely as a causal sense variant of unknown significance in DSP (21254927). Germline in the mouse alters PKP2 distribution without affecting other e. These mutant mice exhibit progressive dilated cardiomyopathy, wity to ventricular arrhythmia following acute ischaemia, but not evidence points calculated = 1.5; Total experimental evidence .5; Final classification = Limited.

				Gui	delines			Po	oints	
		Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
			Variant is de novo	2	0-3	12	1	1.5	1.5	van Hengel J et al. 2013 Jan (PMID:23136403);
		Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10				
	idence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7				
	evel Data Variant Evidenc	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-Level Vari	Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
letic E					Summ LOI		Family Count			
Ger		Segregation	Candidate gene sequencin	g						
		Evidence	Exome/genome or all genes sequin linkage region	uenced						
			Total Summed LOD Score							
	C	ase-Control Study		Gui	delines			Po	oints	
	Data	Туре	Case-Control Quality Criteria				Count		Counted	PMIDs/Notes
		Single Variant Analysis	1. Variant Detection Methodology	0-6						
	ິ	ggregate Variant	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12				

Total Genetic Evidence Points (Maximum 12) 1.5 Guidelines Points **Evidence Category** Evidence Type Default Range Max Count Total Counted PMIDs/Notes **Biochemical Function** 0.5 0 - 2 Function Protein Interaction 0.5 0 - 2 2 1 0.5 0.5 van Hengel J et al. 2013 Jan (PMID:23136403); 0.5 0 - 2 Expression Experimental Evidence Patient cells 1 0 - 2 **Functional Alteration** 2 0.5 0.5 van Hengel J et al. 2013 Jan (PMID:23136403); Non-patient cells 0 - 1 1 0.5 Li J et al. 2012 Feb 15 (PMID:22421363); Non-human model organism 2 0 - 4 1 1 Models Cell culture model 1 0 - 2 Rescue in human 2 0 - 4 1 Rescue in non-human model 4 2 0 - 4 Rescue organism Rescue in cell culture model 1 0 - 2 0 - 2 Rescue in patient cells 1 Total Experimental Evidence Points (Maximum 6) 2

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	1.5	2	3.5	NO
		LIMITED MODERATE STRONG	1-6 7-11 12-18	
CALCULATED C	LASSIFICATION	DEFINITIVE	12-18 AND replicati	on over time
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	Limited	02/	/04/2020
	EXPERT CURATION (DATE)	Limited CTNNA3: Arrythmogenic Right Ventricul Inheritance: Autosomal dominant inherit MONDO:0016587 Expert Panel: Arrythm Cardiomyopathy Three papers were revi (23136403, 21254927, 224213630). In c analyzed in 76 ARVD probands that were DSC2, and JUP. In one of the probands t NM_013266.3(CTNNA3):c.281T>A p.(Va variant was not observed in 245296 refe not present in both healthy parents and occurred de novo. Unfortunately no info testing or family history for ARVD. Anotl heterozygous variant NM_013266.3(CTN (Leu766del). This variant was not found gnomAD but was inherited from her fath ventricular dilation. Her ant inherited th asymptomatic. Yeast two-hybrid studies aberrations (23136403). In another pap one of 55 Danish ARVD patients. The var (1 times homozygous) reference alleles causal variant. In addition the proband c unknown significance in DSP (21254927) catenin encoded by ctnna3 in the mouse affecting other junctional components o mutant mice exhibit progressive dilated remodelling, and increased sensitivity to acute ischaemia, but not spontaneous A evidence points calculated = 1.5; Total e calculated = 2; Total awarded points = 3	ar Cardiomyopathy Mod ance (HP:0000006) HG ogenic Right Ventricular ewed related to CTNNA3 one paper the CTNNA3 ge engative for PKP2, DSP he heterozygous 194Asp) variant was four erence alleles from gnom brother suggesting that rmation was given about ther proband showed the INA3):c.2296_2298del p in 30971 reference allele er that only showed a mi e variant as well but she swith both variants show er a missense variant was ing gnomAD making it less in carry a missense vari alters PKP2 distributior f the areae Compositae. cardiomyopathy, gap jur oventricular arrhythmia xperimental evidence po	NC: 2511 and ARVD ene was , DSG2, nd. This AD and was the variant paternity s from ld right was sef rom ld right was sef some s found in in 276338 s likely as a ant of alphaT- n without These loction following genetic ints

# DES - arrhythmogenic right ventricular cardiomyopathy

Gene:	DES (HGNC:2770)	
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Moderate
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 09/11/2018
Replication over time	e: NO	Contradictory Evidence: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	
Evidence Summary:	Inheritance: Autosomal dominant inheritance Cardiomyopathy SOP: Gene Clinical Validity S Classification (date) Moderate 09/11/2018 Evi with ARVC was published in 2009 and reporte with a severe cardiac phenotype characterize (19879535). Further studies in families with A variant was reported in two pedigrees (20423 Swedish pedigree (22395865) and p.Glu401A predominant left ventricular arrhythmogenic of (29212896). Two cohort studies of 91 and 22 DES and identified a total of three missense w cardiac specimens from affected individuals w disruption of desmin distribution at the interce in cardiomyocytes (20423733, 20829228). Ex variants in ARVC (20829228, 22403400, 292 variant in in vitro expression systems using a protein ad atomic force microscopic imaging protein aggregates in mutant cultured cells ar cardiac muscle of ARVC cases carrying the sa p.Glu401Asp variant in transfected cells show and formation of desmin cytoplasmic aggrega heterozygous DES mutations on filament form utilized dual color photoactivation localization support this gene-disease association. Desmi	promyopathy (ARVC) HGNC: 2770 MONDO_0016587 Mode of (HP:000006) Expert Panel: Arrhythmogenic Right Ventricular tandard Operating Procedures (SOP), Version 6 Calculated dence Summary: The first publication that associated DES variants ed a missense variant (p.Ser13Phe) in 27 individuals in five families d by conduction disease and right ventricular involvement RVC have identified additional missense variants: the p.Asn342Asp 4733); p.His326Arg in one family (24200904); p.Pro419Ser in a large asp was detected in a family with 23 affected individuals showing cardiomyopathy with a high incidence of adverse clinical events ARVC index cases respectively have performed genetic screening of ariants (23168288, 20829228). Immunohistochemistry analysis of with the p.Arg454Trp or p.Asn116Ser variant has shown severe alated discs and formation of cytoplasmic and perinuclear aggregates experimental data from three studies support the causative role of DES 12896). In particular, Klauke B et al. characterized the p.Asn116Ser variety of methods including viscosity analysis of desmin mutant p. Data from these experiments confirmed the presence of fibrous and were consistent with histological examinations of skeletal and ame DES variants (20829228). Similarly, functional studies on the ed disruption of cellular adhesion and intermediate filament structure tates (29212896). Finally, the deleterious structural effects of five nation in vitro and in living cells were investigated in a study that a microscopy (22403400). In summary, there is moderate evidence to in mutations associated with ARVC appear to be very rare and the dilated cardiomyopathy with conduction system abnormalities and cedures (SOP) - Version 7

				delines				oints	
	Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
		Variant is de novo	2	0-3	12	1	2	2	Klauke B et al. 2010 Dec 1 (PMID:20829228);
	Autosomal	Proband with predicted or proven null variant	1.5	0-2	10				
Evidence	Dominant or X- linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	5	2.5	2.5	van Tintelen JP et al. 2009 Nov (PMID:19879535); Otten E et al. 2010 Aug (PMID:20423733); Brodehl A et al. 2013 Dec (PMID:24200904); Bermúdez-Jiménez FJ et al. 2018 Apr 10 (PMID:29212896);
riant	Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
200		Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
						Family Count			
	Segregation Evidence	Candidate gene sequencir	ing 8.43		.3	2	1.5	1.5	van Tintelen JP et al. 2009 Nov (PMID:19879535); Bermúdez- Jiménez FJ et al. 2018 Apr 10 (PMID:29212896);
1	ata ant Evidence	Autosomal Recessive Disease Segregation	Autosomal Dominant or X- linked Disorder Autosomal Recessive Disease Segregation Candidate gene sequencin	Evidence Type     Case Information Type     Default       Autosomal Dominant or X- linked Disorder     Variant is de novo     2       Autosomal Dominant or X- linked Disorder     Proband with predicted or proven null variant     1.5       Autosomal Recessive Disease     Two variants in trans and at least one de novo or a predicted/proven null variant     2       Segregation     Candidate gene sequencing     1	Evidence Type     Case Information Type     Default Range       Autosomal Dominant or X- linked Disorder     Variant is de novo     2     0-3       Proband with predicted or proven null variant     1.5     0-2       Proband with other variant type with some evidence of gene impact     0.5     0-1.5       Autosomal Recessive Disease     Two variants in trans and at least one de novo or a predicted/proven null variant     2     0-3       Segregation     Candidate gene sequencing     8.4	Evidence Type       Case Information Type       Default Range Max         Autosomal Dominant or X-linked Disorder       Proband with predicted or proven null variant type with some evidence of gene impact       1.5       0-2       10         Autosomal Dominant or X-linked Disorder       Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7         Autosomal Dominant or X-linked Disorder       Two variants in trans and at least one de novo or a predicted/proven null variant       2       0-3       12         Autosomal Recessive Disease       Two variants (not predicted/proven null) with some evidence of gene impact in trans       1       0-1.5       12         Segregation       Candidate gene sequencing       8.43	Evidence Type       Case Information Type       Default Range Max       Count         Autosomal Dominant or X-linked Disorder       Proband with predicted or proven null variant       1.5       0-2       10         Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7       5         Autosomal Dominant or X-linked Disorder       Two variants in trans and at least one de novo or a predicted/proven null variant       2       0-3       12       1         Proband with other variant sin trans and at least one de novo or a predicted/proven null variant       2       0-3       12       1         Segregation       Case Information Type       Summed Summary       1       0-1.5       7       5         Segregation       Candidate gene sequencing       8.43       2	Evidence Type       Case Information Type       Default Range Max       Count       Total         Autosomal Dominant or X-linked Disorder       Proband with predicted or proven null variant       1.5       0-2       10       1       2         Autosomal Dominant or X-linked Disorder       Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7       5       2.5         Autosomal Recessive Disease       Two variants in trans and at least one de novo or a predicted/proven null variant       2       0-3       12       1       2         Segregation       Candidate gene sequencing       8.43       2       2       2       3	Evidence Type       Case Information Type       Default Range Max       Count       Total       Counted         Autosomal Dominant or X- linked Disorder       Variant is de novo       2       0-3       12       1       2       2         Proband with predicted or proven null variant       1.5       0-2       10       -       -       -         Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7       5       2.5       2.5         Autosomal Recessive Disease       Two variants in trans and at least one de novo or a predicted/proven null variant       2       0-3       12       -

			- / "							
			Exome/genome or all genes sec in linkage region	luenced						
			Total Summed LOD Score	0	8.4	2				
			Total Summed LOD Scol			-				
	ata	Case-Control Study			delines		<b>.</b> .		ints	
		Туре	Case-Control Quality Criteria	Points/Study		Мах	Count	Points Counted		PMIDs/Notes
	ontrol	Analysis	1. Variant Detection Methodology	0-	6					
	ŭ e	Annuanata Variant	2. Power			12				
	Case	Analysis	3. Bias and confounding	0-	6					
	с		4. Statistical Significance							
			Total Gene	tic Evide	nce Po	ints	(Maxim	um 12)	6	
				Cui	delines			De	ints	
	F	Evidence Category	Evidence Type			-	Count		Counted	PMIDs/Notes
	_		Biochemical Function	0.5	0 - 2					
		Function	Protein Interaction	0.5	0 - 2					
e			Expression	0.5	0 - 2	2	3	1.5	1.5	van Tintelen JP et al. 2009 Nov (PMID:19879535); Otten E et al. 2010 Aug (PMID:20423733); Klauke B et al. 2010 Dec 1 (PMID:20829228);
len			Patient cells	1	0 - 2					
Experimental Evidence	Fu	unctional Alteration	Non-patient cells	0.5	0 - 1	2	8	4	2	Klauke B et al. 2010 Dec 1 (PMID:20829228); Bermúdez-Jiménez FJ et al. 2018 Apr 10 (PMID:29212896); Brodehl A et al. 2012 May 4 (PMID:22403400);
in		Models	Non-human model organism	2	0 - 4					
Expe		Models	Cell culture model	1	0 - 2					
			Rescue in human	2	0 - 4					
		Rescue	Rescue in non-human model organism	2	0 - 4	4				
			Rescue in cell culture model	1	0 - 2					
			Rescue in patient cells	1	0 - 2					
			Total Experime	ntal Evid	ence P	oints	(Maxin	num 6)	3.5	

Assertion criteria	Genetic Evidence	e (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family see control data that su disease ass	upport the gene-	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	6		3.5	9.5	NO
CALCULATED	CLASSIFICATION		LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicat	
Valid contradictory evidence (Y/N)*	NO				
	CALCULATED CLA	SSIFICATION (DATE)	Moderate	02	/04/2020
	EXPER	T CURATION (DATE)	Moderate	09	9/11/2018
			DES: Arrhythmogenic Right Ventricular 2770 MONDO_0016587 Mode of Inherita inheritance (HP:000006) Expert Panel Cardiomyopathy SOP: Gene Clinical Vali (SOP), Version 6 Calculated Classificati Evidence Summary: The first publication ARVC was published in 2009 and report in 27 individuals in five families with a s characterized by conduction disease an (19879535). Further studies in families missense variants: the p.Asn342Asp vai (20423733); p.His326Arg in one family Swedish pedigree (22395865) and p.Glw with 23 affected individuals showing pr arrhythmogenic cardiomyopathy with a events (29212896). Two cohort studies respectively have performed genetic sc of three missense variants (23168288, j analysis of cardiac specimens from affe p.Arg454Trp or p.Asn116Ser variant has distribution at the intercalated discs an	Ince: Autosomal dominal : Arrhythmogenic Right dity Standard Operating on (date) Moderate 09/1 in that associated DES va ed a missense variant (p evere cardiac phenotype d right ventricular involv with ARVC have identifik riant was reported in two (24200904); p.Pro419S u401Asp was detected in idominant left ventricul- high incidence of advers of 91 and 22 ARVC inde reening of DES and idemi 20829228). Immunohist cted individuals with the s shown severe disruption	nt Ventricular Procedures 1/2018 (1/2018 ser13Phe) vement ed additional opedigrees er in a large n a family ar se clinical x cases tified a total ochemistry e n of desmin

perinuclear aggregates in cardiomyocytes (20423733, 20829228). Experimental data from three studies support the causative role of DES variants in ARVC (20829228, 22403400, 29212896). In particular, Klauke B et al. characterized the p.Asn116Ser variant in in vitro expression systems using a variety of methods including viscosity analysis of desmin mutant protein and atomic force microscopic imaging. Data from these experiments confirmed the presence of fibrous protein aggregates in mutant cultured cells and were consistent with histological examinations of skeletal and cardiac muscle of ARVC cases carrying the same DES variants (20829228). Similarly, functional studies on the p.Glu401Asp variant in transfected cells showed disruption of cellular adhesion and intermediate filament structure and formation of desmin cytoplasmic aggregates (29212896). Finally, the deleterious structural effects of five heterozygous DES mutations on filament formation in vitro and in living cells were investigated in a study that utilized dual color photoactivation localization microscopy (22403400). In summary, there is moderate evidence to support this genedisease association. Desmin mutations associated with ARVC appear to be very rare and the observed phenotypes frequently overlap with dilated cardiomyopathy with conduction system abnormalities and occasionally skeletal myopathy.

EVIDENCE SUMMARY

# DSC2 - familial isolated arrhythmogenic right ventricular dysplasia

Gene:	DSC2 (HGNC:3036)		
Disease:	familial isolated arrhythmogenic right ventricular dysplasia (MONDO_0016342)		Definitive
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)		Classification - 09/14/2018
Replication over time	: YES	Contradictory Evide	ence: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	Contributors:	UNC Biocuration Core
Evidence Summary:	variants (e.g. missense, nonsense, frameshift) disease relationship includes case-level data a Variants in this gene have been reported in at 23863954, 17186466, 18957847, 17033975). expression studies, and protein interactions. In with mild palmoplantar keratoderma with or with	h mild palmoplantar I e ClinGen Clinical Val disease as early as 2 have been reported and experimental dat least 13 probands in This gene-disease re n summary, DSC2 is o ithout woolly hair (AF ngs, and has been up ar Cardiomyopathy G	keratoderma with or without woolly hair lidity Framework as of July, 2018. Variants in 2006 (Syrris et al., PMID: 17033975). At least 13 I in humans. Evidence supporting this gene- ta. Summary of Case Level Data: 8.5 points. 6 publications (PMIDs: 17963498, 21062920, elationship is supported by animal models, definitively associated with ARVD (AD) and ARVD R). This has been repeatedly demonstrated in pheld over time. This classification was approved Sene Curation Expert Panel on September 14,

						delines				oints	
		Εv	vidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12				
			Autosomal Dominant or X- inked Disorder	Proband with predicted or proven null variant	1.5	0-2	10	9	7	7	Syrris P et al. 2006 Nov (PMID:17033975); Heuser A et al. 2006 Dec (PMID:17186466); Gerull B et al. 2013 Aug (PMID:23863954); Gehmlich K et al. 2011 Apr 01 (PMID:21062920); Simpson MA et al. 2008 Oct 29 (PMID:18957847);
	Data	t Evidence		Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	4	1.5	1.5	Beffagna G et al. 2007 Oct 26 (PMID:17963498); Gehmlich K et al. 2011 Apr 01 (PMID:21062920);
	Case-Level Da	Variant	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
Gene						Sumn LOI		Family Count			
		Segregation		Candidate gene sequencir	ıg						
			Evidence	Exome/genome or all genes seq in linkage region	uenced						
				Total Summed LOD Score	9						
	a	Case	-Control Study		Gui	delines			Po	oints	
	Dat		Туре	<b>Case-Control Quality Criteria</b>	Points/	Study	Мах	Count	Points	Counted	PMIDs/Notes
	Control	Si	ngle Variant Analysis	1. Variant Detection Methodology	0-	6					
	Case-C	Aggi	regate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12				
				Total Genet	ic Evide	nce Po	ints	(Maxim	um 12)	8.5	
					Gui	delines			Po	oints	
	E	viden	nce Category	Evidence Type				Count		Counted	PMIDs/Notes
				Biochemical Function	0.5	0 - 2					
					1						

	Function	Protein Interaction	0.5	0 - 2	2	1	1	2	Gehmlich K et al. 2011 Apr 01 (PMID:21062920);		
dence		Expression	0.5	0 - 2		2	1		De Bortoli M et al. 2010 Jul (PMID:20197793); Lorimer JE et al. 1994 Oct-Dec (PMID:7711832);		
Evic	Functional Alteration	Patient cells	1	0 - 2	2						
ntal	Functional Alteration	Non-patient cells	0.5	0 - 1	2						
mer	Models	Non-human model organism	2	0 - 4		1	1.5		Brodehl A et al. 2017 Mar 24 (PMID:28339476);		
peri	Models	Cell culture model	1	0 - 2							
Ě		Rescue in human	2	0 - 4							
	Rescue	Rescue in non-human model organism	2	0 - 4	4	1	2	3.5	Heuser A et al. 2006 Dec (PMID:17186466);		
		Rescue in cell culture model	1	0 - 2							
		Rescue in patient cells	1	0 - 2							
	Total Experimental Evidence Points (Maximum 6)							5.5			

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	8.5	5.5	14	YES
CALCULATED	CLASSIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicat	1
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	Definitive	08	3/06/2019
	EXPERT CURATION (DATE)	Definitive The relationship between DSC2 and ard dysplasia (autosomal dominant) and aru dysplasia with mild palmoplantar kerato (autosomal recessive) was evaluated us Framework as of July, 2018. Variants in with this disease as early as 2006 (Syrr 13 variants (e.g. missense, nonsense, fi humans. Evidence supporting this gene level data and experimental data. Summ Variants in this gene have been reporter publications (PMIDs: 17963498, 21062 18957847, 17033975). This gene-disea animal models, expression studies, and DSC2 is definitively associated with AR palmoplantar keratoderma with or withor repeatedly demonstrated in both the re settings, and has been upheld over time by the ClinGen Arrythmogenic Right Ver Curation Expert Panel on September 14	hythmogenic right ventr hythmogenic right vent oderma with or without v sing the ClinGen Clinical DSC2 were first reporte is et al., PMID: 1703397 rameshift) have been rep -disease relationship in ary of Case Level Data: d in at least 13 probands 920, 23863954, 171864 se relationship is suppo protein interactions. In VD (AD) and ARVD with but woolly hair (AR). Thi search and clinical diagy a. This classification was ntricular Cardiomyopath	ricular voolly hair Validity d in humans 5). At least corted in cludes case- 8.5 points. 5 in 6 66, rted by summary, mild s has been nostic s approved

# DSG2 - arrhythmogenic right ventricular cardiomyopathy

Gene:	DSG2 (HGNC:3049)		
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)		Definitive <b>B</b>
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	CI	assification - 09/14/2018
Replication over time	: YES	Contradictory Evidence	: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	Contributors:	UNC Biocuration Core
Evidence Summary:	The relationship between DSG2 and arrhythmo evaluated using the ClinGen Clinical Validity Fr humans with this disease as early as 2006 (Pil cause of ARVC and accounts for 5%-26% of ca disease relationship is well-known, there is a s experimental data available in the literature, the experimental evidence has been reached. Note this gene-disease relationship. This gene-dise expression assays, and protein interactions. In ARVC. This has been repeatedly demonstrated upheld over time. This classification was appro Gene Curation Expert Panel on September 14, <u>Gene Clinical Validity Standard Operating Proc</u>	ramework as of July, 201 lchou et al., PMID: 16505 ases (McNAIIy et al., 200 significant amount of cas berefore the maximum so e, this curation effort ma base relationship is support summary, DSG2 is defir d in both the research an boved by the ClinGen Arry 2018 (SOP Version 6).	8. Variants in DSG2 were first reported in 5173). Variation in DSG2 is a well-known D5; PMID: 20301310). Since this gene- se-level data, segregation data and core for both genetic evidence and ay not be exhaustive of all literature related to orted by animal models, in vitro assays, hitively associated with autosomal dominant ad clinical diagnostic settings, and has been withmogenic Right Ventricular Cardiomyopathy

					Gui	delines			Po	oints	
		E	vidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12	1	2	2	Gandjbakhch E et al. 2009 Mar (PMID:19151369);
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10	6	8	8	Pilichou K et al. 2006 Mar 07 (PMID:16505173); Awad MM et al. 2006 Jul (PMID:16773573); Syrris P et al. 2007 Mar (PMID:17105751);
	a	Evidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	10	2.3	2.3	Pilichou K et al. 2006 Mar 07 (PMID:16505173); Awad MM et al. 2006 Jul (PMID:16773573); Rasmussen TB et al. 2013 May (PMID:23381804);
	Dat	Variant	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-Level		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
Geneti						Summ LOI		Family Count			
		Segregation Evidence		Candidate gene sequencir	ng						
				Evidence Exome/genome or all genes seque in linkage region							
				Total Summed LOD Score	9						
	Data	Cas	e-Control Study Type	Case-Control Quality Criteria		delines Study		Count		oints Counted	PMIDs/Notes
	ontrol	S	-	1. Variant Detection Methodology	0-	6					
	<b>0</b>	Agg	gregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	ver s and confounding 0-		12				
		Total Genetic Evidence Points		nts	(Maxim	um 12)	12				
					Gui	delines			Dr	oints	
	Ev	ide	ence Category	Evidence Type				Count		Counted	PMIDs/Notes
				<b>Biochemical Function</b>	0.5	0 - 2		1	1		Harmon RM et al. 2013 Dec (PMID:24205984);
		I	Function	Protein Interaction	0.5	0 - 2	2	1	0.5	2	Chen X et al. 2002 Mar 22 (PMID:11790773);
				Expression	0.5	0 - 2		1	0.5	1	Schäfer S et al. 1994 Apr (PMID:8143788);

ć.	Functional Alteration	Patient cells	1	0 - 2	2				
ider		Non-patient cells	0.5	0 - 1					
nental Ev	Models	Non-human model organism	2	0 - 4		3	4	4	Rizzo S et al. 2012 Sep 01 (PMID:22764152); Pilichou K et al. 2009 Aug 03 (PMID:19635863); Kant S et al. 2015 Aug (PMID:26085008);
berin		Cell culture model	1	0 - 2					
EXI	Rescue	Rescue in human	2	0 - 4	4				
		Rescue in non-human model organism	2	0 - 4					
		Rescue in cell culture model	1	0 - 2					
		Rescue in patient cells	1	0 - 2					
		Total Experimen							

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	6	18	YES
CALCULATED	CLASSIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicat	ion over time
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	Definitive	08	/06/2019
	EXPERT CURATION (DATE)	Definitive The relationship between DSG2 and arrl cardiomyopathy (autosomal dominant) Clinical Validity Framework as of July, 2 reported in humans with this disease as 16505173). Variation in DSG2 is a well-h for 5%-26% of cases (McNAlly et al., 20 gene-disease relationship is well-known case-level data, segregation data and e literature, therefore the maximum score experimental evidence has been reache be exhaustive of all literature related to gene-disease relationship is supported expression assays, and protein interact definitively associated with autosomal of repeatedly demonstrated in both the re- settings, and has been upheld over time by the ClinGen Arrythmogenic Right Ver Curation Expert Panel on September 14.	hythmogenic right ventri was evaluated using the 2018. Variants in DSG2 wo carly as 2006 (Pilchou e cnown cause of ARVC and 005; PMID: 20301310). Si n, there is a significant a xperimental data availab e for both genetic eviden d. Note, this curation eff this gene-disease relati- by animal models, in vitr ions. In summary, DSG2 dominant ARVC. This has search and clinical diagn a. This classification was ntricular Cardiomyopathy	ClinGen ere first et al., PMID: d accounts ince this mount of le in the ce and ort may not onship. This o assays, is been ostic approved

### DSP - arrhythmogenic cardiomyopathy with woolly hair and keratoderma

Gene:	DSP (HGNC:3052)			
Disease:	arrhythmogenic cardiomyopathy with woolly hair and keratoderma (MONDO_0011581)	Definitive <b>B</b>		
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 07/12/2019		
Replication over time	: YES	Contradictory Evidence: NO		
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP			
Evidence Summary:	Carvajal syndrome characterized by woolly ha pattern, homozygous mutations in DSP were the description of a heterozygous mutation in variant with the disease, PMID 12373648. The performed in different ethnicities, PMID 1594 21397041, PMID 24938629. The initial descri in families with DSP mutations, PMID 1606175 the arrhythmia phenotype and Cx43 mislocali DSP had increased cardiomyocyte apoptosis, DSP protein expression in DSP mutation carri this particular disease has been repeatedly de has been upheld over time (in general, at lease role of the gene in the specified disease. In su			

Gene Clinical Validit	v Standard Operatin	a Procedures (	(SOP) - Version 7
	<u>y otanaana operatin</u>	<u>g i i occuurcs (</u>	

								P	oints	
		Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
			Variant is de novo	2	0-3	12				
		Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10	8	12	10	Castelletti S et al. 2017 Dec 15 (PMID:28527814);
	:	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	2	1	1	Castelletti S et al. 2017 Dec 15 (PMID:28527814); Rampazzo A et al. 2002 Nov (PMID:12373648);
	Case-Level Data	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-Le	Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
enetic				Sumn LOI		med Fami DD Cour				
ő		Segregation	Candidate gene sequencir	g	3.9	1	1			Rampazzo A et al. 2002 Nov (PMID:12373648);
		Evidence	Exome/genome or all genes seq in linkage region	uenced				1	1	
			Total Summed LOD Score	•	3.9	1				
	Data	ase-Control Study Type	Case-Control Quality Criteria		delines 'Study		Count		oints Counted	PMIDs/Notes
	ontrol	Single Variant Analysis	1. Variant Detection Methodology	0-	6					
	Case-Control	Aggregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	0-6					
			Total Genet	ic Evide	nce Po	ints	(Maxim	um 12)	12	
								_		
	Evidence Category Evidence Type Do				delines Range		Count		oints Counted	PMIDs/Notes
		achiec ouregoly		Scradit	nange	Max	Jount	Total	Jounted	r Mids/Notes

	Function	<b>Biochemical Function</b>	0.5	0 - 2					
		Protein Interaction	0.5	0 - 2	2			0.5	
nce		Expression	0.5	0 - 2		1	0.5		Rasmussen TB et al. 2013 Jul (PMID:23137101);
/ide	Functional Alteration	Patient cells	1	0 - 2	2				
Ē	Functional Alteration	Non-patient cells	0.5	0 - 1	Z				
enta	Models	Non-human model organism	2	0 - 4		1	2	2	Gomes J et al. 2012 Aug (PMID:22240500);
rim		Cell culture model	1	0 - 2					
xpe		Rescue in human	2	0 - 4					
	Rescue	Rescue in non-human model organism	2	0 - 4	4				
		Rescue in cell culture model	1	0 - 2					
		Rescue in patient cells	1	0 - 2					
	Total Experimental Evidence Points (Maximum 6)								

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	2.5	14.5	YES
CALCULATED	CLASSIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicat	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	Definitive	02	/03/2020
	EXPERT CURATION (DATE)	Definitive	07	//12/2019
	EVIDENCE SUMMARY	The DSP gene was the first ARVC-gene initial mutation description was done in woolly hair, keratoderma and ARVC, it is recessive pattern, homozygous mutatio year 2000, PMID 11063735. This was fo heterozygous mutation in DSP in an Itali segregation of the variant with the dise: have been replicated worldwide in seven ethnicities, PMID 15941723, PMID 2576 20864495, PMID 21397041, PMID 2493 recognized also a high frequency of left with DSP mutations, PMID 16061754, PI generated able to replicate the arrhythm mislocalization, PMID 22240500. A tran mutation carriers has also been reporte gene in this particular disease has been the research and clinical diagnostic sett (in general, at least 3 years). No convin- contradicts the role of the gene in the s on this overwhelming evidence, DSP is o arrhythmogenic cardiomyopathy with w maximum association score was achieve main reports.	Carvajal syndrome char s transmitted in a autoso ns in DSP were describe llowed by the description ian family with ARVC and ase, PMID 12373648. Th ral studies performed in 5472, PMID 23954618, I 8629. The initial descrip ventricular compromise MID 28527814. A murine siggenic mouse overexpre- te apoptosis, cardiac fib iormal DSP protein expre d, PMID 23137101. The r repeatedly demonstrate tings, and has been uphe cing evidence has emerg pecified disease. In sum definitely associated wit oolly hair and keratodern	acterized by mal d in in the n of a l clear co- ese findings different >MID tions in families model was essing a rosis and ession in DSP ole of this ed in both eld over time led that mary, based h ma,

# JUP - arrhythmogenic right ventricular cardiomyopathy

Gene:	JUP (HGNC:6207)	
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Definitive <b>B</b>
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 07/27/2018
Replication over time	:YES	Contradictory Evidence: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	
Evidence Summary:	10902626, 15851108, 27170944, 11691526, 1 25705887, 25087486, 21668431, 20130592, nucleotide deletion (c.2038_2039delTG; p.Tr with palmoplantar keratoderma and woolly ha syndromic ARVC (McCoy et al, PMID 1090262 histopathologic cardiac effects from loss-of-1 pathogenic variants in JUP account for a low the relatively low percentage, null and misser This leads to strong genetic evidence for the	JUP and ARVC (2945574, 21668431, 2945574, 9610536, 18937352, 6893920, 29802319, 31275992, 25820315, 25820315, 25765472, 17924338, 20031617). The initial discovery of a homozygous two- b680Gly_fs) in JUP underlying Naxos disease, which includes ARVC ir, led to further focus on this and other desmosome genes in non- 26). Murine models support the functional, arrhythmic, and function variants in Jup (PMID 27170944; 25705887). Heterozygous percentage of non-syndromic ARVC (0.5%; PMID 25820315). Despite ase variants have evidence of impact in multiple families with ARVC. role of pathogenic variants in JUP for dominant, non-syndromic ARVC borts this association (score 5.5), with final classification: Strong. cedures (SOP) - Version 7

		G		Gui	delines	;		Po	oints		
		E	vidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12				
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10	9	13.5	10	McKoy G et al. 2000 Jun 17 (PMID:10902626);
		vidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	1	0.5	0.5	Asimaki A et al. 2007 Nov (PMID:17924338);
	Case-Level Data	Variant Evidence	Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-Le			Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
enetic						Sumn LOI		Family Count			
ŏ			Segregation	Candidate gene sequencir	ıg	0.6	5	2	0		McKoy G et al. 2000 Jun 17 (PMID:10902626);
			Evidence	Exome/genome or all genes seq in linkage region	uenced	nced			U	0	
				Total Summed LOD Score	9	0.6	6				
	Data	Cas	e-Control Study Type	Case-Control Quality Criteria		delines 'Study		Count		oints Counted	PMIDs/Notes
	ontrol	5	-	1. Variant Detection Methodology	0-	6					
	Case-Control Data	Ag	gregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12				
				Total Genet	ic Evide	nce Po	ints	(Maxim	um 12)	10.5	
					Gui	delines			Dr	oints	
				Evidence Type	oui	4011103					PMIDs/Notes
					Default Range Max Co			Count	Total	Counted	
				Biochemical Function	0.5	0 - 2					
			Function	Protein Interaction	0.5	0 - 2	2			0.5	
Ļ				Expression	0.5	0 - 2		1	0.5		Kaplan SR et al. 2004 May (PMID:15851108);
	Functional Alteration		ional Alteration	Patient cells	1	0 - 2	2	1	1	1	Kaplan SR et al. 2004 May (PMID:15851108);

JCe		Non-patient cells	0.5	0 - 1					
videı	Models	Non-human model organism	2	0 - 4		2	4		Zhang Z et al. 2015 Apr (PMID:25705887);
al E	Modela	Cell culture model	1	0 - 2					
lent		Rescue in human	2	0 - 4					
xperim	Rescue	Rescue in non-human model organism	2	0 - 4	4	1	2	4	Zhang Z et al. 2015 Apr (PMID:25705887);
ш		Rescue in cell culture model	1	0 - 2					
		Rescue in patient cells	1	0 - 2					
	Total Experimental Evidence Points (Maximum 6)						5.5		

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	10.5	5.5	16	YES
CALCULATED	CLASSIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicat	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	Definitive	05	5/13/2020
	EXPERT CURATION (DATE)	Definitive Twenty-one papers were reviewed relat 21668431, 2945574, 9610536, 189373 11691526, 16893920, 29802319, 31275 25765472, 25705887, 25087486, 2166 20031617). The initial discovery of a ho (c.2038_2039delTG; p.Trp680Gly_fs) in which includes ARVC with palmoplantar further focus on this and other desmose (McCoy et al, PMID 10902626). Murine arrhythmic, and histopathologic cardiac variants in JUP account for a low percer PMID 25820315). Despite the relatively variants have evidence of impact in mul to strong genetic evidence for the role of dominant, non-syndromic ARVC (score supports this association (score 5.5), w	ed to JUP and ARVC (29 52, 10902626, 15851100 992, 25820315, 258203 8431, 20130592, 17924 mozygous two-nucleotic JUP underlying Naxos d keratoderma and woolly ome genes in non-syndro models support the func c effects from loss-of-fu 887). Heterozygous pat ntage of non-syndromic low percentage, null an tiple families with ARVC of pathogenic variants in 10.5). The experimental	3, 27170944, 315, 338, de deletion lisease, y hair, led to pmic ARVC ctional, nction hogenic ARVC (0.5%; d missense . This leads J UP for evidence

# LDB3 - arrhythmogenic right ventricular cardiomyopathy

Gene:	LDB3 (HGNC:15710)				
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Disputed <b>B</b>			
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 09/12/2019			
Replication over time	: NO	Contradictory Evidence: NO			
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP				
Evidence Summary:	which Sanger sequencing failed to find a diseau proband (DSP, JUP, DSC2, DSG2, PKP2). The a panel in order to discover a candidate disease- LDB3 causing the aminoacid substitution Thr38 interpretation (VUS, LB). This variant shows a b even though the proband and family carriers do	A study (25041374) investigated a family affected by ARVC on se-causing mutation in any of the five desmosomal genes in the uthors performed Next Generation Sequencing by using a 134 genes causing gene. Genetic screening identified a missense variant on 51Ala, this variant was reported in ClinVar as conflicting high MAF in the general population to be associated with the disease b have ARVC. There is disputed evidence that the identified LDB3 there is no known disease mechanism that would link LDB3 with			

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				Gui	idelines	;		Pr	oints		
		E	Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12		<u> </u>		
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10				
	:			Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	1	0.1	0.1	Lopez-Ayala JM et al. 2015 Aug (PMID:25041374);
	Case-Level Data	Variant Evidence	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-L		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
enetic						Summ LOE		Family Count			
ő			Segregation	Candidate gene sequencin	ıg				1 '	( F	
		Evidence		Exome/genome or all genes sequences in linkage region	uenced						
				Total Summed LOD Score	ŧ						
	Data	Cas	se-Control Study Type	Case-Control Quality Criteria		idelines /Study	-	B Points Max Count Points Counted			PMIDs/Notes
	ontrol	S	Analysis	1. Variant Detection Methodology		0-6					
	Case-Control	Aggregate Variant Analysis 4. Statistical Significance		0-	0-6						
		_		Total Genet	ic Evide	nce Po	ints	(Maxim	um 12)	0.1	
					Gu	idelines	5 <b></b>		P'	oints	
	Ev	vide	ence Category	Evidence Type				Count		Counted	PMIDs/Notes
ø				Biochemical Function	0.5	0 - 2					
ence		'	Function	Protein Interaction	0.5	0 - 2	2			1 1	
vid				Expression	0.5	0 - 2	1 '			1 1	
tal	F		ional Altoration	Patient cells	1	0 - 2	_				
nen	Fur	unctional Alteration		Non-patient cells	0.5	0 - 1	2				
Experimental Evidence		Models		Non-human model organism	2	0 - 4					
Ř				Cell culture model	1	0 - 2	1 '			1 1	

	Rescue in human	2	0 - 4							
Rescue	Rescue in non-human model organism	2	0 - 4	4						
	Rescue in cell culture model	1	0 - 2							
	Rescue in patient cells	1	0 - 2							
	Total Experimental Evidence Points (Maximum 6) 0									

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)		
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)		
Assigned Points	0.1	0	0.1	NO		
		LIMITED	1-6			
		MODERATE	7-11			
		STRONG	12-18			
CALCULATED	CLASSIFICATION	DEFINITIVE	12-18 AND replicat	ion over time		
Valid contradictory evidence (Y/N)*	NO					
	CALCULATED CLASSIFICATION (DATE)	Limited	02	/04/2020		
	MODIFY CALCULATED CLASSIFICATION	YES				
	MODIFIED CLASSIFICATION (DATE)	Disputed		/04/2020		
	REASON(S) FOR CHANGE	Only a single variant was found, and the MAF of that variant was above the ARVC EP cut-off.				
	EXPERT CURATION (DATE)	Disputed	09	)/12/2019		
	EVIDENCE SUMMARY	The association of LDB3 with ARVC is disputed. A study (25041374) investigated a family affected by ARVC on which Sanger sequencing failed to find a disease-causing mutation in any of the five desmosomal genes in the proband (DSP, JUP, DSC2, DSG2, PKP2). The authors performed Next Generation Sequencing by using a 134 genes panel in order to discover a candidate disease-causing gene. Genetic screening identified a missense variant on LDB3 causing the aminoacid substitution Thr351Ala, this variant was reported in ClinVar as conflicting interpretation (VUS, LB). This variant shows a high MAF in the general population to be associated with the disease even though the proband and family carriers do have ARVC. There is disputed evidence that the identified LDB3 variant contribute to the ARVC phenotype and there is no known disease mechanism that would link LDB3 with ARVC.				

### LMNA - arrhythmogenic right ventricular cardiomyopathy

Gene:	LMNA (HGNC:6636)				
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Limited			
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 09/06/2019			
Replication over time	:NO	Contradictory Evidence: NO			
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP				
Evidence Summary:	without desmosomal variants that carried LMN, two had microscopic tissue evaluation confirmi phenotype. One variant, p. Arg644Cys under 2 This study also included experimental evidence delocalization of plakoglobin, which has been r (25837155) in 2015 showed segregation in a la remaining 7 affected individuals only met borde two LMNA variants in two probands. One only r frequent PVCs. Experimental evidence was incl replacement of the myocardium. LMNA mutation	ants with ARVC was published in 2012 and reported four patients A variants (22199124). These patients met 2010 TCC for ARVC and ng interstitial fibrosis and fatty replacement suggesting ARVC 015 ACMG criteria no longer is classified as a pathogenic variant. A as immunohistochemistry staining of the biopsies did show eported as pathologic for ARVC phenotype. Another study rge Italian family; however only the proband met ARVC TFC, the erline criteria for ARVC. Another study in 2016 (26620845) identified net borderline ARVC criteria with severe RV involvement and uded as RV endomyocardial biopsy did demonstrate fibrous tissue ons associated with ARVC appear to be very rare and the observed diomyopathy with conduction system abnormalities and atrial edures (SOP) - Version 7			

					Gui	delines	;		Po	oints	
		E	vidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12				
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10	1	1.5	1.5	Kato K et al. 2016 Oct (PMID:26620845);
Genetic Evidence		vidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	4	1.5	1.5	Quarta G et al. 2012 May (PMID:22199124); Kato K et al. 2016 Oct (PMID:26620845);
	vel Data	Variant Evidence	Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
	Case-Level Data			Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
letic E						Summed LOD		Family Count			
Ger		Segregation Evidence		Candidate gene sequencir	ng	3.61		4	1	1	Quarta G et al. 2012 May (PMID:22199124); Kato K et al. 2016 Oct (PMID:26620845); Forleo C et al. 2015 Apr 2 (PMID:25837155);
				Exome/genome or all genes sequenced in linkage region							
				Total Summed LOD Score		3.61					
	a a	Cas	e-Control Study		Guidelines				Points		
	Dat	Type Case-Control Quality Criteria		Points/	Study	Мах	Count	Points	Counted	PMIDs/Notes	
	ontrol	5	J. J	1. Variant Detection Methodology	0-	6					
	Case-Control Data	Ag	Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12				
		Total Genetic Evidence Points (Max		(Maxim	um 12)	4					
					Gui	delines	oints				
	E	vidence Category		Evidence Type		lidelines It Range Max C		Count			PMIDs/Notes
				Biochemical Function	0.5	0 - 2					
			Function	Protein Interaction	0.5	0 - 2	2				
										1	

Ce		Expression	0.5	0 - 2					
videı	Functional Alteration	Patient cells	1	0 - 2	2	1	1	1	Quarta G et al. 2012 May (PMID:22199124);
Ē	Functional Alteration	Non-patient cells	0.5	0 - 1	Z			I	
enta	Models	Non-human model organism	2	0 - 4					
rin	Models	Cell culture model	1	0 - 2					
adx		Rescue in human	2	0 - 4					
ш	Rescue	Rescue in non-human model organism	2	0 - 4	4				
		Rescue in cell culture model	1	0 - 2					
		Rescue in patient cells	1	0 - 2					
		Total Experimen	tal Evid	lence Pe	oints	(Maxir	num 6)	1	

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)	
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)	
Assigned Points	4	1	5	NO	
		LIMITED	1-6		
		MODERATE	7-11		
		STRONG	12-18		
CALCULATED C	CLASSIFICATION	DEFINITIVE	12-18 AND replication over time		
Valid contradictory evidence (Y/N)*	NO				
	CALCULATED CLASSIFICATION (DATE)	Limited	05	/08/2020	
	EXPERT CURATION (DATE)	Limited	09/06/2019		
	EVIDENCE SUMMARY	The first publication that associated LM published in 2012 and reported four pat that carried LMNA variants (22199124). ARVC and two had microscopic tissue er fibrosis and fatty replacement suggesti Arg644Cys under 2015 ACMG criteria n variant. This study also included experi immunohistochemistry staining of the b plakoglobin, which has been reported a: Another study (25837155) in 2015 show family; however only the proband met A individuals only met borderline criteria t (26620845) identified two LMNA varian borderline ARVC criteria with severe RV Experimental evidence was included as demonstrate fibrous tissue replacement mutations associated with ARVC appear phenotypes frequently overlap with dila system abnormalities and atrial arrhyth	ients without desmoson These patients met 201 valuation confirming into ng ARVC phenotype. On- o longer is classified as mental evidence as iopsies did show deloca is pathologic for ARVC pl ved segregation in a larg RVC TFC, the remaining for ARVC. Another study ts in two probands. One involvement and freque RV endomyocardial biop t of the myocardial biop t of the myocardian LM to be very rare and the ted cardiomyopathy wit	al variants 0 TCC for erstitial e variant, p. a pathogenic lization of nenotype. e Italian 7 affected in 2016 only met nt PVCs. sy did NA observed	

### MYBPC3 - arrhythmogenic right ventricular cardiomyopathy

Gene:	MYBPC3 (HGNC:7551)				
Disease: arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)		Limited 🔁			
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 08/06/2019			
Replication over time	:NO	Contradictory Evidence: NO			
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP				
Evidence Summary:	Inheritance: Autosomal dominant inheritance (H Cardiomyopathy SOP: Gene Clinical Validity Sta Classification (date) Limited 22/02/2019 Evider with ARVC. Screening of ARVC patient cohorts (29709087, 27194543). In these studies, a total reported carrying MYBPC3 missense variants. I unclear as they were either VUS (e.g. p.Arg238 variants in other genes associated with cardion identified MYBPC3 p.Phe305Profs variant did r publication presented a single ARVC case with summary, there is limited evidence to support t	rdiomyopathy (ARVC) HGNC: 7551 MONDO_0016587 Mode of AP:0000066) Expert Panel: Arrhythmogenic Right Ventricular andard Operating Procedures (SOP), Version 6 Calculated for MYBPC3 mutations has been performed in two studies I of 151 ARVC patients were investigated and three individuals were However, the significance of these variants in the context of ARVC is Cys) or MYBPC3 variant carriers were also double heterozygotes for hyopathies (29709087, 27194543). In one ARVC pedigree the ot segregate with ARVC in the family (28699631). A recent a missense variant (p.Glu1179Lys) in MYBPC3 (28843747). In his gene-disease association. There is no clear evidence that the RVC phenotype and there is no known disease mechanism that			

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E			Guidelines Default Range Max Count			Points		DNID-/Neter	
	vidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
		Variant is de novo	2	0-3	12				
	Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10				
vidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	4	1	1	Murray B et al. 2018 Jul (PMID:29709087); Medeiros-Domingo A et al. 2017 Jun 1 (PMID:27194543); Choung HYG et al. 2017 Oct (PMID:28843747);
Variant E	Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
		Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
						Family Count			
	Segregation	Candidate gene sequencin	g						
	Evidence	Exome/genome or all genes sequin linkage region	uenced						
		Total Summed LOD Score	)						
Case-Control Study Type		Case-Control Quality Criteria				Count			PMIDs/Notes
5	U U		0-	6					
Aggregate Variant 2. Power		0-	-6						
		Total Genet	ic Evide	nce Po	ints	(Maxim	um 12)	1	
			c:	dolinca			De	into	
vide	ence Category	Evidence Type				Count			PMIDs/Notes
		<b>Biochemical Function</b>	0.5	0 - 2					
Function		Protein Interaction	0.5	0 - 2	2				
	Variant Evidence	Dominant or X- linked Disorder Autosomal Recessive Disease Segregation Evidence Case-Control Study Type Single Variant Analysis Aggregate Variant Analysis	Autosomal Dominant or X- linked Disorder       proven null variant         Proband with other variant type with some evidence of gene impact       Proband with other variant type with some evidence of gene impact         Autosomal Recessive Disease       Two variants in trans and at least one de novo or a predicted/proven null variant         Segregation Evidence       Two variants (not predicted/proven null) with some evidence of gene impact in trans         Segregation Evidence       Candidate gene sequencin Exome/genome or all genes seq in linkage region         Case-Control Study Type       Case-Control Quality Criteria         Single Variant Analysis       1. Variant Detection Methodology         Aggregate Variant Analysis       1. Statistical Significance         Vidence Category       Evidence Type         Biochemical Function       Biochemical Function	Autosomal Dominant or X- linked Disorderproven null variant1.5Proband with other variant type with some evidence of gene impact0.5Autosomal Recessive DiseaseTwo variants in trans and at least one de novo or a predicted/proven null variant2Segregation EvidenceCandidate gene sequencing Exome/genome or all genes sequenced in linkage region1Single Variant Analysis1. Variant Detection Methodology0.5Aggregate Variant Analysis1. Variant Detection Methodology0-Single Variant Analysis0-0-Single Variant Analysis0-0-Single Variant Analysis0-0-Single Variant Analysis0-0-Single Variant Analysis0-0-Single Variant Analysis0-0-SubjectServer Single Server0-Single Variant Analysis0-0-Single Variant Analysis0-0-Single Variant Analysis0-0-Single Variant Analysis0-0-Single Variant Analysis0-0- <tr< th=""><th>Autosomal Dominant or X- linked Disorderproven null variant1.50-2Proband with other variant type with some evidence of gene impact0.50-1.5Autosomal Recessive DiseaseTwo variants in trans and at least one de novo or a predicted/proven null variant20-3Segregation EvidenceTwo variants (not predicted/proven null) with some evidence of gene impact in trans10-1.5Segregation EvidenceCandidate gene sequencing Exome/genome or all genes sequenced in linkage regionSumm LOICase-Control Study TypeCase-Control Quality Criteria 3. Bias and confounding 4. Statistical Significance0-6Aggregate Variant Analysis1. Variant Detection 3. Bias and confounding 4. Statistical Significance0-6Vidence CategoryEvidence TypeDefault RangeBiochemical Function0.50-2</th><th>Autosomal pominant or X- linked Disorderproven null variant1.50-210Proband with other variant type with some evidence of gene impact0.50-1.57Autosomal Recessive DiseaseTwo variants in trans and at least one de novo or a predicted/proven null variant20-3Recessive DiseaseTwo variants (not predicted/proven null) with some evidence of gene impact10-1.57Segregation EvidenceCandidate gene sequencing in trans10-1.512Case-Control Study TypeCandidate gene sequencing case-Control Quality CriteriaSummed Points/Study MaxSingle Variant Analysis1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance0-612Aggregate Variant Analysis1. Variant Detection Biochemical Function0-612Biochemical Function0.50-212</th><th>Autosomal Dominant or X- linked Disorder       proven null variant       1.5       0-2       10         Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7       4         Autosomal Inked Disorder       Two variants in trans and at least one de novo or a predicted/proven null variant       2       0-3       1       1         Autosomal Recessive Disease       Two variants in trans and at least one de novo or a predicted/proven null variant       1       0-1.5       7       4         Segregation Evidence       Candidate gene sequencing       1       0-1.5       7       Family Count         Candidate gene sequencing       Image: sequenced in linkage region       Image: sequenced in linkage       Image: sequenced in linkage       Image: sequenced in linkage       Image: sequenced in linkage       Image: sequenced in linka</br></br></th><th>Autosomal Dominant or X- linked Disorder       proven null variant       1.5       0-2       10       1         Mutosomal Dominant or X- linked Disorder       Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7       4       1         Autosomal Recessive Disease       Two variants in trans and at least one de novo or a predicted/proven null variant       2       0-3       12       12       12         Segregation Evidence       Two variants (not predicted/proven null) with some evidence of gene impact in trans       1       0-1.5       7       4       1         Candidate gene sequencing       I       0-1.5       7       4       1         Candidate gene sequencing       Exome/genome or all genes sequenced in linkage region       5       1       0       1       1       0       1</th><th>Autosomal Dominant or X- linked Disorder       proven null variant       1.5       0-2       10       Image: Constraint of Constraint of</th></tr<>	Autosomal Dominant or X- linked Disorderproven null variant1.50-2Proband with other variant type with some evidence of gene impact0.50-1.5Autosomal Recessive DiseaseTwo variants in trans and at least one de novo or a predicted/proven null variant20-3Segregation EvidenceTwo variants (not predicted/proven null) with some evidence of gene impact in trans10-1.5Segregation EvidenceCandidate gene sequencing Exome/genome or all genes sequenced in linkage regionSumm LOICase-Control Study TypeCase-Control Quality Criteria 3. Bias and confounding 4. Statistical Significance0-6Aggregate Variant Analysis1. Variant Detection 3. Bias and confounding 4. Statistical Significance0-6Vidence CategoryEvidence TypeDefault RangeBiochemical Function0.50-2	Autosomal pominant or X- linked Disorderproven null variant1.50-210Proband with other variant type with some evidence of gene impact0.50-1.57Autosomal Recessive DiseaseTwo variants in trans and at least one de novo or a predicted/proven null variant20-3Recessive DiseaseTwo variants (not predicted/proven null) with some evidence of gene impact10-1.57Segregation EvidenceCandidate gene sequencing in trans10-1.512Case-Control Study TypeCandidate gene sequencing case-Control Quality CriteriaSummed Points/Study MaxSingle Variant Analysis1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance0-612Aggregate Variant Analysis1. Variant Detection Biochemical Function0-612Biochemical Function0.50-212	Autosomal Dominant or X- linked Disorder       proven null variant       1.5       0-2       10         Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7       4         Autosomal 	Autosomal Dominant or X- linked Disorder       proven null variant       1.5       0-2       10       1         Mutosomal Dominant or X- linked Disorder       Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7       4       1         Autosomal Recessive Disease       Two variants in trans and at least one de novo or a predicted/proven null variant       2       0-3       12       12       12         Segregation Evidence       Two variants (not predicted/proven null) with some evidence of gene impact in trans       1       0-1.5       7       4       1         Candidate gene sequencing       I       0-1.5       7       4       1         Candidate gene sequencing       Exome/genome or all genes sequenced in linkage region       5       1       0       1       1       0       1	Autosomal Dominant or X- linked Disorder       proven null variant       1.5       0-2       10       Image: Constraint of

ce		Expression	0.5	0 - 2					
vider	Functional Alteration	Patient cells	1	0 - 2	2				
al Ev	Functional Alteration	Non-patient cells	0.5	0 - 1	Z				
enta	Models	Non-human model organism	2	0 - 4					
Ë.	Models	Cell culture model	1	0 - 2					
adx		Rescue in human	2	0 - 4					
Ű	Rescue	Rescue in non-human model organism	2	0 - 4	4				
		Rescue in cell culture model	1	0 - 2					
		Rescue in patient cells	1	0 - 2					
		Total Experimen	tal Evid	lence Po	s (Maxi	mum 6)	0		

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	1	0	1	NO
CALCULATED	CLASSIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replication over time	
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DAT			2/04/2020
	EXPERT CURATION (DAT	MYBPC3: Arrhythmogenic Right Ventric 7551 MONDO_0016587 Mode of Inherita inheritance (HP:0000006) Expert Pane Cardiomyopathy SOP: Gene Clinical Val (SOP), Version 6 Calculated Classificat Evidence Summary: There is limited evi with ARVC. Screening of ARVC patient of been performed in two studies (297090 total of 151 ARVC patients were investig reported carrying MYBPC3 missense va these variants in the context of ARVC is (e.g. p.Arg238Cys) or MYBPC3 variant heterozygotes for variants in other gen (29709087, 27194543). In one ARVC pe p.Phe305Profs variant did not segregat (28699631). A recent publication prese missense variant (p.Glu1179Lys) in MYE is limited evidence to support this gene clear evidence that the identified MYBP	cular Cardiomyopathy (A ance: Autosomal dominar l: Arrhythmogenic Right idity Standard Operating ion (date) Limited 22/02, dence that MYBPC3 is a cohorts for MYBPC3 mut 187, 27194543). In these gated and three individua iriants. However, the sig carriers were also doubl es associated with cardii edigree the identified MY te with ARVC in the famil ented a single ARVC case BPC3 (28843747). In sun -disease association. Th	RVC) HGNC: nt Ventricular Procedures /2019 ssociated ations has studies, a als were nificance of ther VUS e omyopathies 'BPC3 y e with a nmary, there here is no o the ARVC

# MYH7 - arrhythmogenic right ventricular cardiomyopathy

Gene:	MYH7 (HGNC:7577)							
Disease: arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)		Limited 🔂						
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 08/06/2019						
Replication over time	:NO	Contradictory Evidence: NO						
Expert Panel:								
Evidence Summary:	Inheritance: Autosomal dominant inheritance (H Cardiomyopathy SOP: Gene Clinical Validity Sta Classification (date) Limited 22/03/2019 Evider with ARVC. Screening of ARVC patient cohorts 27194543, 29253866 and 30385303). In these individuals were reported carrying MYH7 varian these variants in the context of ARVC is unclean as causative in hypertrophic cardiomyopathy (e p.Met877lle variant did not segregate with ARV support this gene-disease association. There is	omyopathy (ARVC) HGNC: 7577 MONDO_0016587 Mode of IP:000006) Expert Panel: Arrhythmogenic Right Ventricular indard Operating Procedures (SOP), Version 6 Calculated for MYH7 mutations has been performed in four studies (29709087, e studies, a total of 245 ARVC patients were investigated and eight ts (a deletion and seven missense). However, the significance of a sthey were either VUS (e.g. p.Arg1846Cys) or previously reported .g. p.Lys847del). In one ARVC pedigree the identified MYH7 C in the family (28699631). In summary, there is limited evidence to a no clear evidence that the identified MYH7 variants contribute to ease mechanism that would link MYH7 with ARVC. edures (SOP) - Version 7						

					Gui	delines	;		Points			
		E	vidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes	
		Variant Evidence	Autosomal Dominant or X- linked Disorder	Variant is de novo	2	0-3	12					
				Proband with predicted or proven null variant	1.5	0-2	10	1	0.5	0.5	Murray B et al. 2018 Jul (PMID:29709087);	
				Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	5	1.25	1.25	Murray B et al. 2018 Jul (PMID:29709087); Klauke B et al. 2017 Dec 18 (PMID:29253866); Medeiros-Domingo A et al. 2017 Jun 1 (PMID:27194543);	
	Case-Level Data		Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3						
Genetic Evidence	Case-L			Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12					
tic	1							Family				
ene						LOI	D	Count				
G			Segregation	Candidate gene sequencir	g							
			Evidence	Exome/genome or all genes seq in linkage region	uenced							
				Total Summed LOD Score	9							
	a	Cas	e-Control Study		Gui	delines	;		Po	oints		
	Dat	Туре		Case-Control Quality Criteria	Points/	Study	Мах	Count	Points	Counted	PMIDs/Notes	
	ontrol	Single Variant 1. Variant Detect Analysis Methodology		1. Variant Detection Methodology	0-	6						
	Case-Control Data	Ag	gregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12					
		Total Genet				tic Evidence Points			(Maximum 12) 1.75			
					Guidelines Points							
				Guidennes				Points		PMIDs/Notes		
					Default Range Max Count Total Counted							
				<b>Biochemical Function</b>	0.5	0 - 2						
			Function	Protein Interaction	0.5	0 - 2	2					
				Expression	0.5	0 - 2						
- 1												

S	Functional Alteration	Patient cells	1	0 - 2	2			
Eviden		Non-patient cells	0.5	0 - 1				
	Models	Non-human model organism	2	0 - 4				
ental	Models	Cell culture model	1	0 - 2				
ε		Rescue in human	2	0 - 4	4			
Experi	Rescue	Rescue in non-human model organism	2	0 - 4				
		Rescue in cell culture model	1	0 - 2				
		Rescue in patient cells	1	0 - 2				
		Total Experimen	tal Evid	0				

	se-level, family segregation, or case- control data that support the gene- disease association <b>1.75</b>	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing
	1 75			evidence over time (>3 yrs)
Assigned Points	1.75	0	1.75	NO
CALCULATED CLASS	SIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicat	ion over time
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE) EXPERT CURATION (DATE)	Limited Limited MYH7: Arrhythmogenic Right Ventricula 7577 MONDO_0016587 Mode of Inherita inheritance (HP:0000006) Expert Panel Cardiomyopathy SOP: Gene Clinical Vali (SOP), Version 6 Calculated Classificati Evidence Summary: There is limited evid ARVC. Screening of ARVC patient cohor performed in four studies (29709087, 2' 30385303). In these studies, a total of 2 investigated and eight individuals were deletion and seven missense). However, the context of ARVC is unclear as they w or previously reported as causative in hy p.Lys847del). In one ARVC pedigree the variant did not segregate with ARVC in t there is limited evidence to support this no clear evidence that the identified MY phenotype and there is no known diseas	08 r Cardiomyopathy (ARV0 nce: Autosomal dominar : Arrhythmogenic Right ' dity Standard Operating on (date) Limited 22/03/ lence that MYH7 is asso ts for MYH7 mutations h 7194543, 29253866 and 245 ARVC patients were reported carrying MYH7 the significance of thes rere either VUS (e.g. p. A ypertrophic cardiomyopa identified MYH7 p.Met8 he family (28699631). In gene-disease associatii H7 variants contribute to	it Ventricular Procedures 2019 ciated with as been I variants (a e variants in rg1846Cys) athy (e.g. 771le n summary, on. There is o the ARVC

### MYL2 - arrhythmogenic right ventricular cardiomyopathy

Gene:	MYL2 (HGNC:7583)						
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	No Known Disease Relationship 🖯					
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 05/24/2019					
Replication over time	: NO	Contradictory Evidence: NO					
Expert Panel: Arrhythmogenic Right Ventricular Cardiomyopathy EP							
Evidence Summary:	Inheritance: Autosomal dominant inho Cardiomyopathy SOP: Gene Clinical V Classification (date) No reported evid involved in ARVC. This gene has been patients: a cohort of 14 Spanish unre	ular Cardiomyopathy (ARVC) HGNC: 7583 MONDO_0016587 Mode of eritance (HP:0000006) Expert Panel: Arrhythmogenic Right Ventricular /alidity Standard Operating Procedures (SOP), Version 6 Calculated dence 22/03/2019 Evidence Summary: There is no evidence that MYL2 is n investigated for pathogenic variants in two populations of gene-elusive ARVC lated patients (22421524) and a cohort of 137 ARVC patients meeting 2010 087). No variants in MYL2 were reported. ating Procedures (SOP) - Version 7					

					delines			Po	oints		
		Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes	
			Variant is de novo	2	0-3	12					
		Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10					
	and but	linked Diserder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7					
	Case-Level Data	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3						
Genetic Evidence	Case-L	Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12					
enetic E					Sumn LOI		Family Count				
Ō		Segregation	Candidate gene sequencin	g							
		Evidence	Exome/genome or all genes sequenced in linkage region		d						
			Total Summed LOD Score								
	, E У	Type Case-Control Quality Criteria		Gui	delines	elines		Points			
	Dat	Туре	<b>Case-Control Quality Criteria</b>	Points/	Study	Max	Count	Points	Counted	PMIDs/Notes	
	Control	Single Variant Analysis	1. Variant Detection Methodology	0-	6						
		Aggregate Variant	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12					
			Total Geneti	ic Evide	nce Po	ints	(Maxim	um 12)	0		

Guidelines

Points

PMIDs/Notes

			Default	Range	Мах	Count	Total	Counted	
Funati		<b>Biochemical Function</b>	0.5	0 - 2	2				
Function	on	Protein Interaction	0.5	0 - 2					
		Expression	0.5	0 - 2					
Functional A	Iteration	Patient cells	1	0 - 2	2				
		Non-patient cells	0.5	0 - 1					
Model	le	Non-human model organism	2	0 - 4	4				
Model	5	Cell culture model	1	0 - 2					
		Rescue in human	2	0 - 4					
Rescu	e	Rescue in non-human model organism	2	0 - 4					
		Rescue in cell culture model	1	0 - 2					
		Rescue in patient cells	1	0 - 2					
		Total Experimer	tal Evic	lence Po	oints	s (Maxir	num 6)	0	

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)			
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)			
Assigned Points	0	0	0	NO			
		LIMITED	1-6				
		MODERATE	7-11				
		STRONG					
CALCULATED	CLASSIFICATION	DEFINITIVE	12-18 AND replication over time				
Valid contradictory evidence (Y/N)*	NO						
		No Known Disease Relationship		100 10000			
	CALCULATED CLASSIFICATION (DATE)			/08/2020			
	EXPERT CURATION (DATE)		isinp	/24/2019			
		MYL2: Arrhythmogenic Right Ventricula 7583 MONDO_0016587 Mode of Inherita					
		inheritance (HP:0000006) Expert Panel: Arrhythmogenic Right Ventricular Cardiomyopathy SOP: Gene Clinical Validity Standard Operating Procedures (SOP), Version 6 Calculated Classification (date) No reported evidence					
		22/03/2019 Evidence Summary: There i	s no evidence that MYL2	is involved			
		in ARVC. This gene has been investigate populations of gene-elusive ARVC patie					
		unrelated patients (22421524) and a co					
	EVIDENCE SUMMARY	2010 Task Force criteria for ARVC (2970 reported.	9087). No variants in M	/L2 were			

# MYL3 - arrhythmogenic right ventricular cardiomyopathy

Gene:	MYL3 (HGNC:7584)					
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Limited				
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 09/13/2019				
Replication over time	: NO	Contradictory Evidence: NO				
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP					
Evidence Summary:	mutations has been performed in two studies (2 were investigated for putative pathogenic varian Arg154His was identified in one patient. This pr current ACMG criteria and has been demonstra this variant has not been linked to ARVC phenor (22421524) 14 ARVC patients were investigated	ed with ARVC. Screening of ARVC patient cohorts for MYL3 29709087, 22421524). In first study (29709087) 137 ARVC patients ints. A missense variant causing the aminoacid substitution eviously report variant is classified as likely pathogenic according to te in vitro to disturb the binding of this protein to myosin. However, type and no segregation data were available. In the second study d but no MYL3 variants were reported. There is no clear evidence C phenotype and there is no known disease mechanism that would edures (SOP) - Version 7				

					Gui	delines	6		Po	oints	
		F	Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12				
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10				
		vidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	1	0.25	0.25	Murray B et al. 2018 Jul (PMID:29709087);
	Case-Level Data	Variant Evidenc	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-L		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
enetic						Sumn LOI		Family Count			
ő			Segregation	Candidate gene sequencir	ıg						
			Evidence	Exome/genome or all genes seq in linkage region	uenced						
				Total Summed LOD Score	;						
	a a	Cas	se-Control Study		Gui	delines	6		Po	oints	
	Dat	Type Case-Control Quality Criteria			Points	/Studv	Мах	Count	Points	Counted	PMIDs/Notes
	5			Case-Control Quality Criteria	,						
	ontr	:	Single Variant Analysis	1. Variant Detection Methodology	0-	-					
	Case-Control		-	1. Variant Detection		6	12				
	Case-Contr		Analysis Igregate Variant	<ol> <li>Variant Detection</li> <li>Methodology</li> <li>Power</li> <li>Bias and confounding</li> </ol>	0-	6		(Maxim	um 12)	0.25	
	Case-Contr		Analysis Igregate Variant	<ol> <li>Variant Detection</li> <li>Methodology</li> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0- 0- ic Evide	6	ints	(Maxim		0.25	
		Ag	Analysis Igregate Variant	<ol> <li>Variant Detection</li> <li>Methodology</li> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0- 0- ic Evide Gui	6 nce Po delines	ints	-	Po		PMIDs/Notes
0		Ag	Ānalysis Igregate Variant Analysis	<ol> <li>Variant Detection Methodology</li> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol> Total Generation	0- 0- ic Evide Gui	6 nce Po delines	ints	-	Po	oints	PMIDs/Notes
ence		Ag Evide	Ānalysis Igregate Variant Analysis	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance Total Gener Evidence Type	0- ic Evide Gui Default	6 nce Po delines Range	ints	-	Po	oints	PMIDs/Notes
Evidence		Ag Evide	Analysis Igregate Variant Analysis ence Category	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance Total Genet Evidence Type Biochemical Function	0- ic Evide Gui Default 0.5	6 nce Po delines Range 0 - 2	ints S Max	-	Po	oints	PMIDs/Notes
tal Evidence	E	Ag	Analysis Igregate Variant Analysis ence Category Function	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance <b>Total Genet</b> <b>Evidence Type</b> Biochemical Function Protein Interaction	0- ic Evide Gui Default 0.5 0.5	6 nce Po delines Range 0 - 2 0 - 2	ints Max 2	-	Po	oints	PMIDs/Notes
mental Evidence	E	Ag	Analysis Igregate Variant Analysis ence Category	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance <b>Total Genet</b> <b>Evidence Type</b> Biochemical Function Protein Interaction Expression	0- ic Evide Gui Default 0.5 0.5 0.5	6 6 delines Range 0 - 2 0 - 2 0 - 2	ints S Max	-	Po	oints	PMIDs/Notes
Experimental Evidence	E	Ag	Analysis Igregate Variant Analysis ence Category Function	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance Total Genet Evidence Type Biochemical Function Protein Interaction Expression Patient cells	0- ic Evide Gui Default 0.5 0.5 0.5 1	6 delines Range 0 - 2 0 - 2 0 - 2 0 - 2	ints Max 2	-	Po	oints	PMIDs/Notes

	Rescue in human	2	0 - 4				
Rescue	Rescue in non-human model organism	2	0 - 4	4			
	Rescue in cell culture model	1	0 - 2				
	Rescue in patient cells	1	0 - 2				
	Total Experimen	tal Evid	lence P	oints	s (Maximum 6)	0	

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)	
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)	
Assigned Points	0.25	0	0.25	NO	
		LIMITED MODERATE STRONG	1-6 7-11 12-18		
CALCULATED	CLASSIFICATION	DEFINITIVE	12-18 AND replication over time		
Valid contradictory evidence (Y/N)*	NO				
	CALCULATED CLASSIFICATION (DATE)	Limited		/04/2020	
	EXPERT CURATION (DATE)	Limited There is limited evidence that MYL3 is a ARVC patient cohorts for MYL3 mutatio studies (29709087, 22421524). In first patients were investigated for putative variant causing the aminoacid substitut patient. This previously report variant is according to current ACMG criteria and disturb the binding of this protein to my been linked to ARVC phenotype and no the second study (22421524) 14 ARVC MYL3 variants were reported. There is r MYL3 contribute to the ARVC phenotypy mechanism that would link MYL3 with A	ssociated with ARVC. So ns has been performed in study (29709087) 137 A pathogenic variants. A m ion Arg154His was ident s classified as likely path has been demonstrate in rosin. However, this varia segregation data were av patients were investigat to clear evidence that the e and there is no known of	n two RVC issense ified in one ogenic o vitro to nt has not railable. In ed but no e identified	

# PKP2 - arrhythmogenic right ventricular cardiomyopathy

Gene:	PKP2 (HGNC:9024)					
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Definitive 🕄 Classification - 03/08/2018				
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)					
Replication over time	: YES	Contradictory Evidence: NO				
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	Contributors:	UNC Biocuration Core			
Evidence Summary:	evaluated using the ClinGen Clinical Validity Fr in humans with this disease as early as 2004 ( ARVC and accounts for 34%-74% of cases (Mo variants listed in ClinVar for ARVC (missense, r 2018; PMID: 30619891). This gene-disease re level data, segregation data and experimental both genetic evidence and experimental evide exhaustive of all literature related to this gene- animal models, in vitro assays, and protein inter-	amework as of Sep Gerull et al., PMID: cNAlly et al., 2005; nonsense, frameshi lationship is well-kn data is available in nce has been reach disease relationshi eractions. In summa nonstrated in both t was approved by th on October, 26, 2018	ft, complex rearrangements, etc) (Novelli et al., nown and therefore a significant amount of case- the literature, therefore the maximum score for ned. Note, this curation effort may not be ip. This gene-disease relationship is supported by ary, PKP2 is definitively associated with autosoma the research and clinical diagnostic settings, and ne ClinGen Arrythmogenic Right Ventricular 8 (SOP Version 6).			

		Gui	delines			Po	oints			
	I	Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
			Variant is de novo	2	0-3	12				
		Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10	17	25.5	10	Gerull B et al. 2004 Nov (PMID:15489853); Syrris P et al. 2006 Jan 24 (PMID:16415378);
	vidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	2	1	1	Gerull B et al. 2004 Nov (PMID:15489853); Syrris P et al. 2006 Jan 24 (PMID:16415378);
Level Data	Variant E	Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Case-L			Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
	Segregation						Family Count			
			Candidate gene sequencir	ng	4.5	2	3			Syrris P et al. 2006 Jan 24 (PMID:16415378);
		Evidence	Exome/genome or all genes seq in linkage region	uenced				1		
			Total Summed LOD Score	4.52		52				
ta	Cas	se-Control Study		Gui	delines	lelines		Points		
Da		Туре	Case-Control Quality Criteria	Points/	Study	Мах	Count	Points	Counted	PMIDs/Notes
ontrol	:	U U	1. Variant Detection Methodology	0-	6					
Case-C	Ag	Analysis	4. Statistical Significance							
			Total Genet	ic Evide	nce Po	ints	(Maxim	um 12)	12	
				Gui	delines			Dr	oints	
E	vid	ence Category	Evidence Type				Count			PMIDs/Notes
			<b>Biochemical Function</b>	0.5	0 - 2					
		Function	Protein Interaction	0.5	0 - 2	2	1	1.5	2	Chen X et al. 2002 Mar 22 (PMID:11790773);
		i anction	Expression	0.5	0 - 2	2	1	0.5	2	Mertens C et al. 1996 Nov (PMID:8922383);
		Case-Control Data Case-Level Data	generation     Dominant or X-linked Disorder       bind     Autosomal       Recessive     Disease       Disease     Disease       generation     Evidence       single Variant     Analysis       Aggregate Variant     Analysis	Perform       Variant is de novo         Autosomal Dominant or X- linked Disorder       Proband with predicted or proven null variant         Autosomal Dominant or X- linked Disorder       Proband with predicted or proven null variant         Autosomal Recessive Disease       Two variants in trans and at least one de novo or a predicted/proven null variant         Segregation Evidence       Candidate gene sequencir Exome/genome or all genes seq in linkage region         Segregation Evidence       Case-Control Study Type         Augregate Variant Analysis       1. Variant Detection Methodology         Aggregate Variant Analysis       1. Variant Detection Methodology         Augregate Variant Analysis       Sias and confounding 4. Statistical Significance         Function       Evidence Category         Function       Protein Interaction	Evidence Type         Case Information Type         Default           Autosomal Dominant or X- inked Disorder         Variant is de novo         2           Autosomal Dominant or X- inked Disorder         Proband with predicted or proven null variant         1.5           Autosomal Dominant or X- inked Disorder         Two variants in trans and at least one de novo or a predicted/proven null variant         2           Autosomal Recessive Disease         Two variants in trans and at least one de novo or a predicted/proven null) with some evidence of gene impact in trans         1           Segregation Evidence         Candidate gene sequencing Exome/genome or all genes sequenced in linkage region         Points/           Single Variant Analysis         1. Variant Detection Methodology         0-           Aggregate Variant Analysis         1. Variant Detection Methodology         0-           Single Variant Analysis         1. Variant Detection Methodology         0-           Jais and confounding A. Statistical Significance         0-           Jais and confounding A. Statistical Significance         0-           Biochemical Function         0.5           Protein Interaction         0.5	Evidence Type         Case Information Type         Default Range           Autosomal Dominant or X- linked Disorder         Proband with predicted or proven null variant         1.5         0-2           Proband with other variant type with some evidence of gene impact         0.5         0-1.5           Autosomal Dominant or X- linked Disorder         Two variants in trans and at least one de novo or a predicted/proven null variant         2         0-3           Autosomal Recessive Disease         Two variants in trans and at least one de novo or a predicted/proven null variant         2         0-3           Segregation Evidence         Two variants (not predicted/proven null writh some evidence of gene impact in trans         1         0-1.5           Segregation Evidence         Candidate gene sequencing         4.5         Summ LOI           Segregation Evidence         Case-Control Study Type         Summ LOI         0-1.5           Single Variant Analysis         1. Variant Detection Methodology         0-6           Aggregate Variant Analysis         1. Variant Detection Methodology         0-6           Bias and confounding 4. Statistical Significance         0-6           Evidence Type         Evidence Type         Default Range           Biochemical Function         0.5         0-2	Autosomal Dominant or X- linked Disorder       Variant is de novo Proband with predicted or proven null variant       1.5       0-2       10         Proband with other variant type with some evidence of gene impact       0.5       0-1.5       7         Autosomal necessive Disease       Two variants in trans and at least one de novo or a predicted/proven null variant       2       0-3       12         Segregation Evidence       Two variants (not predicted/proven null) with some evidence of gene impact       1       0-1.5       12         Segregation Evidence       Candidate gene sequencing       4.52       12         Case-Control Study Type       Case-Control Quality Criteria       Guidelines Points/Study Max         Single Variant Analysis       1       0-6       12         Aggregate Variant Analysis       1       0-6       12         Bias and confounding 4. Statistical Significance       0-6       12         Function       Evidence Type       Default Range Max         Biochemical Function       0.5       0-2       2	Evidence Type         Case Information Type         Default Range Wat Sound         Count           Autosomal Dominant or X- linked Disorder         Proband with predicted or proven null variant         1.5         0-2         10         17           Proband with other variant type with some evidence of gene impact         0.5         0-1.5         7         2           Autosomal Dominant or X- linked Disorder         Two variants in trans and at least one de novo or a predicted/proven null variant         2         0-3         12         1           Autosomal Recessive Disease         Two variants in trans and at least one de novo or a predicted/proven null variant         2         0-3         1         2         1 <t< td=""><td>Evidence Type         Case Information Type         Default Regeneration         Count         Total           Autosomal Dominant or X- linked Disorder         Proband with predicted or proven null variant         1.5         0-2         10         17         25.5           Autosomal Dominant or X- linked Disorder         Proband with other variant type with some evidence of gene predicted/proven null variant         0.5         0-1.5         7         2         1           Autosomal Recessive Disease         Two variants in trans and at least one de novo or a predicted/proven null variant         2         0-3         12         -         -         -         -         -         -         1         -</td><td>Evidence Type         Case Information Type         Default Range Harmen Function         Total         Counted           Autosomal Dominant or X- inked Disorder         Variant is de novo         2         0-3         12         0         10         17         25.5         10           Autosomal Dominant or X- inked Disorder         Proband with other variant type with some evidence of gene impact         0.5         0-1.5         7         2         1         1           Autosomal Dominant or X- inked Disorder         Two variants in trans and at least one de novo or a predicted/proven null variant         2         0-3         2         1         1           Recessive Disease         Two variants (not predicted/proven null with some evidence of gene impact in trans         1         0-1.5         7         2         1         1           Segregation Evidence         Candidate gene sequencing         4.52         3         1</td></t<>	Evidence Type         Case Information Type         Default Regeneration         Count         Total           Autosomal Dominant or X- linked Disorder         Proband with predicted or proven null variant         1.5         0-2         10         17         25.5           Autosomal Dominant or X- linked Disorder         Proband with other variant type with some evidence of gene predicted/proven null variant         0.5         0-1.5         7         2         1           Autosomal Recessive Disease         Two variants in trans and at least one de novo or a predicted/proven null variant         2         0-3         12         -         -         -         -         -         -         1         -	Evidence Type         Case Information Type         Default Range Harmen Function         Total         Counted           Autosomal Dominant or X- inked Disorder         Variant is de novo         2         0-3         12         0         10         17         25.5         10           Autosomal Dominant or X- inked Disorder         Proband with other variant type with some evidence of gene impact         0.5         0-1.5         7         2         1         1           Autosomal Dominant or X- inked Disorder         Two variants in trans and at least one de novo or a predicted/proven null variant         2         0-3         2         1         1           Recessive Disease         Two variants (not predicted/proven null with some evidence of gene impact in trans         1         0-1.5         7         2         1         1           Segregation Evidence         Candidate gene sequencing         4.52         3         1

e e									
denc	Functional Alteration	Patient cells	1	0 - 2	2	1	1	1.5	Caspi O et al. 2013 Dec (PMID:24200905);
L vid	Functional Alteration	Non-patient cells	0.5	0 - 1	2	1	0.5	1.5	Hall C et al. 2009 (PMID:19533476);
iental I	Models	Non-human model organism	2	0 - 4		2	3		Grossmann KS et al. 2004 Oct 11 (PMID:15479741); Cruz FM et al. 2015 Apr 14 (PMID:25857910);
erim		Cell culture model	1	0 - 2					
EXp		Rescue in human	2	0 - 4	4			3	
	Rescue	Rescue in non-human model organism	2	0 - 4				5	
		Rescue in cell culture model	1	0 - 2					
		Rescue in patient cells	1	0 - 2					
		Total Experimen	tal Evid	6					

Assertion criteria	Genetic Evidence	e (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family se control data that s disease as	upport the gene-	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	12	2	6	18	YES
CALCULATED C	CLASSIFICATION		LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicati	on over time
Valid contradictory evidence (Y/N)*	NO				
	CALCULATED CLA	SSIFICATION (DATE)	Definitive	02,	/04/2020
	EXPER	RT CURATION (DATE)	Definitive	03,	/08/2018
	E	EVIDENCE SUMMARY	The relationship between PKP2 and arrh cardiomyopathy (autosomal dominant) Clinical Validity Framework as of Septer first reported in humans with this disea: PMID: 15489853). PKP2 is the major ca for 34%-74% of cases (McNAIIy et al., 2 over 250 PKP2 variants listed in ClinVar frameshift, complex rearrangements, et 30619891). This gene-disease relations significant amount of case-level data, s data is available in the literature, theref genetic evidence and experimental evid curation effort may not be exhaustive of disease relationship. This gene-disease models, in vitro assays, and protein inte definitively associated with autosomal of repeatedly demonstrated in both the re- settings, and has been upheld over time by the ClinGen Arrythmogenic Right Ver Curation Expert Panel on October, 26, 2	was evaluated using the f nber, 2018. Variants in PI se as early as 2004 (Geru usative gene for ARVC ar 005; PMID: 20301310). T for ARVC (missense, nor ic) (Novelli et al., 2018; F ship is well-known and th egregation data and expe ore the maximum score f ence has been reached. I f all literature related to t relationship is supporte tractions. In summary, PI dominant ARVC. This has search and clinical diagn . This classification was stricular Cardiomyopathy	ClinGen KP2 were JII et al., Id accounts There are Issense, MID: erefore a erefore a erefore a erefore a erefore a erefore both Note, this his gene- d by animal (P2 is been ostic approved

# RYR2 - arrhythmogenic right ventricular cardiomyopathy

Gene:	RYR2 (HGNC:10484)	
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Refuted <b>B</b>
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 07/19/2019
Replication over time	: NO	Contradictory Evidence: <u>YES</u>
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	
Evidence Summary:	12106942, 12169647, 12459180, 12596074, 129 15831148, 15951021, 16084945, 16096717, 162 17363426, 17980246, 18326664, 18483626, 18 21977247, 22068070, 22090716, 22374134, 22 25411383, 25445213, 26082335, 26743400, 2 29543670, Rampazzo A et al., Hum Mol Genet linkage to chromosome 1q42-q43 and variants also described as CPVT with fibro-fatty replace 1995; 4(11):2151–2154; 11078270; 11159936). A in family 105 that has two variants on one allele of fibrofatty infiltration or structural abnormalit (16873551). In several papers RYR2 missense of these variants were also relatively often presen diagnosis is not provided, segregation informat (28750076, 26743400, 25041964, 16084945, observed phenotype in the original three public	

				Gui	delines			Po	oints	
		Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
			Variant is de novo	2	0-3	12				
		Autosomal	Proband with predicted or proven null variant	1.5	0-2	10				
	Data ant Evidence		Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	8	1.25	1.25	Roux-Buisson N et al. 2014 Nov (PMID:25041964); Deshpande SR et al. 2016 Apr (PMID:26743400); Forleo C et al. 2017 July 27 (PMID:28750076); d'Amati G et al. 2005 Jul (PMID:16084945); Hata Y et al. 2016 July (PMID:27005929); Akilzhanova A et al. 2014 Jun 30 (PMID:24978818);
	se-Level Dai Variant	Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
	Case		Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
Genetic Evidence					Summ LOI		Family Count			
leti		Segregation	Candidate gene sequencir	ıg						
Ger		Evidence	Exome/genome or all genes seq in linkage region	uenced						
			Total Summed LOD Score	9						
	C	ase-Control Study Type	Case-Control Quality Criteria	Guidelines Points Points/Study Max Count Points Count						PMIDs/Notes
		Single Variant Analysis	case control guarty officina	0-	-	max	Count	i oliita		
			1. Variant Detection							

Case-Control Data	Aggregate Variant Analysis	Methodology 2. Power 3. Bias and confounding 4. Statistical Significance	0-6	12	1	0	0	Milting H et al. 2006 Aug 1 (PMID:16769042);
		Total Genet	ic Evidence Po	ints	(Maxim	um 12)	1.25	
			Guidelines	5		Po	oints	

			Gui	delines	;		Pe	oints	
	Evidence Category	Evidence Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
		<b>Biochemical Function</b>	0.5	0 - 2					
	Function	Protein Interaction	0.5	0 - 2	2	1	0	0	Tiso N et al. 2002 Dec 13 (PMID:12459180);
e		Expression	0.5	0 - 2					
den	Functional Alteration	Patient cells	1	0 - 2	2				
Ē	Functional Alteration	Non-patient cells	0.5	0 - 1	2				
ntal	Models	Non-human model organism	2	0 - 4					
me		Cell culture model	1	0 - 2					
Experimental Evidence		Rescue in human	2	0 - 4				] [	
Ĕ	Rescue	Rescue in non-human model organism	2	0 - 4	4				
		Rescue in cell culture model	1	0 - 2				] [	
		Rescue in patient cells	1	0 - 2					
		Total Experime	ntal Evid	ence Po	oints	(Maxim	າum 6)	0	

Assertion criteria	Genetic Evider	nce (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)		
Description	control data that	segregation, or case- support the gene- association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)		
Assigned Points	1.	.25	0	1.25	NO		
			LIMITED	1-6			
			MODERATE	7-11			
			STRONG	12-18			
	LASSIFICATION		DEFINITIVE	12-18 AND replicat	ion over time		
Valid contradictory evidence (Y/N)*	YES	Kannankeril F	PJ et al. 2006 Aug 8 (PMID:168	373551);			
	CALCULATED C	LASSIFICATION (DATE)	Limited	05	/13/2020		
	MODIFY CALCUL	ATED CLASSIFICATION	YES				
	MODIFIED C	LASSIFICATION (DATE)	Refuted This classification was refuted becau		/13/2020		
	RE	ASON(S) FOR CHANGE	original publications that reported RYR2 variants in ARVD should be catecholamine-induced ventricular tachycardia (CPVT) rather than ARVD. Subsequent variants found in this gene in ARVD patients were uninformative or too frequent to be disease-causing.				
	EXP	ERT CURATION (DATE)	Refuted	07	/19/2019		
			Refuted07/19/2019Fifty-seven papers were reviewed related to RYR2 and ARVD (9628868,11078270, 11159936, 11807805, 12015469, 12106942, 12169647,12459180, 12596074, 12919952, 15046075, 15176428, 15336972,15451514, 15544015, 15831148, 15951021, 16084945, 16096717,16239587, 16407108, 16733711, 16769042, 16873551, 16873551,17363426, 17980246, 18326664, 18483626, 18515204, 19029124,19167631, 19863545, 20045464, 20301310, 21977247, 22068070,22090716, 22374134, 22450909, 22453944, 23978697, 24447446,24978818, 25041964, 25411383, 25445213, 26082335, 26743400,27000522, 27005929, 27548259, 27635072, 28750076, 29497013,29543670, Rampazzo A et al., Hum Mol Genet 1995). Three publicationsfrom the same research group found linkage to chromosome 1q42-q43 andvariants in RYR2 in families with right ventricular cardiomyopathy (ARVC2)also described as CPVT with fibro-fatty replacement of the right ventricle(Rampazzo A et al., Hum Mol Genet 1995; 4(11):2151-2154; 11078270;11159936). A mouse model made from one of the variants (RyR2 R176Q/_)found in family 105 that has two variants on one allele (RT6Q/T2504M),showed a CPVT like phenotype without evidence of fibrofatty infiltration orstructural abnormalities characteristic of arrhythmogenic right ventriculardysplasia (16873551). In several papers RYR2 missense variants weredescribed in possible ARVD index patients. Some of these variants werealso relatively often present in reference alleles from the gnomAD database,clear ARVD diagnosis is not provided, segregation information is not				

informative and/or CPVT was also present in the family (28750076, 26743400, 25041964, 16084945, 27005929). In a recent review it was also recognized that the observed phenotype in the original three publications that reported RYR2 variants in ARVD for the first time should be catecholamine-induced ventricular tachycardia rather than ARVD, and this gene is no longer considered as ARVD causing (29543670). This gene is therefore refuted as a candidate for ARVD.

EVIDENCE SUMMARY

# SCN5A - arrhythmogenic right ventricular cardiomyopathy

Gene:	SCN5A (HGNC:10593)	
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Limited 🔁
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 06/06/2019
Replication over time	: NO	Contradictory Evidence: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	
Evidence Summary:	mutations has been performed in four studies (2 (2589161) reported the investigation on 6 young fibrillation. One of these patients died suddenly changes in the right ventricle, a decrease numb screening revealed a variant on SCN5A, however classification of the variant was present. The set patient presenting an enlarged right ventricle w showed sacculations in the so-called triangle of identified a loss-of-function variant on SCN5A, classification of the variant was present. The the presenting monomorphic and polymorphic non- complete RBBB, mild dilatation and hypokinesia hypertrophy and fibrosis, but no myocardial tiss intron 21 of SCN5A gene c.3840+1 G>A, which segregation data were available and patient's pl study (28069705) investigated the entire exome unrelated Caucasian patients with a clinical diag missense variant in a female patient causing the analysed a 'validation cohort' of 281 unrelated p 5 patients; among these a missense variant cau high frequency in the general population. Two p pathogenic variant on PKP2 and an additional va- deletion (Leu729del), however cascade genetic not fulfill definite ARVC criteria. Finally genetic a female but segregation study in the family don't Experimental data from this last study (2806970 generated an induced pluripotent stem cell-der technology. Whole-cell patch clamping revealed fluorescence microscopy showed reduced abur However, experimental data do not showed the alterations such as myocardial fibrotic replacem	

	Evidence Type			Gui	delines	5		P	oints		
		Evidence Type	Case Information Type	Default Range Max Count			Total	Counted	PMIDs/Notes		
			Variant is de novo	2	0-3	12					
	dence	denc	Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10	1	1	1	Te Riele AS et al. 2017 Jan (PMID:28069705);
evel Data	Variant Evi	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	6	2	2	Erkapic D et al. 2008 Jul (PMID:18375968); Te Riele AS et al. 2017 Jan (PMID:28069705);	
Case-Lev	Ň	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3						
		Recessive				12			1		

<b>Genetic Evidence</b>		Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5					
Genet					Summ LOI		Family Count			
		Segregation	Candidate gene sequencir	1.2	1		0	0	Te Riele AS et al. 2017 Jan (PMID:28069705);	
		Evidence	Exome/genome or all genes seq in linkage region				U	U		
			Total Summed LOD Score	Э	1.2					
	Data	Case-Control Study Type Case-Control Quality Criteria Po			delines Study		Count		ints Counted	PMIDs/Notes
	ontrolD	Single Variant	1. Variant Detection Methodology	İ	0-6					
	Case-Co	Aggregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-		12				
			Total Gener	tic Evide	nce Po	ints	(Maxim	um 12)	3	
	E	vidence Category	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes	
			<b>Biochemical Function</b>	0.5	0 - 2					
		Function	Protein Interaction	0.5	0 - 2	2				
e			Expression	0.5	0 - 2					
den	Fu	Inctional Alteration	Patient cells	1	0 - 2	2	2	2	2	Te Riele AS et al. 2017 Jan (PMID:28069705);
Ē			Non-patient cells	0.5	0 - 1	-			-	
nta		Models	Non-human model organism	2	0 - 4					
Experimental Evidence			Cell culture model	1	0 - 2		1	1		Te Riele AS et al. 2017 Jan (PMID:28069705);
per			Rescue in human	2	0 - 4					
ĥ		Rescue	Rescue in non-human model organism	2	0 - 4	4			1	
			Rescue in cell culture model	1	0 - 2					
			Rescue in patient cells	1	0 - 2					
			Total Experimer	ALC: NO.			A	-	3	

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)		
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)		
Assigned Points	3	3	6	NO		
		LIMITED	1-6			
		MODERATE	7-11			
		STRONG	12-18			
CALCULATED C	CLASSIFICATION	DEFINITIVE	DEFINITIVE 12-18 AND replication over			
Valid contradictory evidence (Y/N)*	NO					
	CALCULATED CLASSIFICATION (DATE)	Limited	01/	24/2020		
	EXPERT CURATION (DATE)	Limited	06/	06/06/2019		
		There is limited evidence that SCN5A is ARVC patient cohorts for SCN5A mutati studies (2589161, 24388542, 1837596 (2589161) reported the investigation on electrically resuscitated after ventricula died suddenly during a four years follow changes in the right ventricle, a decreas typical features of ARVC. Genetic screet however no further information about g classification of the variant was present	ons has been performed i 8, 28069705). The first s 1 6 young patients who we ar fibrillation. One of thes /-up and autopsy revealed se number of myocardial d ning revealed a variant or enomic localization and	in four itudy ere de patients d fibrofatty cells as n SCN5A,		

reported the case of a 50 year old female patient presenting an enlarged right ventricle with structural myocardial changes. Right ventricular angiography showed sacculations in the so-called triangle of dysplasia resembling ARVC structural changes. Genetic testing identified a loss-offunction variant on SCN5A, however no further information about genomic localization and classification of the variant was present. The third study (18375968) reported the case of 58 years old man presenting monomorphic and polymorphic non-sustained ventricular tachycardias, chest pain and dyspnea at rest, complete RBBB, mild dilatation and hypokinesia of the right ventricular and bioptic investigation revealed cardiac hypertrophy and fibrosis, but no myocardial tissue degeneration. Genetic screening identified a splice error on intron 21 of SCN5A gene c.3840+1 G>A, which results in a loss of function of the sodium channel. However, no segregation data were available and patient's phenotype does not fulfil a definite ARVC diagnosis. The most recent study (28069705) investigated the entire exome for pathogenic variants among a 'discovery cohort' of six unrelated Caucasian patients with a clinical diagnosis of ARVC. Genetic screening identified a heterozygous SCN5A missense variant in a female patient causing the aminoacid substitution Arg1898His. Subsequently, authors analysed a 'validation cohort' of 281 unrelated patients for SCN5A variants. Authors identified 5 different variants in 5 patients; among these a missense variant causing the aminoacid substitution Ser1787Asn was excluded due its high frequency in the general population. Two patients were digenic variants carriers, both presenting a different pathogenic variant on PKP2 and an additional variant on SCN5A. Another patient carried a heterozygous in frame deletion (Leu729del), however cascade genetic screening revealed that family members carrying this variants did not fulfill definite ARVC criteria. Finally genetic screening identified a missense variant Tyr416Cys in a 55 years old female but segregation study in the family don't demonstrate the link of this variant with the clinical phenotype. Experimental data from this last study (28069705) analyzed the role of SCN5A Arg1898His variant. Authors generated an induced pluripotent stem cell-derived cardiomyocytes and then corrected them by using CRISP/Cas9 technology. Whole-cell patch clamping revealed a 36% reduction in peak sodium current and super-resolution and fluorescence microscopy showed reduced abundance of both SCN5A and CDH2 clusters at the intercalated disc. However, experimental data do not showed the link of electrical abnormalities to structural changes typical of ARVC alterations such as myocardial fibrotic replacement. In summary, there is limited evidence to support gene-disease association. There is no clear evidence that the identified SCN5A variants contribute to the ARVC phenotype and there is no known disease mechanism that would link SCN5A with ARVC.

EVIDENCE SUMMARY

## TGFB3 - arrhythmogenic right ventricular cardiomyopathy

Gene:	TGFB3 (HGNC:11769)	
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Limited
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 08/16/2019
Replication over time	: NO	Contradictory Evidence: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	
Evidence Summary:	(HP:0000006) HGNC: 11769 MONDO:0016587 Eleven papers were reviewed related to TGFB a 15639468, 11127465, 12529708, 22878021, 24 started in 1994 with linkage to markers on chro linkage to this region in several other Italian fan in 2000, 2003, 2005 and reviewed in 2012 (111 96: 191-194). In six of 28 families linkage to 144 were obtained with markers closely linked to AF (affected only LOD score of 2.71) another famil contained 40 known genes; 6 of them (POMT2) unsuccessfully screened for pathogenic ARVC coding variant (Chr14(GRCh37):g.76447266C> c36G>A) was identified in TGFB. This variant an unrelated ARVD proband a TGFB variant was NM_003239.4(TGFB3):c.*495C>T, in the paper reference alleles from gnomAD. Both variants w a 2.5 times increased activity compared to wild two unrelated families with linkage to this regio promoter region and that in one of these two fa- identified (15639475). Two coding variants of u	•

				Gui	delines	;		Po	oints	
		Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
			Variant is de novo	2	0-3	12				
			Proband with predicted or proven null variant	1.5	0-2	10				
	Evidence		Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	2	0.2	0.2	Beffagna G et al. 2005 Feb 1 (PMID:15639475);
	Variant Ev		Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
	Case-L		Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
Genetic Evidence					Summed LOD		Family Count			
ene		Segregation	Candidate gene sequencir	g	4.4	1	1			Beffagna G et al. 2005 Feb 1 (PMID:15639475);
0		Evidence	Exome/genome or all genes seq in linkage region	uenced					1 "	
			Total Summed LOD Score		4.4	1				
	Ca	se-Control Study Type	Case-Control Quality Criteria		delines 'Study		Count		oints Counted	PMIDs/Notes

	Analysis	1. Variant Detection Methodology	0-0	6					
	분 옷 Aggregate Variant	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-6		12				
_		Total Genet	tic Evide	nce Poi	ints	(Maxim	um 12)	1.2	
			Gui	idelines	; ;		Pc	oints	
	Evidence Category	Evidence Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
		<b>Biochemical Function</b>	0.5	0 - 2		<u> </u>			
	Function	Protein Interaction	0.5	0 - 2	2			1	
e		Expression	0.5	0 - 2	$\left[ \right]'$			i	
Evidence	E matienal Alteration	Patient cells	1	0 - 2					
Ēvic	Functional Alteration	Non-patient cells	0.5	0 - 1	2	1	1		Beffagna G et al. 2005 Feb 1 (PMID:15639475);
Ital	Madala	Non-human model organism	2	0 - 4					
	Models			0 - 2	1 7	· · · · · · · · · · · · · · · · · · ·	1	( E	
men		Cell culture model	1	0 - 2	1 L	L	L	· _	
Experimental		Cell culture model Rescue in human		0 - 2	1	—		1	

1

Rescue in non-human model

organism

Rescue in cell culture model

Rescue in patient cells

Rescue

2

1

1 Total Experimental Evidence Points (Maximum 6)

0 - 4

0 - 2

0 - 2

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	1.2	1	2.2	NO
CALCULATED C	LASSIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicat	1
Valid contradictory evidence (Y/N)*	NO			
	CALCULATED CLASSIFICATION (DATE)	Limited	02	2/04/2020
	EXPERT CURATION (DATE)	TGFB: Arrythmogenic Right Ventricular Inheritance: Autosomal dominant inheri MONDO:0016587 Expert Panel: Arrythm Cardiomyopathy Eleven papers were rev (7951245, 15639475, 20864495, 2222: 11127465, 12529708, 22878021, 24238 2012; 96: 191-194). It all started in 199 chromosome 14q42.3 in a large Italian f linkage to this region in several other It. of candidate genes by the same group i 2012 (11127465, 12529708, 15639475, 96: 191-194). In six of 28 families linkag families, significantly positive lod score closely linked to ARVD1 locus (11127461 5.2 (affected only LOD score of 2.71) an 1.51. The critical interval for ARVD1 con (POMT2, KIAA0759, KIAA1036, C140rf4 unsuccessfully screened for pathogenic exons (12529708). In family 112 a non-c (Chr14(GRCh37):g.76447266C>T; NM_ paper indicated as c366>A) was ident observed 10 times in 249028 reference unrelated ARVD proband a TGFB variant (Chr14(GRCh37):g.764250356>A: NM_ paper indicated as c.1723C>T). This va reference alleles from gnomAD. Both va C2C12 expression assay and both show compared to wildtype (15639475). In th that in two unrelated families with linka mutations in TGFB3 coding sequences, in one of these two families, a large dela	tance (HP:000006) HC nogenic Right Ventricula viewed related to TGFB a 32248, 20124997, 15633 4504, Rampazzo A. Cardi 4 with linkage to marker amily (7951245) and fol alian families and seque n 2000, 2003, 2005 and Rampazzo A. Cardiovasi ge to 14q23-q24 was foi to swere obtained with ma 5). One family 112 had a to ther family 113 had a to the family 113 had a to the family 114 had a to the family 115 had a to the family 115 had a to the family 116 had a to the family 117 had a to the family 118 had a to the family 11	SNC: 11769 r and ARVD 9468, iovasc Res. s on lowed by nce analysis reviewed in c Res. 2012; and; in two arkers LOD score of OD score of G of them c coding G>A, in the nt is an 5C>T, in the n 30272 uciferase l activity zo describes 1 no on and that

EVIDENCE SUMMARY

gene was identified (15639475). Two coding variants of unknown significance were observed in this gene in two ARVD probands in another study (24238504). Total genetic evidence points calculated = 1.2; Total experimental evidence points calculated = 1; Total awarded points = 2.2; Final classification = Limited.

### TJP1 - arrhythmogenic right ventricular cardiomyopathy

Gene:	TJP1 (HGNC:11827)	
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Limited
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 02/08/2019
Replication over time	:NO	Contradictory Evidence: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	
Evidence Summary:	meeting 2010 TFC that was found to have a var patients found another patient with a variant in sequenced and in 2 patients with DCM and VT, these cases, two probands clearly met 2010 TF characterization in this paper showed that it int	d with ARVC. Published in 2018 (30354300), there was one family iant in TJP1: p.Y669C. Targeted sequencing of an additional 40 ACM TJP1 p.R265W. An additional 43 Dutch/German patients were TJP1 variants were found but one had a pathogenic DSP variant. Of C. One proband had histology consistent with ARVC. Functional eracts with the gap junction, but not more specific phenotype. k of proof of segregation in families leaves TJP1 with only limited

Guidelines Points Evidence Type **Case Information Type** Default Range Max Count Total Counted PMIDs/Notes Variant is de novo 2 0-3 12 Proband with predicted or Autosomal 1.5 0-2 10 proven null variant Dominant or Xlinked Disorder Proband with other variant type Variant Evidence with some evidence of gene 0.5 0-1.5 7 2 1 1 De Bortoli M et al. 2018 Oct (PMID:30354300); impact **Case-Level Data** Two variants in trans and at 0-3 least one de novo or a 2 predicted/proven null variant Autosomal Recessive Two variants (not 12 Disease **Genetic Evidence** predicted/proven null) with 0-1.5 1 some evidence of gene impact in trans Summed Family LOD Count Segregation Candidate gene sequencing 0 0 Evidence Exome/genome or all genes sequenced 0.9 2 De Bortoli M et al. 2018 Oct (PMID:30354300); in linkage region Total Summed LOD Score 0.9 Guidelines Points **Case-Control Study** Case-Control Data **Case-Control Quality Criteria** PMIDs/Notes Points/Study Max Count Points Counted Type Single Variant 1. Variant Detection 0-6 Analysis Methodology 2. Power 12 Aggregate Variant 3. Bias and confounding 0-6 Analysis 4. Statistical Significance **Total Genetic Evidence Points (Maximum 12)** 1 Guidelines Points Default Range Max Count Total Counted Evidence Type PMIDs/Notes **Evidence Category Biochemical Function** 0.5 0 - 2 Evidence Function 0 - 2 2 **Protein Interaction** 0.5 0 - 2 Expression 0.5 Patient cells 0 - 2 1 Experimental **Functional Alteration** 2 Non-patient cells 0.5 0 - 1 2 0 - 4 Non-human model organism Models Cell culture model 0 - 2 1

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Rescue in human

2

0 - 4

Rescue	Rescue in non-human model organism	2	0 - 4							
	Rescue in cell culture model	1	0 - 2							
		Rescue in patient cells	1	0 - 2	1					
	Total Experimental Evidence Points (Maximum 6) 0									

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)		
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)		
Assigned Points	1	0	1	NO		
		LIMITED	1-6			
		MODERATE	7-11			
		STRONG	12-18			
CALCULATED	CLASSIFICATION	DEFINITIVE	12-18 AND replicat	ion over time		
Valid contradictory evidence (Y/N)*	NO					
	CALCULATED CLASSIFICATION (DATE)	Limited	05	/08/2020		
		Limited		02/08/2019		
	EXPERT CURATION (DATE) EVIDENCE SUMMARY	There is limited evidence that TJP1 is as 2018 (30354300), there was one family to have a variant in TJP1: p.Y669C. Targ ACM patients found another patient with additional 43 Dutch/German patients we DCM and VT, TJP1 variants were found b variant. Of these cases, two probands c had histology consistent with ARVC. Fu paper showed that it interacts with the phenotype. Therefore, limited experime segregation in families leaves TJP1 with	sociated with ARVC. Pul meeting 2010 TFC that eted sequencing of an a h a variant in TJP1 p.R26 ere sequenced and in 2 p out one had a pathogenic learly met 2010 TFC. On nctional characterization gap junction, but not mo ntal studies, and lack of	blished in was found dditional 40 5W. An patients with c DSP e proband n in this re specific proof of		

## TMEM43 - arrhythmogenic right ventricular dysplasia 5

Gene:	TMEM43 (HGNC:28472)				
Disease:	arrhythmogenic right ventricular dysplasia 5 (MONDO_0011459)	Definitive ① Classification - 10/26/2018			
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)				
Replication over time:	YES	Contradictory Evide	nce: NO		
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	Contributors:	UNC Biocuration Core		
Evidence Summary:	missense) have been reported in humans. How majority of genetic evidence comes from case p.Ser358Leu, which has been reported in more (Merner et al., 2008, PMID 18313022; Christer Hodgkinson et al., 2013, PMID 22725725; Milt also supported by an animal model, expression associated with autosomal dominant arrhythm demonstrated in both the research and clinical	ramework as of July 1 as 2008 (Merner et a vever, the pathogenic -level data and segre e than 20 families wit nsen et al. 2011, PMID ing et al., 2014, PMID n stuies, and in vitro a ogenic right ventricu I diagnostic settings, rythmogenic Right Ve	10th, 2019. Variants in TMEM43 were first II., PMID 18313022). At least 9 variants (mostly city of most of the variants is unknown. The egation data for one founder variant, th ARVC and occurred de novo in one individual 0 21214875; Baskin et al., 2013, PMID 23812740; 0 24598986). This gene-disease relationship is assays. In summary, TMEM43 is definitively lar dysplasia . This has been repeatedly and has been upheld over time. This entricular Cardiomyopathy Gene Curation Expert		

					Gui	delines	;		Po	oints	
		E	vidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12	1	3	3	Baskin B et al. 2013 Nov (PMID:23812740);
			Autosomal	Proband with predicted or proven null variant	1.5	0-2	10				
		Evidence	Dominant or X- linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7	16	3.6	3.6	Merner ND et al. 2008 Apr (PMID:18313022); Christensen AH et al. 2011 Sep (PMID:21214875); Baskin B et al. 2013 Nov (PMID:23812740); Honda T et al. 2016 May (PMID:26840987); Milting H et al. 2015 Apr 7 (PMID:24598986); Haywood AF et al. 2013 Apr (PMID:23161701);
	Level Data	Variant	Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-Level			Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
Geneti	Genetic					Summed LOD		Family Count			
			Segregation	Candidate gene sequencir	ng	26.49		2	1.5	1.5	Merner ND et al. 2008 Apr (PMID:18313022); Milting H et al. 2015 Apr 7 (PMID:24598986);
		Evidence	Exome/genome or all genes sequen in linkage region		enced						
				Total Summed LOD Score	re 26.4		26.49				
	Data	Cas	e-Control Study Type	Case-Control Quality Criteria		delines 'Study		Count		oints Counted	PMIDs/Notes
	Control	S	Single Variant Analysis	1. Variant Detection Methodology	0-	6					
	Case-Co	Ag	gregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	0-6					
				Total Genet	ic Evide	nce Po	ints	(Maxim	um 12)	8.1	
					Gui	delines	;		Po	oints	
	E	vide	ence Category	Evidence Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				<b>Biochemical Function</b>	0.5	0 - 2					
-											

	Function	Protein Interaction	0.5	0 - 2	2			1			
ence		Expression	0.5	0 - 2		2	1		Merner ND et al. 2008 Apr (PMID:18313022); Christensen AH et al. 2011 Sep (PMID:21214875);		
vide	Functional Alteration	Patient cells	1	0 - 2	2						
alE	Functional Alteration	Non-patient cells	0.5	0 - 1	2						
Tent	Models	Non-human model organism	2	0 - 4		1	3		Zheng G et al. 2019 Feb (PMID:29980933);		
erin		Cell culture model	1	0 - 2		1	1		Siragam V et al. 2014 Oct 24 (PMID:25343256);		
Exp		Rescue in human	2	0 - 4							
	Rescue	Rescue in non-human model organism	2	0 - 4	4			4			
		Rescue in cell culture model	1	0 - 2							
		Rescue in patient cells	1	0 - 2							
		Total Experimen	ntal Evid	5							

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	8.1	5	13.1	YES
		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
CALCULATED	CLASSIFICATION	DEFINITIVE	12-18 AND replicati	ion over time
Valid contradictory evidence (Y/N)*	NO CALCULATED CLASSIFICATION (DATE)	Definitive	02,	/04/2020
	EXPERT CURATION (DATE)	Definitive	10,	/26/2018
	EVIDENCE SUMMARY	The relationship between TMEM43 and dysplasia (autosomal dominant) was ev Validity Framework as of July 10th, 201' reported in humans with this disease as 18313022). At least 9 variants (mostly of humans. However, the pathogenicity of The majority of genetic evidence comess segregation data for one founder varian reported in more than 20 families with <i>A</i> individual (Merner et al., 2008, PMID 18 PMID 21214875; Baskin et al., 2013, PM 2013, PMID 22725725; Milting et al., 20 disease relationship is also supported b stuies, and in vitro assays. In summary, with autosomal dominant arrhythmogen has been repeatedly demonstrated in b diagnostic settings, and has been uphel approved by the ClinGen Arrythmogenic Gene Curation Expert Panel on October	aluated using the ClinGer 9. Variants in TMEM43 w a early as 2008 (Merner e missense) have been repu- most of the variants is un from case-level data anu it, p.Ser358Leu, which ha ARVC and occurred de no U313022; Christensen et ID 23812740; Hodgkinso 14, PMID 24598986). Hoy an animal model, expre TMEM43 is definitively a hic right ventricular dysp oth the research and clini d over time. This classifi 2 Right Ventricular Cardic	n Clinical ere first et al., PMID orted in nknown. d as been vo in one al. 2011, n et al., is gene- ession issociated lasia . This ical cation was omyopathy

## TNNC1 - arrhythmogenic right ventricular cardiomyopathy

Gene:	TNNC1 (HGNC:11943)					
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	No Known Disease Relationship 🖯				
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 09/13/2019				
Replication over time	: NO	Contradictory Evidence: NO				
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP					
Evidence Summary: There is no evidence that TNN1C is involved in ARVC. This gene has been investigated for pathogenic variants in a cohort of 137 ARVC patients meeting 2010 Task Force criteria for ARVC (29709087). No variants in TNN1C were reported.						

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					Gui	delines			Po	oints	
	_	E	vidence Type	Case Information Type		-		Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12				
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10				
		vidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7				
	Case-Level Data	Variant Evidence	Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-L			Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
enetic						Summ LOI		Family Count			
õ			Segregation	Candidate gene sequencin	ıg						
			Evidence	Exome/genome or all genes seq in linkage region	uenced						
				Total Summed LOD Score	9						
	~ (	Case-Control Study Gu							Po	oints	
	Dai	Type Case-Control Quality Criteria						Count		Counted	PMIDs/Notes
	ontrol	5	Single Variant Analysis	1. Variant Detection Methodology	0-	0-6					
	Case-Control	Ag	gregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-						
				ic Evide	c Evidence Points (Maximum 12) 0						
					Gui	delines			Po	oints	
	E١	vide	ence Category	Evidence Type				Count		Counted	PMIDs/Notes
				<b>Biochemical Function</b>	0.5	0 - 2					
			Function	Protein Interaction	0.5	0 - 2	2				
e				Expression	0.5	0 - 2					
den	Fue	ncti	ional Alteration	Patient cells	1	0 - 2	2				
Ĕ		net		Non-patient cells	0.5	0 - 1	2				
ntal			Models	Non-human model organism	2	0 - 4					
Experimental Evidence		_		Cell culture model	1	0 - 2					
per				Rescue in human	2	0 - 4					
Ã			Rescue	Rescue in non-human model organism	2	0 - 4	4				
				Rescue in cell culture model	1	0 - 2					
				Rescue in patient cells	1	0 - 2					
				Total Experimen	tal Evid	ence Po	oints	(Maxim	num 6)	0	

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)		
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)		
Assigned Points	0	0	0	NO		
		LIMITED	1-6			
		MODERATE	7-11			
		STRONG	12-18	•		
				12-16 18 AND replication over time		
CALCOLATED	LASSIFICATION	DEFINITIVE	12-16 AND replica	lion over time		
Valid contradictory evidence (Y/N)*	NO					
	CALCULATED CLASSIFICATION (DATE)	No Known Disease Relationship	05	5/08/2020		
	EXPERT CURATION (DATE)	No Known Disease Relation	ship <sup>0:</sup>	9/13/2019		
	EVIDENCE SUMMARY	There is no evidence that TNN1C is invol investigated for pathogenic variants in a meeting 2010 Task Force criteria for AR\ TNN1C were reported.	ved in ARVC. This gene cohort of 137 ARVC pa	tients		

## TNNI3 - arrhythmogenic right ventricular cardiomyopathy

Gene:	TNNI3 (HGNC:11947)							
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	No Known Disease Relationship 🔂						
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 07/16/2019						
Replication over time	NO	Contradictory Evidence: NO						
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP							
Evidence Summary:	Evidence Summary: There is only one case reported of a TNNI3 variant in an ARVC patient (30385303) in a Chinese patient. This proband presented in VT of LBBB superior axis morphology and has TWI in leads V1-V4, meeting ARVC TFC criteria. This variant, however is present in higher than expected prevalence in the East Asian population. Otherwise, in other studies (29709087) of 137 patients sequenced for TNNI3, no pathogenic variants were found. Therefore, there is currently no evidence to suggest a role of TNNI3 in pathogenesis of ARVC. Gene Clinical Validity Standard Operating Procedures (SOP) - Version 7							

					Gui	delines	;		Po	ints	
		E	Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
				Variant is de novo	2	0-3	12				
			Autosomal	Proband with predicted or proven null variant	1.5	0-2	10				
		ridence	Dominant or X- linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7				
	Case-Level Data	Variant Evidence	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-L		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
enetic						Sumn LOI		Family Count			
ŏ			Segregation Evidence	Candidate gene sequencin	g						
				Exome/genome or all genes sequin linkage region	uenced						
				Total Summed LOD Score	9						
	Data	Case-Control Study Type Case-Control Quality Criteria				delines 'Studv		Count		ints Counted	PMIDs/Notes
	5	Single Variant 1. Variant Detection				-					
	ont	Analysis		Methodology	0-6						
	Case-Control	Aggregate Variant Analysis     2. Power       3. Bias and confounding     0-6       4. Statistical Significance		6							
				Total Genet	ic Evide	nce Po	ints	(Maxim	um 12)	0	
					Cui	delines			De	ints	
	E	vide	ence Category	Evidence Type				Count		Counted	PMIDs/Notes
				<b>Biochemical Function</b>	0.5	0 - 2					
			Function	Protein Interaction	0.5	0 - 2	2				
e				Expression	0.5	0 - 2					
Evidence	Em	nct	tional Alteration	Patient cells	1	0 - 2	2				
Ē	T U	iict		Non-patient cells	0.5	0 - 1	2				
ntal			Models	Non-human model organism	2	0 - 4					
Experimental				Cell culture model	1	0 - 2					
per				Rescue in human	2	0 - 4					
ŵ			Rescue	Rescue in non-human model organism	2	0 - 4	4				
				Rescue in cell culture model	1	0 - 2					

Rescue in patient cel	1	1 0	- 2							I
Total Experimental Evidence Points (Maximum 6)							(	D		

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)			
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)			
Assigned Points	0	0	0	NO			
CALCULATED	CLASSIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicat				
Valid contradictory evidence (Y/N)*	NO						
	CALCULATED CLASSIFICATION (DATE)	No Known Disease Relationship	05	/08/2020			
	EXPERT CURATION (DATE)	<b>No Known Disease Relationship</b> 07/16/2019 There is only one case reported of a TNNI3 variant in an ARVC patient (30385303) in a Chinese patient. This proband presented in VT of LBBB superior axis morphology and has TWI in leads V1-V4, meeting ARVC TFC criteria. This variant, however is present in higher than expected prevalence in the East Asian population. Otherwise, in other studies (29709087) of 137 patients sequenced for TNNI3, no pathogenic variants were found. Therefore, there is currently no evidence to suggest a role of TNNI3 in					
	EVIDENCE SUMMARY	Therefore, there is currently no evidence to suggest a role of TNNI3 in pathogenesis of ARVC.					

## TNNT2 - arrhythmogenic right ventricular cardiomyopathy

Gene:	TNNT2 (HGNC:11949)						
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	No Known Disease Relationship 🕄					
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 07/16/2019					
Replication over time	: NO	Contradictory Evidence: NO					
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP						
Evidence Summary:	ence Summary: There is no evidence that TNNT2 is involved in ARVC. This gene has been investigated for pathogenic variants in two populations of gene-elusive ARVC patients: a study of 84 Chinese gene-elusive ARVC patients and a cohort of 137 North American ARVC patients (29709087). No variants in TNNT2 were reported. Gene Clinical Validity Standard Operating Procedures (SOP) - Version 7						

					Gui	delines			Po	ints	
		E	Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
		Autosomal		Variant is de novo	2	0-3	12				
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10				
		vidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7				
	Case-Level Data	Variant Evidence	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-L		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
enetic						Summ LOI		Family Count			
G			Segregation	Candidate gene sequencin	g						
		Evidence		Exome/genome or all genes sequenced in linkage region							
				Total Summed LOD Score							
	Data	Case-Control Study Type Case-Control Quality C		Case-Control Quality Criteria		delines Study		Count		ints Counted	PMIDs/Notes
	ontrol	Single Variant Analysis		1. Variant Detection Methodology	0-	6					
	Case-Control	Aggregate Variant Analysis2. Power3. Bias and confounding 4. Statistical Significance		0-	0-6						
		Total Geneti				c Evidence Points (Maximum 12) 0					
	Guidelines								um 12)	0	
	E	vid	Evidence Category Evidence Type De					(Maximi			
			ence Category	Evidence Type		delines			Po	0 ints Counted	PMIDs/Notes
			ence Category	Evidence Type Biochemical Function		delines			Po	ints	PMIDs/Notes
			ence Category Function		Default	delines Range			Po	ints	PMIDs/Notes
e				Biochemical Function	Default 0.5	delines Range 0 - 2	Max		Po	ints	PMIDs/Notes
dence	<b>E</b> 1		Function	Biochemical Function Protein Interaction	Default 0.5 0.5	delines Range 0 - 2 0 - 2	Max 2		Po	ints	PMIDs/Notes
Evidence	Fu			Biochemical Function Protein Interaction Expression	Default 0.5 0.5 0.5	delines Range 0 - 2 0 - 2 0 - 2	Max		Po	ints	PMIDs/Notes
ntal Evidence	Fu		Function	Biochemical Function Protein Interaction Expression Patient cells	Default 0.5 0.5 0.5 1	delines Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 2	Max 2		Po	ints	PMIDs/Notes
imental Evidence	Fu		Function	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells	Default 0.5 0.5 0.5 1 0.5	delines Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1	Max 2		Po	ints	PMIDs/Notes
perimental Evidence	Fu		Function	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism	Default 0.5 0.5 0.5 1 0.5 2	delines Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1 0 - 4	Max 2		Po	ints	PMIDs/Notes
Experimental Evidence	Fu		Function	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism Cell culture model	Default 0.5 0.5 1 0.5 2 1	delines         Range         0 - 2         0 - 2         0 - 2         0 - 2         0 - 2         0 - 2         0 - 2         0 - 2         0 - 2         0 - 2         0 - 2         0 - 2	Max 2		Po	ints	PMIDs/Notes
Experimental Evidence	Fu		Function ional Alteration Models	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism Cell culture model Rescue in human Rescue in non-human model	Default 0.5 0.5 1 0.5 2 1 2 2	delines Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1 0 - 4 0 - 2 0 - 4	Max 2 2		Po	ints	PMIDs/Notes
Experimental Evidence	Fu		Function ional Alteration Models	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism Cell culture model Rescue in human Rescue in non-human model organism	Default           0.5           0.5           0.5           1           0.5           2           1           2           2           2           2           2           2           2	delines Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1 0 - 4 0 - 2 0 - 4 0 - 4	Max 2 2		Po	ints	PMIDs/Notes

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)			
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)			
Assigned Points	0	0	0	NO			
		LIMITED	1-6				
		MODERATE	7-11				
		STRONG	12-18	}			
CALCULATED	CLASSIFICATION	DEFINITIVE	12-18 AND replica	2-18 AND replication over time			
Valid contradictory evidence (Y/N)*	NO						
	CALCULATED CLASSIFICATION (DATE)	No Known Disease Relationship	0	05/08/2020			
	EXPERT CURATION (DATE)	No Known Disease Relationship 07/16/2019					
	EVIDENCE SUMMARY	There is no evidence that TNNT2 is involved in ARVC. This gene has been investigated for pathogenic variants in two populations of gene-elusive ARVC patients: a study of 84 Chinese gene-elusive ARVC patients and a cohort of 137 North American ARVC patients (29709087). No variants in TNNT2 were reported.					

## TPM1 - arrhythmogenic right ventricular cardiomyopathy

Gene:	TPM1 (HGNC:12010)						
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	No Known Disease Relationship 🖯					
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 09/13/2019					
Replication over time	e: NO	Contradictory Evidence: NO					
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP						
Evidence Summary: There is no evidence that TMP1 is involved in ARVC. This gene has been investigated for pathogenic variants in a cohort of 137 ARVC patients meeting 2010 Task Force criteria for ARVC (29709087). No variants in TMP1 were reported.							

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					Gui	delines			Po	ints			
		F	Evidence Type	Case Information Type		-		Count	Total	Counted	PMIDs/Notes		
		Autosomal		Variant is de novo	2	0-3	12						
			Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10						
		Evidence	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7						
	Case-Level Data	Variant Ev	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3							
Genetic Evidence	Case-L		Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12						
enetic						Summ LOI		Family Count					
Ö			Segregation	Candidate gene sequencin	g								
		Evidence		Exome/genome or all genes sequin linkage region	uenced								
				Total Summed LOD Score	;								
	а (	Case-Control Study			Gui	delines			Po	ints			
	Dai	Type Single Variant Analysis		<b>Case-Control Quality Criteria</b>	Points/	Study	Мах	Count	Points	Counted	PMIDs/Notes		
	ontro			1. Variant Detection Methodology	0-	6							
	Case-Control	Ag	gregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12						
-	_			4. Statistical Significance Total Genet	ic Evide	nce Poi	nts	(Maxim	um 12)	0			
					IC EVICE	10010	(Maxim	am 12)	•				
		Guidelines Points											
-	Εv	vide	ence Category	Evidence Category Evidence Type [									
					Default	Range		Count		ints Counted	PMIDs/Notes		
			Function	<b>Biochemical Function</b>	Default 0.5	Range 0 - 2	Max	Count			PMIDs/Notes		
e			Function	Biochemical Function Protein Interaction	Default 0.5 0.5	<b>Range</b> 0 - 2 0 - 2		Count			PMIDs/Notes		
ance			Function	Biochemical Function Protein Interaction Expression	Default 0.5 0.5 0.5	Range 0 - 2 0 - 2 0 - 2	Max	Count			PMIDs/Notes		
vidence	Fur		Function	Biochemical Function Protein Interaction Expression Patient cells	Default 0.5 0.5 0.5 1	Range 0 - 2 0 - 2 0 - 2 0 - 2	Max	Count			PMIDs/Notes		
al Evidence	Fur			Biochemical Function Protein Interaction Expression Patient cells Non-patient cells	Default 0.5 0.5 0.5 1 0.5	Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1	Max 2	Count			PMIDs/Notes		
nental Evidence	Fur			Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism	Default 0.5 0.5 1 0.5 2	Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1 0 - 1	Max 2	Count			PMIDs/Notes		
erimental Evidence	Fur		ional Alteration	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism Cell culture model	Default 0.5 0.5 1 0.5 2 1	Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1 0 - 1 0 - 2	Max 2	Count			PMIDs/Notes		
Experimental Evidence	Fur		ional Alteration Models	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism Cell culture model Rescue in human Rescue in non-human model	Default 0.5 0.5 1 0.5 2	Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1 0 - 1	Max 2	Count			PMIDs/Notes		
Experimental Evidence	Fur		ional Alteration	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism Cell culture model Rescue in human Rescue in non-human model organism	Default           0.5           0.5           0.5           1           0.5           2           1           2           2	Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 2 0 - 4 0 - 4 0 - 4	<b>Мах</b> 2 2	Count			PMIDs/Notes		
Experimental Evidence	Fur		ional Alteration Models	Biochemical Function Protein Interaction Expression Patient cells Non-patient cells Non-human model organism Cell culture model Rescue in human Rescue in non-human model	Default 0.5 0.5 1 0.5 2 1 2 2	Range 0 - 2 0 - 2 0 - 2 0 - 2 0 - 1 0 - 1 0 - 4 0 - 2 0 - 4	<b>Мах</b> 2 2	Count			PMIDs/Notes		

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)		
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)		
Assigned Points	0	0	0	NO		
		LIMITED	1-6			
		MODERATE	7-11			
		STRONG		12-18 AND replication over time		
		DEFINITIVE				
		DEFINITIVE	12-16 AND Teplica	tion over time		
Valid contradictory evidence (Y/N)*	NO					
	CALCULATED CLASSIFICATION (DATE)	No Known Disease Relationship	05	5/08/2020		
	EXPERT CURATION (DATE)	No Known Disease Relation		9/13/2019		
	EVIDENCE SUMMARY	There is no evidence that TMP1 is involve investigated for pathogenic variants in a meeting 2010 Task Force criteria for ARV were reported.	ed in ARVC. This gene h cohort of 137 ARVC pa	tients		

## TTN - arrhythmogenic right ventricular cardiomyopathy

Gene:	TTN (HGNC:12403)	
Disease:	arrhythmogenic right ventricular cardiomyopathy (MONDO_0016587)	Limited
Mode of Inheritance:	Autosomal dominant inheritance (HP:0000006)	Classification - 08/06/2019
Replication over time	:NO	Contradictory Evidence: NO
Expert Panel:	Arrhythmogenic Right Ventricular Cardiomyopathy EP	
Evidence Summary:	(HP:0000006) HGNC:12403 MONDO:0016587 papers were reviewed related to TTN and ARVE 24082139, 25445213, 29221435, 21810661). In variants in TTN. After evaluation of the family m low penetrance or negligible pathogenicity on to variant in an ARVD patient that was also found group potentially relevant information was found previously analyzed ARVD linked genes (DSC2, nonsynonymous variants were identified in seven heterozygote having two TTN variants. This is m in gnomAD missense variants are very common 18 and 1134 times) making them less likely as a The variant NM_133378.4 (TTN): c.8687C>T; p. (probably) affected with the genotype of whom in an Ig10 domain, was further tested in an in vi 23297410). Both found that the variant introduce protein was tested and the TTN protein contain	yopathy Mode of Inheritance: Autosomal dominant inheritance Expert Panel: Arrythmogenic Right Ventricular Cardiomyopathy Nine 0 (23297410, 23299917, 25157032, 29750433, 24055113, in a paper the authors found in 11 of 35 ARVD patients missense members they conclude that TTN missense variants had either a very he disease (29750433). Gonzalez-Garay et al found a missense 19 times in gnomAD (25157032). Only in two papers from the same d. 38 ARVD families were analyzed for the TTN gene because DSG2, DSP, and PKP2) were negative. Eight unique TTN en unrelated ARVC probands with one proband that was a compound not strange to find because the gene is huge and in reference alleles b. Five of these variants occur relatively often in gnomAD (between disease causing variant. One of these variants could be of interest. T2896I showed co-segregation (published lod score of 2.41) in 9 a six of them had ARVD (21810661, 25157032). The variant, present tro functional assay by two independent groups (21810661, ced an aberrant function. Unfortunately only a very small part of the s many of these domains therefore masking it difficult to judge if the nt. Total awarded points = 1.00; Final classification = limited. edures (SOP) - Version 7

				Gui	delines	;		Po	oints	
		Evidence Type	Case Information Type	Default	Range	Мах	Count	Total	Counted	PMIDs/Notes
			Variant is de novo	2	0-3	12				
		Autosomal Dominant or X-	Proband with predicted or proven null variant	1.5	0-2	10				
	oo no pi	linked Disorder	Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7				
	evel Data	Autosomal	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3					
Genetic Evidence	Case-Level	Recessive Disease	Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5	12				
netic E					Summed LOD		Family Count			
Ge		Segregation	Candidate gene sequencin	g 2.4		1 1				Taylor M et al. 2011 Aug 23 (PMID:21810661);
		Evidence	Exome/genome or all genes seq in linkage region	uenced				0.5	0.5	
			Total Summed LOD Score		2.4	1				
	Data	ase-Control Study Type	Case-Control Quality Criteria	• •••	delines 'Study		Count		oints Counted	PMIDs/Notes
	ntrol	Single Variant Analysis	1. Variant Detection Methodology	0-	6					
	Case-Control	Aggregate Variant Analysis	<ol> <li>Power</li> <li>Bias and confounding</li> <li>Statistical Significance</li> </ol>	0-	6	12				

Total Genetic Evidence Points (Maximum 12) 0.5										
			Guidelines Points							
		211401100 1.340		nange	max			Counted	PMIDs/Notes	
		<b>Biochemical Function</b>	0.5	0 - 2						
	Function	Protein Interaction	0.5	0 - 2	2					
		Expression	0.5	0 - 2						
ence		Patient cells	1	0 - 2	2					
Experimental Evidence	Functional Alteration	Non-patient cells	0.5	0 - 1		2	0.5	0.5	Taylor M et al. 2011 Aug 23 (PMID:21810661); Anderson BR et al. 2013 Feb 22 (PMID:23297410);	
ente	Models	Non-human model organism	2	0 - 4						
ŗ	Models	Cell culture model	1	0 - 2						
xpe		Rescue in human	2	0 - 4						
	Rescue	Rescue in non-human model organism	2	0 - 4	4					
		Rescue in cell culture model	1	0 - 2						
		Rescue in patient cells	1	0 - 2						
		Total Experimen	tal Evid	ence Po	oints	(Maxir	num 6)	0.5		

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)			
Description	Case-level, family segregation, or case- control data that support the gene- disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)			
Assigned Points	0.5	0.5	1	NO			
CALCULATED	CLASSIFICATION	LIMITED MODERATE STRONG DEFINITIVE	1-6 7-11 12-18 12-18 AND replicati	7-11			
Valid contradictory evidence (Y/N)*	NO						
	CALCULATED CLASSIFICATION (DATE)	Limited	02/04/2020				
	EXPERT CURATION (DATE)	Limited 08/06/2019 TTN: Arrythmogenic Right Ventricular Cardiomyopathy Mode of Inheritance: Autosomal dominant inheritance (HP:0000006) HGNC:12403 MOND0:0016587 Expert Panel: Arrythmogenic Right Ventricular Cardiomyopathy Nine papers were reviewed related to TTN and ARVD (23297410, 23299917, 25157032, 29750433, 24055113, 24082139, 25445213, 29221435, 21810661). In a paper the authors found in 11 of 35 ARVD patients missense variants in TTN. After evaluation of the family members they conclude that TTN missense variants had either a very low penetrance or negligible pathogenicity on the disease (29750433). Gonzalez-Garay et al found a missense variant in an ARVD patient that was also found 19 times in gnomAD (25157032). Only in two papers from the same group potentially relevant information was found. 38 ARVD families were analyzed for the TTN gene because previously analyzed ARVD linked genes (DSC2, DSC2, DSP, and PKP2) were negative. Eight unique TTN nonsynonymous variants were identified in seven unrelated ARVC probands with one proband that was a compound heterozygote having two TTN variants. This is not strange to find because the gene is huge and in reference alleles in gnomAD missense variants are very common. Five of these variants occur relatively often in gnomAD (between 18 and 1134 times) making them less likely as a disease causing variant. One of these variants could be of interest. The variant NM_133378.4 (TTN): c.8687C>T; p.T2896I showed co-segregation (published lod score of 2.41) in 9 (probably) affected with the genotype of whom six of them had ARVD (21810661, 25157032). The variant, present in an 1g10 domain, was further tested in an in vitro functional assay by two independent groups (21810661, 23297410). Both found that the variant introduced an aberrant function. Unfortunately only a very small part of the protein was tested and the TTN protein contains many of these domains therefore masking it difficult to					