Desmosomal Genes

Subjects: Cardiac & Cardiovascular Systems | Dermatology

Contributor: Mathilde C. S. C. Vermeer , Daniela Andrei , Luisa Marsili , J. Peter van Tintelen , Herman H. W. Silljé , Maarten P. van den Berg , Peter van der Meer , Maria C. Bolling

Desmosomes are mirroring, transmembrane protein chains that connect the intermediate filament networks of neighbouring cells. Each chain continuously (dis)assembles due to the turnover of five desmosomal protein types: desmoplakin, plakoglobin, plakophilins, desmocollins and desmogleins. The expression of two genes is critical to the formation of all desmosomes: namely *DSP*, encoding two differently spliced desmoplakin proteins (DPI and DPII) and *JUP*, encoding plakoglobin (PG). Meanwhile, plakophilins, desmocollins and desmogleins are expressed in a tissue-specific manner and are therefore encoded by multiple genes.

cardiocutaneous syndromes genotype–phenotype correlation

functional analysis of genetic variants

1. Introduction

The plakophilin and desmocollin gene family each contain three subtypes (PKP1, PKP2 and PKP3, encoding proteins PP1, PP2 and PP3 and DSC1, DSC2 and DSC3, encoding proteins DC1, DC2 and DC3), while the desmoglein gene family contains four subtypes (DSG1, DSG2, DSG3 and DSG4, encoding proteins DG1, DG2, DG3 and DG4). Keratinocytes of the skin and adnexes express both DP isoforms and PG, in addition to any of the aforementioned PP1-3, DC1-3 and DG1-4 combinations. Each specific composition is in accordance with the differentiation status of keratinocytes in the epidermis [1]. Desmosomal proteins are crucial for epidermal integrity and proper epidermal proliferation and differentiation, and irregularities thereof may cause a skin phenotype $\frac{2}{2}$. Desmosomal proteins also accommodate hair growth and irregularities thereof. The hair follicle contains keratinocytes in an inner and an outer root sheath. In straight hairs, shafts are straight and homogenous, without clear delimitations, but in coiled hair, these shafts have retro-curvatures ^{[3][4][5]}. This curve is achieved via a rotation mechanism of aberrantly proliferating and differentiating cells in the inner root sheath [2][6]. Unlike the skin, the protein composition of desmosomes in cardiac tissue is fixed and consists of DPI, PG, PP2, DC2 and DG2. In the heart, desmosomal anomalies typically disrupt the mechanical continuity of cardiac muscle fibres, which is essential for proper conductance and cardiac muscle contraction. Desmosomes are crucial for the anchorage of cardiomyocytes at the intercalated disc parallel to the direction of strain, where they internally dock the desmin network \square . Thus far, variants in desmosomal genes DSP, JUP and DSC2 have been associated with a cardiocutaneous phenotype.

2. Reported DSP Variants

DSP encodes for two differently spliced DP proteins: DPI (332 kDa) and a smaller DPII isoform (260 kDa) that contains a shorter rod domain ^[8]. The latter is created by an alternative donor splice site in exon 23. The N-terminal plakin-domain binds with PPs and PG, while domains B and C at the C-terminal side bind to intermediate filaments (**Figure 1**; full report in **Table 1**). In cardiac muscle, *DSP* is predominantly spliced into DPI, while the skin contains both isoforms equally. The ClinVar database reported 3290 variants in *DSP*. Of these, 495 were claimed (likely) pathogenic; 1026 (likely) benign; 161 show conflicting interpretations and 1608 have an unknown significance. Only 48 variants were substantiated by functional evidence, including data from transgenic mouse models (see **Figure 1**). This indicates that over 98% of all *DSP* variants were merely predicted by in silico algorithms. For the majority of variants (36/48), the predictions on protein level were correct, while only partially correct in 2/48 variants and incorrect in 5/48 variants. In 5/48 variants, the functional evidence was too elusive to draw conclusions. Moreover, the in silico prediction algorithms frequently contradicted one another, providing little help in assessing the pathogenicity of *DSP* variants.



Figure 1. Location of functionally investigated DSP variants.

Table 1. F	-unctionally	analysed	DSP	variants.
------------	--------------	----------	-----	-----------

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMGI Class F	n Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
c.88G > A	p.(Val30Met)	N- terminus	В	>Protein expressed -PolyPhen-2> Benign	Altered DP function; Mutant DP protein	Binding to PG abolished (Co- IP); DP localization in	Match	(het) PPK; (het) WH ²	(het) ACM

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
				(0.000) -SIFT> NOT tolerated -MutPred2> Benign (0.092)	expressed, normal size and amount (WB) [2[10]]11].	cytoplasm (transfection) ^[2] ; DP normal in myocardial and epidermal tissue. Exhibit weaker binding to iASPP (transfection) [11] Mouse DSP ^{WTT/8BG > A} [9].			
c.269A > G	p.(Gln90Arg)	N- terminus	В	>Protein expressed -PolyPhen-2> Probably damaging (0.967) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.757)	Altered DP function; Mutant DP protein expressed, normal size and amount (WB) ^{[2][11]} .	Binding to PG abolished (Co- IP); DP localization to cytoplasm (transfection) ^[9] . Mouse DSP ^{WT/269A > G}	Match	n.s.	(het) ACM
c.273 + 5G > A	Multiple splice products	Intron splice site (N- terminus)	US	-Human Splicing Finder> Broken WT donor site - MaxEntScan> Alteration of WT donor site, probably affecting splicing > Altered splicing, out of frame> PTC > NMD	Partial loss of DP: 20% less DP product on WB. No alternatively spliced transcripts discovered in patient-derived cells (12113), but did so in in vitro splicing assay (transfection). However, not functional 123.	 -In combination with c.6687del> Reduced DP protein on blot and staining in explanted heart and hiPSC-CMs and primary KCs Lal(24) -Dislocation of DP after 2D mechanical stretch; resulted in reduced count and density of desmosomes (EM) in dynamic EHTs leading to lower force and eteroce Id4 	Partial match, normal splicing left.	(comp.het) PPK; WH with <i>DSP:</i> c.6687delA	(comp.het) ACM/ NCCM :with <i>DSP:</i> c.6687delA

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
c.699G > A	p.(Trp233*)	Plakin- domain	Ρ	>PTC > NMD, no protein -MutPred- LOF> Borderline pathogenic (0.55385)	Partial loss of DP; Mutant RNA not detected in patient cells. Mutant DP is unstable (transfection- WB) ^[9] .	Perinuclear aggregates of DP (transfection IF) ^[9] .	Partial match, but not with transfection IF/WB	n.s.	(het) ACM
c.832del	p.(Ala278Pro fs*39)	Plakin- domain	Ρ	>PTC > NMD, no protein	Altered DP function; Truncated DP normally expressed and protein runs at 60 kDa (315 aa) (transfection- WB) -Leads to truncated DSP mRNA, also indicating that mRNA translation following the truncation was completely impaired.	c.832del overexpression led to upregulation of PG and downregulation of β-catenin in the nuclei, without affecting their expression in the cytoplasm (transfection)	Mismatch	п.ร.	(het) ACM
c.861T > G	p.(Asn287Lys)	Plakin- domain	LP	>Protein expressed -PolyPhen-2> Probably damaging (0.997) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.699)	Altered DP function; Mutant DP expressed [16].	Aberrant DP and Cx43 localization (transfection-IF) [16]	Match	(hom)PPK; (hom)WH; (hom)EBS	n.o.
c.897C > G	p.(Ser299Arg)	Plakin- domain	LP	>Protein expressed -PolyPhen-2> Probably	Altered DP function; Mutant DP expressed [11].	Exhibit weaker binding to iASPP = desmosome regulator	Match	n.s.	(het) ACM

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
				damaging (0.999) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.672)		(transfection)			
c.939 + 1G > A	p.(Gln331*)	Donor site intron 7 (Plakin- domain)	Ρ	>PTC > NMD, no protein	Partial loss of DP; Absence of detection of mRNA in multiple patient KCs, reported by two studies, suggests efficient NMD [121][18], Only 20% DPI and 50% DPI is left on WB [19].	-Major abnormalities in the spinous layer of the epidermis. The intercellular space is widened and KCs contain abnormal cytoplasmic densities [18]. -Small desmosomes and fewer in number; perinuclear keratin distribution ⁷ . - DC3 seems reduced on WB; volume densities of desmosomal proteins seem different from control [19].	Match	(het) PPK	n.r.
c.969_974del	p. (Lys324_Glu325del)	Plakin- domain	LP	>Protein expressed -MutPred- Indel> Benign (0.19566)	Partial loss of DP; Reduced expression of both native DP isoforms in cytoskeletal and cytoplasmic protein fractions (WB) [10], suggesting instable	DP expression was significantly reduced in myocardial tissue and epidermal biopsies (IF) ^[10] .	Mismatch	(hom)PPK; (hom)WH	(hom) ACM, bi- ventricular

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
					protein> incomplete degradation.				
c.1348C > G	p.(Arg451Gly)	Plakin- domain	US	>Protein expressed -PolyPhen-2> Probably damaging (1.000) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.756)	Partial loss of DP; 50% reduced DPI&II protein in EHTs (WB) [20]. -mRNA levels of DSP not reduced compared to WT [20]. > instable protein degradation.	50% reduced DP signal and 70% reduced Cx43 in myocardial tissues (IF); Proteolytic degradation by calpain, leading to DP insufficiency [20].	Mismatch	n.r.	(het) ACM, bi- ventricular
c.1372A > T	p.(Asn458Tyr)	Plakin- domain	US	>Protein expressed -PolyPhen-2> Possibly damaging (0.939) -SIFT> Tolerated -MutPred2> Benign (0.323)	Altered DP function; Mutant DP expressed [16].	Altered EB1 binding and Cx43 localization (transfection IF) 159	Match	n.o.	(het) ACM
c.1408A > G	p.(Lys470Glu)	Plakin- domain	US	>Protein expressed -PolyPhen-2> Benign (0.082) -SIFT> Tolerated -MutPred2> Benign (0.408)	Altered DP function; Conformational alternation, but overall folded structure of DP is remained [21]. Mutant DP expressed (WB) [16].	Mutant is incorporated into the desmosome [10]	Match	n.s./n.o.	(hom) ACM
c.1598T > C	p.(Ile533Thr)	Plakin- domain	US	>Protein expressed -PolyPhen-2> Probably damaging (0.998)	Altered DP function; Mutant DP expressed (WB) ^[16] .	Altered EB1 binding and Cx43 localization (transfection IF)	Match	n.o.	(het) ACM

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
				-SIFT> NOT tolerated -MutPred2> Benign (0.442)					
c.1696G > A	p.(Ala566Thr)	Plakin- domain	US	>Protein expressed -PolyPhen-2> Benign (0.007) -SIFT> Tolerated -MutPred2> Benign (0.153)	Altered DP function; Mutant DP expressed (WB) [16]	Mutant is incorporated into the desmosome [10].	Match	n.o.	(het) ACM
c.1853A > C	p.(His618Pro)	Plakin- domain	LP	>Protein expressed -PolyPhen-2> Possibly damaging (0.602) -SIFT> NOT tolerated -MutPred2> Benign (0.540)	Altered DP function; Mutant DP expressed (WB) ^[22] .	Mutant localizes to membrane, affected Cx43 localization (transfection studies/skin biopsies). Desmosome aggregation ^[22] .	Match	(het) PPK; (het) WH; (het) EBS	(het) CM
c.1865T > C	p.(Leu622Pro)	Plakin- domain	LP	>Protein expressed -PolyPhen-2> Probably damaging (0.998) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.828)	Altered DP function; Mutant DP expressed (WB) ^[22] .	Mutant localizes to membrane, affected Cx43 localization (transfection studies/skin biopsies). Desmosome aggregation ^[22] .	Match	(het) PPK; (het) WH; (het) EBS	(het) CM
c.1755dup	p.(His586Thr fs*9)	Plakin domain	Ρ	>PTC > NMD, no protein	Altered DP function; Truncated DP protein, (65	n.r.	Mismatch	n.s.	(het) ACM, LV mostly

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
					kDa) (WB), truncation of ROD and C- terminus ^[23] .				
c.2422C > T	p.(Arg808Cys)	Plakin- domain	US	>Protein expressed -PolyPhen-2> Benign (0.047) -SIFT> NOT tolerated -MutPred2> Benign (0.409)	Unclear; Conformational alteration (transfection), but overall folded structure of DP is remained [21]. Needs further confirmation in patient cells, whether expressed or not.	n.r.	Unclear	n.s.	(het) ACM
c.3799C > T	p.(Arg1267*)	ROD domain (DPI)	Ρ	>PTC > NMD, no protein -MutPred- LOF> Borderline pathogenic (0.5552)	Partial loss of DPI; Instable mutant DPI protein (NMD?) [24]. -Highly reduced DSP mRNA expression (NMD?) [24]. -Complete loss of DPI in patient skin, DPII has normal expression as expected (WB) [24].	n.r.	Match	(hom)PPK epidermolytic; (hom)WH	(hom) ACM/ DCM
c.3805C > T	p.(Arg1269*)	ROD domain (DPI)	Ρ	>PTC > NMD, no protein -MutPred- LOF> Borderline	Partial loss of DPI; Broken down by NMD. DPI/DPI-II protein ratios lower in variant	Decreased DP expression in endomyocardial biopsies. DPI deficiency (IF)	Match	(het) PPK; (het) WH	(het) DCM, bi- ventricular

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
				pathogenic (0.55487)	carriers compared with WT individuals. -DPI/DPII expression ratio reduced by 28% in mutant cells. 15-fold lower mutant than WT ^[10] .				
c.5051A > G	p.(His1684Arg)	ROD domain (DPI)	US	>Protein expressed -PolyPhen-2> Possibly damaging (0.956) -SIFT> NOT tolerated -MutPred2> Benign (0.256)	Altered DPI function: No effect on amount or size of DPI protein on WB [23]. DPII should not be affected.	Affects action potential and duration; multiple ion channel dysfunction in hiPSC-CMs ^[25] .	Match	n.r.	(het) CM, conduction disease
c.5208_5209del	p.(Gly1737Thrfs*7)	ROD domain (DPI)	Ρ	>PTC > NMD, no protein	Partial loss of DPI/Unclear? Truncated DPI protein predicted to run at similar height as DPII, yet no increase in this band was observed in skin biopsies (WB) ^[26] . DPII should not be affected, but data are unclear.	n.r.	Unclear	(hom) PPK acantholytic; (hom)WH;	(hom) NCCM, bi- ventricular, severe
c.5596C > T	p.(Gln1866*)	ROD domain (DPI)	LP	>PTC > terminal exon, NOT NMD > protein expressed	Altered DPI function; Truncated DPI protein (160 kDa) observed in skin biopsies	n.r.	Match	n.s.	(het) ACM, LV dilation

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
					^[27] . DPII should not be affected.				
c.5800C > T	p.(Arg1934*)	ROD domain (DPI)	LP	>PTC > terminal exon, NOT NMD > protein expressed	Altered DPI function; Truncated DPI protein (243 kDa) (WB) ^[28] . DPII should not be affected. -Aberrant mRNA transcripts. Not NMD.	Stable expressed DP protein, which is recruited into desmosomes, although more punctate staining was observed (IF)	Match	(comp.het) (lethal) EBS, PPK and WH, with <i>DSP:</i> c.6091_6092del ^[28]	n.r.
c.6091_6092del	p. (Leu2031Glyfs*29)	PRD (A domain)	LP	>PTC > terminal exon, NOT NMD > protein expressed	Altered DP function; Truncated DP-1 protein (228 kDa) (WB) ^[28] . Not clear what happens with DPII. -Aberrant mRNA transcripts. Not NMD.	Stable expressed DP protein, which is recruited in desmosomes, although more punctate staining was observed (IF)	Match	(comp.het) (lethal) EBS, PPK; and WH, with <i>DSP</i> : c.5800C > T ^[28]	n.r.
c.6166G > C	p.(Gly2056Arg)	PRD (A domain)	US	>Protein expressed -PolyPhen-2> Probably damaging (1.000) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.872)	Altered DP function; Expressed in insoluble fraction of bacterial cells (transfection WB) ^[29] . Low expression in HeLa cells. Likely expressed mutant.	n.r.	Probable match	(hom) PPK	(hom) ACM, LV involvement
c.6247C > T	p.(Arg2083Cys)	PRD (A domain)	US	>Protein expressed -PolyPhen-2>	Altered DP function; Expressed in	n.r.	Probable match	n.r.	(het) LQTS

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMC Class	GIn Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart	l in blue; n.a. (not
				Probably damaging (1.000) -SIFT> NOT tolerated -MutPred2> Benign (0.443)	soluble fraction of bacterial cells (transfection WB), thus correctly folded [29] Likely expressed					pe); WB ecay); fs induced s); EBS
					mutant, needs confirmation in patient cells.					athy, not
				>Protein	Altered DP function;					npaction
				expressed -PolyPhen-2> Possibly	soluble fraction of bacterial cell					comp.het
c.6307A > G	p.(Lys2103Glu)	PRD (A domain)	US	damaging (0.860) -SIFT> Tolerated -MutPred2> Benign (0.417)	transfection, thus correctly folded (WB) 129]. Likely expressed mutant, needs confirmation in patient cells.	n.r.	Probable match	n.r.	(het) DCM	
						Fibrosis and fat deposition in the				mice ^{[<u>41</u>].}
					Altered DP	heart with reduction in Cx43.			[42][43][44	at cause
		PPD		>PTC > terminal	function; Several truncated DP	disorganized IDs, but staining		(comp.het) EBS,	(comp.het)	1 = 5 or
c.6310del	p. (Thr2104GInfs*12)	(A domain)	LP	exon, NOT NMD > protein	proteins shown on WB, but	DG2 seemed normal; severe	Match	PPK and WH: with <i>DSP:</i> c.7964C > A	Bi-ventricular CM: with <i>DSP:</i> c.7964C > A)39 + 1G
				expressed	predicted to be 238 kDa ^[30]	DPI&II on IF ex vivo skin. β-				d before
						catenin expression was				pectedly
						IF in skin ^[30] .				resulted
c.6577G > A	p.(Glu2193Lys)	PRD (A	US	>Protein expressed	Altered DP function:	n.r.	Probable match	(comp.het) Alopecia PPK. with	(comp.het) DCM, with	affected

both soloms, except for variants $c.3799C \ge 1$, $c.3805C \ge 1$ and $c.5208_52090e$. The latter are located in the ROD domain of DPI and therefore only affect DPI, but not DPII. Interpreting the phenotype of patients, DP deficiency (\le 50% native DPI) seems to be associated with severe cardiomyopathy, while DP deficiency in the skin (\le 50% native DPI and DPII) is mostly associated with PPK and WH. Recessive variants that caused loss of DPI but not DPII, or extreme deficient levels of both DPI and DPII (<20%), were associated with skin fragility ^[26].

2.2. DSP Variants Causing an Altered DP Protein

The majority of functionally investigated *DSP* variants (36/48) led to an altered DP protein, due to 23 dominantly and 13 recessively inherited variants. Missense variants were the predominate source for altered DP proteins (n = 27), while the remaining nine variants were due to nonsense or nonsense-inducing variants. Out of the 36 variants, two variants were located near the N-terminus, ten were located in the plakin domain, three in the ROD domain of DPI, six in domain A, five in domain B, two in the linkers, five in domain C and three near the C-terminus. All but one (c.6687del) of the nonsense-inducing variants in the terminal exon of *DSP* skipped NMD. As expected, the phenotype of patients with an altered DP protein indicated that a recessive mode of inheritance was more severe than a dominant mode of inheritance, mostly due to absence of native protein in the former. Cardiomyopathy was observed in 31/36 of the variant carriers, while it went unobserved or unreported in the others. In the skin, 11/36

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart	t n = 2).
[<u>45]</u>		domain)		-PolyPhen-2> Possibly damaging (0.950) -SIFT> Tolerated [46] -MutPreu2> Benign (0.346)	Expressed in insoluble fraction in bacterial cells (transfection WB) [29]. Likely expressed mutant, needs confirmation in patient cells.			DSP:c.7567delAAGA	DSP:c.7567delAAGA	(n = 7, 2) (11), PPs (cted the B and C (nts was
c.6687del	p. (Arg2229Serfs*32) [<mark>47</mark>]	PRD (B domain)	LP	>PTC > terminal exon, NOT NMD > protein expressed	Partial loss of DP: NMD of product (WB, NMD inhibitor exp.), 50% reduced protein levels [13][14] -mRNA 50% reduced [14].	-Reduced DP protein on blot and staining in explanted heart, hiPSC-CMs and primary KCs [13] [14] -Mislocalisation of DP after 2D mechanical stretch; in combination with c.273 + 5G > A resulted in reduced count and density of desmosomes in hiPSC-derived dynamic EHTs leading to lower force and stress [14] -Faster differentiation observed in primary KCs of patients. Mechanical stretch provoked cell-contact defects [13].	Mismatch NMD active in terminal exon!	(het)PPK; (comp.het)WH: with DSP: c.273 + 5G > A	Lethal ACM/ NCCM (comp.het) ACM/ NCCM (bi- ventricular) (het)	tion and Fhe nine oth in the would be egaining nt alleles vels. For pe, as it
c.6885A > T	p.(GIn2295His)	PRD (B domain)	US	>Protein expressed -PolyPhen-2> Probably	Altered DP function; Likely truncated DP	Severe binding deficiency with intermediate filaments	Probable match	n.r.	(hom) DCM	

The *JUP* gene encodes for the 82 kDa PG protein, also known as γ -catenin. PG contains an N-terminal headdomain, 12 armadillo domains and a C-terminal tail-domain (**Figure 2**). PG belongs to the catenin protein family and is highly homologous to β -catenin, a potent transcription factor of the canonical Wnt/ β -catenin signalling pathway. PG is an important desmosomal protein, comprising the outer dense plaque of the desmosome and connecting the transmembrane DG and DC proteins to DP and PP. β -catenin and PG can be substituted for one another, as β -catenin can be incorporated into desmosomes, while PG can also act as a nuclear transcription factor ^[48]. The ClinVar database has reported 838 variants in *JUP*. Of these, 30 are claimed (likely) pathogenic; 307 (likely) benign; 70 show conflicting interpretations, and 431 have an unknown significance. Merely eight variants where substantiated by functional evidence, including data from transgenic mouse and zebrafish models (see **Figure 2**). As for *DSP* variants, effects of over 98% of all *JUP* variants were merely predicted by algorithms. The predictions on protein level were correct in 4/8 variants, incorrect in 3/8 variants, while the functional data remained inconclusive in 1/8 variants.

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biologic Effect	al	Prediction: Functional	Skin	Heart		¥
				damaging (0.999) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.833)	protein expressed.	(transfec	tion IF)					
c.7012G > A	p.(Gly2338Arg)	PRD (B domain)	US	>Protein expressed -PolyPhen-2> Probably damaging (1.000) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.910)	Altered DP function; Insoluble fraction in bacterial cell transfection (WB) ^[29] . Likely expressed mutant, needs confirmation in patient cells.	n.r.		Probable match	n.r.	(het) CM	a	shift-PTC
c.7027G > A	p.(Glu2343Lys)	PRD (B domain)	US	>Protein expressed -PolyPhen-2> Benign (0.077) -SIFT> Tolerated -MutPred2> Benign (0.386)	Altered DP function; Likely truncated DP protein expressed. Soluble fraction in bacterial cell transfection, thus correctly folded (WB) [29].	Altered b with vime and kera (transfec [<u>31</u>]	inding entin tin8/18 tion IF)	Probable match	n.r.	(het) AC ACM, w <i>PKP2</i> :c.	:M ith 1468C > T	nse phenotype
c.7096C > T	p.(Arg2366Cys)	PRD	LP	>Protein	Altered DP	Severe b	oinding	Probable	(hom)EBS;	n.r.		
HGVS Nomenclatur (DNA)	HGVS re Nomenclatur (Protein)	e Pi De	rotein omain	ACMGIn Class Pro	Fu Silico mF edictions Pro Stu	nctional RNA and otein udies	Biolo	gical Effect	Prediction: Functional	Skin	Heart	
c.71C > A	p.(Glu2_Met43 not p.(Ser24*) predicted	3del) H as c	Head domain	> N -N LP L SI Sc fc pr	Au FTC > MD, no MD, no MutPred- OF> too MutPred- OF> too MutPred- or equence or in rediction (V -S JU le co	ltered PG unction; runcated -terminal rotein acking the st 42 aa, anslation e-initiation let43) with educed xpression the skin VB) [49]. Similar UP mRNA evels as in portrol [49].	Redu expro WB) disru distri and l	uced PG ession (IF; and pted bution of DP DG1 (IF) ^[49] .	Mismatch	(hom)EBS; (hom)PPK; (hom)WH	n.o.	
c.116_118dup	p.(Ser39dup)	ł	Head Iomain	US > e: -N Ir	Protein A xpressed fu MutPred- M idel> pr si	ltered PG inction: lutant PG rotein size milar as	-Pati displ decre signa and	ent heart ayed a ease in al of DP, PG Cx43 (IF) ^[50]	Match	n.o.	(het) ACM	

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
				Pathogenic (0.76492)	WT (82 kDa; WB) [50]51]. See comment on biological effect [51].	 Transfection of HEK293 with mutant construct showed increased size of PG (90 kDa) due to ubiquitin binding (WB); cytoplasmic localization of mutant-PG (IF); higher proliferation and lower apoptosis; fewer and smaller desmosomes in mutant PG cells (EM) [50] Additional binding properties of mutant PG to TAIP-2 and HRC- BP (Co-IP and yeast-two-hybrid) [50] Diminished cell stiffness, but not cell adhesion [51]. 			
c.201del	p.(Ser68Ala fs*92)	Head domain	Ρ	>PTC > NMD, no protein	Loss of PG?: Highly reduced levels of JUP mRNA (normal splicing), no WB performed [52]	-Absence of PG protein staining in skin biopsies (IF); small desmosomes and wide intercellular spaces (EM) ^[52] .	Match	(hom)EBS; (hom)PPK; (hom) alopecia	(hom) ACM
c.469-8_469 -1del	p. (Val157_Lys161del)	Armadillo Domain 1	LP	>Protein expressed -MutPred- Indel> Pathogenic (0.78939)	Unclear; 15 nucleotides shorter cDNA fragments when	Cryptic splice acceptor site activation in exon 4 ^[53] .	Unclear	n.r.	(het) ACM

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
					compared to controls, no WB performed [53].				
c.1615C > T	p.(Gln539*)	Armadillo Domain 10	Ρ	>PTC > NMD, no protein - MutPred- LOF> Borderline pathogenic (0.62246)	Loss of PG; No truncated, or full- length PG protein detected in patient's skin extracts (WB) [54]. -Apart from the strong reduction of JUP (90% reduction), DSP and DSG1 mRNAs were also markedly decreased [54].	-Complete loss of PG protein in the patient's skin (WB and IF, both with N-terminal and C- terminal antibody); No skin barrier formation; significant reduction of DP and DG3 in patient skin (IF). Only few, abnormal desmosomes were formed ^[54] . - Strong reduction PG in the myocardium ^[54] .	Match	(hom) lethal EBS	n.o. at young age
c.1729C > T	p.(Arg577Cys)	Armadillo Domain 10	LP	>Protein expressed -PolyPhen- 2> Probably damaging (1.000) -SIFT> Tolerated - MutPred2> Pathogenic (0.720)	Altered PG function: Mutant PG had similar size as WT and was not reduced on blot according to the study [55]	-On WB, DG2 and Cx43 protein levels were reduced in mutant expression cells, and desmosomal junctions were destabilized (transfection studies) ^[55] .	Match	n.r.	(het) ACM
c.2038_2039del	p.(Trp680Gly fs*11)	Tail domain	Ρ	>PTC > NMD, no protein	Altered PG function; C-terminal truncated	-Reduced Cx43 and PG in patient ventricles and absence of	Mismatch	(hom)PPK; (hom)WH [59]	(hom) ACM [<u>59]</u>

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMGIn Silico Class Prediction	Functional mRNA and s Protein Studies	Biological Effect	Prediction: Functional	Heart
				PG protein is abundantly expressed (56 aa missing) (WB of biopsied LV and RV of multiple patients) [51][56][57]	phosphorylated Cx43 (IF; WB). A decreased number of gap junctions in patient's myocardium (EM) (57) - Diminishes cell adhesion, but not the cell compliance (51) -Mouse JUP knockin c.2038 2039del (58)	Mismatch human: mice	ł e r
					-The mouse data contradict the		2
					human data and suggest that mutant mRNA is broken down by NMD in mice, and not much protein is produced (WB does show truncated		E
					protein). The authors reason		۲
			[<u>61][62</u>]		that although the deletion is located		À
					in exon <mark>64</mark> the PTC is located in		Ξ
					the terminal exon (exon 12) >	[52]]
					homozygous mice die at		<u>94</u>
					postnatal day 1, while cardiac	[52]	(
					development went normal,		l F
					mice had severe skin fragility.		,
					-Fusion of the last 5 exons in mice,		ŀ
					produced the truncated protein		L. 1
			[<u>48][58]</u>		fully, did not cause lethality;		

predicted to cause reduced or depleted PG levels need to be investigated.

3.2. JUP Variants Causing an Altered PG Protein

Five functionally investigated variants (5/8) resulted in an altered PG protein. These resulted from three recessively inherited nonsense-inducing variants, resulting in either a N-terminal (Glu2_Met43del) or C-terminal (Trp680Glyfs*11 and Met686Asnfs*5) truncated protein. In addition, two dominantly inherited variants, Ser39dup and Arg577Cys, caused ACM and resulted in proteins comparable to the size of native PG. Unlike the C-terminal truncations, the recessive N-terminal truncation induced skin fragility with PPK and WH, but no cardiac dysfunction. The variant causative for this N-terminal truncation c.71C > A, introduces a PTC at Ser24, but translation reinitiation took place at position Met43, which resulted in deletion of the first 42 amino acids. This suggests that any nonsense-inducing variant located between JUP:c.1_126 will likely cause translation re-initiation and a similar

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMGI Class I	n Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Skin Functional	Heart	CM, PPK knockin
						however, mice did not develop cardiac dysfunction at 11 months of age.			withoutwithoutwereto their
c.2057_2058del	p.(Met686Asn fs*5)	Tail domain	n.a.	>PTC > NMD, no protein	58] Altered PG function; Transfected myocytes showed a C-terminal 75 kDa truncated protein (WB) ^[60] .	Cardiac specific Zebrafish JUP ^{VTT/2057_2058del} [60] - The zebrafish mutated myocytes showed significant reduction of I _{Na} and I _{K1} current densities. EM showed disruption of cell– cell contact. (GAL4/UAS transactivation system was used to induce cardiac specific expression of the human 2057_2058del variant in zebrafish) [60].	Mismatch, but no patients n.r. were traced.	(hom) ACM claimed, but no patients were traced	of exons, . months mblance ed to be at would se native with PG variants, nermore,
			protein expressed	fraction (normal si (only 285 aa, comp	 Set 2002 transloc: the solul fraction WB), patient e voluble where it: where it: voluble volub	nLeu, ated to ble of extract s high ph). s ed with			-tor more

The *DSC2* gene encodes for two transmembrane cadherin isoforms: DC2a (99 KDa) and DC2b (93 KDa). The DC2a isoform contains the complete intracellular segment (ICS), whereas this domain is 53 amino acids shorter in DC2b ^[65], due to alternative splicing of exon 16 (**Figure 3**). Both isoforms are first processed into a precursor protein, followed by a mature protein that can be incorporated into desmosomes. Maturely processed DC2 serves as a transmembrane desmosomal protein, important for extracellular cell–cell attachment. The ClinVar database has reported 1209 variants in *DSC2*. Of these, 102 were claimed (likely) pathogenic; 409 (likely) benign; 85 show conflicting interpretations and 613 have an unknown significance. Notably, merely 15 variants were substantiated by functional evidence, including data from transgenic mouse and zebrafish models (see **Figure 3**). The same trend seen for *DSP* and *JUP* variants, is also observed for *DSC2*, indicating that over 98% of all variants have not been functionally investigated. The predictions on protein level were correct in 11/15 variants, while incorrect in 3/15 variants and unclear in 1/15 variants.

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMGIn Silico Class Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin Heart	Les Altes
				to wildtype 2871 aa)	phosphorylation (Ser33/37- Thr41) and degradation of β -catenin; abolition of β - catenin phosphorylation in the non- soluble fraction was associated with its translocation into CMs nuclei			осоон 901
kale is the second seco	TELE	, t ^e ²				CS of DC Terminal * cardiocL	 Altered protein Loss of protein Unclear (het) Recessive (hom) 	 Frameshift-PTC Nonsense (PTC) Missense Indel 5'UTR

Figure 3. Location of functionally investigated *DSC2* variants.

Table 3. Functionally analysed	DSC2 variants.
--------------------------------	----------------

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction Functional	Skin	Heart
c1445G > C	NC_000018.10:g.31103416C > G	5'UTR	В	Not applicable (5'UTR), cannot be predicted	Altered DC2 function; n.s. -Luciferase assay >a decreased transcriptional activity for HEK cells transfected with the DC2 mutant (c1445C) construct ^[66] .	Altered transcription factor binding in the presence of the mutant allele.	Mismatch by definition	n.r.	(het) ACM
c.140_147del	p.(Lys47Arg fs*2)	PRO peptide- domain	LP	>PTC > NMD, no protein	Partial loss of DC2: Patient had reduced levels (>50%) of DC2 in skin biopsy (WB) [§7].	n.r. -of note: a relative with only DSC2:c.1559T > C (missense) had no phenotype [67].	Match	n.r.	(comp.het) NCCM/HCM with DSC2:c.1559T > C

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction Functional	Skin	Heart
c.304G > A	p.(Glu102Lys)	PRO peptide- domain	LB	>Protein expressed -PolyPhen-2> Benign (0.016) -SIFT> Tolerated -MutPred2> Benign (0.158)	Altered DC2 function; n.s., but mutant expressed in cells.	IF shows that the mutant protein localizes in a dotted pattern predominantly in the cytoplasm (COS-1 cells, neonatal rat CM transfection)	Match	n.r.	(het) ACM
c.394C > T	p.(Arg132Cys)	In between PRO peptide and EC1- domain	US	>Protein expressed -PolyPhen-2> Probably damaging (1.000) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.823)	Partial loss of DC2; 50% reduced levels of DSC2 mRNA in explanted heart and hiPSC-CMs; reduced DC2 protein in explanted heart (WB) [99]	-Reduced levels of all desmosomal genes in explanted heart and hiPSC- CMs, reduction of PG at ID in heart; mutant hiPSC-CMs had shortened action potential durations associated with reduced calcium current density and increased potassium current density ISB_ -Increased PPARy expression and contractile and electric disturbances observed in patient hiPSC- CMs [20] -Zebrafish DSC2 ^{WT/C.394C} > T [69]	Mismatch	n.r.	(het) ACM

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	iln Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional	Skin	Heart
c.609C > T	p.(Arg203Cys)	EC1 domain	US	>Protein expressed -PolyPhen-2> Probably damaging (1.000) -SIFT> NOT tolerated -MutPred2> Pathogenic (0.899)	Altered DC2 function; Complete defect in processing into the mature form [21]. (WB)	-The mutant protein remains in an unprocessed pro-protein form (COS-1 cells transfection) [71] -In HL-1 cells, the mutant protein fails to localize at the desmosomes of intercalated disc structures [71]	Match	n.r.	(het) ACM
c.631-2A > G	p.(lle211Met fs*11)	EC1 domain	Ρ	>PTC > NMD, no protein	Partial loss of DC2: Patient heart tissue shows 60% DC2 reduction (WB) ^[72] -Reduced mRNA DSC2 (only 3% compared to WT) ^[72]	-n.r. -Zebrafish KD of DSC2 and DSC2 ^{WT/631-2A} > G [72]	Match	n.o.	(het) ACM
c.824C > T	p.(Thr275Met)	EC2 domain	US	>Protein expressed -PolyPhen-2> Probably damaging (0.999) -SIFT> NOT tolerated -MutPred2> Benign (0.563)	Altered DC2 function; Partial defects in processing into the mature form [71]. (WB)	-Only a proportion of the partly functional DC2 mutant protein is still incorporated into the desmosomes; affects PG at the intercalated disc (COS-1 cells transfection) [71].	Match	n.r.	(hom) ACM

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction Functional	Skin	Heart	
c.1034T > C	p.(Ile345Thr)	EC2 domain	US	>Protein expressed -PolyPhen-2> Possibly damaging (0.756) -SIFT> NOT tolerated -MutPred2> Benign (0.591)	Altered DC2 function; n.s., but mutant expressed in cells.	-In transfected neonatal rat cardiomyocytes and HL-1 cells, the mutant protein localizes in the cytoplasm (IF)	Match	n.r.	(het) ACM	
c.1559T > C	p.(Ile520Thr)	EC4 domain	LB	>Protein expressed -PolyPhen-2> Probably damaging (0.973) -SIFT> NOT tolerated -MutPred2> Benign (0.601)	Altered DC2 function; Protein is expressed, similar size as wildtype (WB) ^[62] . Unsure if the protein is really altered, or that it maintains all functions ^[67] .	n.r. -of note: a relative with only <i>DSC2</i> :c.1559T > C (missense) had no phenotype [97].	Match	n.r.	(comp.het) NCCM/HCM with DSC2:c.140_147del	
c.1660C > T	p.(Gln554*)	EC4 domain	Ρ	>PTC > NMD, no protein - MutPredLOF> borderline pathogenic (0.51161)	Altered DC2 function; Truncated DC2 protein (75 kDa), wildtype is 150 kDa (transfection WB). Less mature protein, more pre-protein than normal [73].	-Heart biopsies shows DC2 staining in hom-carriers (protein is expressed); mutant protein localizes only partially at cell membrane and predominantly in cytoplasm (transfection IF WB) ^[73] . -Transfected cells show that the secreted truncated isoforms are not anchored in	Mismatch	Mild PPK at pressure points, in one hom- and one het-carrier (possibly secondary to farm work)	(hom) ACM (LV affected mainly)	l in b P (li red); nedi; uripc

(cardiomyopathy); ACM (arrhythmogenic cardiomyopathy); NCCM (non-compaction cardiomyopathy); HCM (hypertrophic cardiomyopathy); LV (left ventricle); hom (homozygous > phenotype observed in homozygous carriers); comp.het (compound heterozygous > phenotype observed in compound heterozygous carriers); het (heterozygous > phenotype observed in heterozygous carriers).

4.1. DSC2 Variants Causing DC2 Reduction

No patients with complete absence of DC2 protein have been reported. Instead, four variants (4/15), located before the terminal exon, resulted in both DC2a and DC2b protein reduction. The recessively (c.1913_1916delAGAA; $\leq 10\%$ protein left ^[74]) and dominantly (c.631-2A > G; 40% protein left) inherited nonsense-inducing variants both caused ACM in patients. Compound heterozygosity of out-of-frame indel variant c.140_147delAACTTGT resulted in NCCM and hypertrophy, which is the only functionally investigated *DSC2* variant associated with cardiomyopathy other than ACM ^[67]. The missense variant c.394C > T caused 50% protein reduction via instable protein degradation and caused ACM in a dominant mode of inheritance. Altered electrical properties, a key characteristic of ACM, have been observed in patient hiPSC-CMs containing this missense variant ^[69]. Moreover,

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACM0 Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction Functiona	l [:] Skin	Heart	[<u>69][72</u>]	⁻ he ACM []] . One of
						the plasma membrane ^[74] .					disease
[<u>72</u> c.1841del [<u>79]</u>	p.(Ser614lle fs*11)	EA domain	Ρ	>PTC > NMD, no protein	Unclear?; Truncated isoforms expressed (transfection IF, WB), but needs patient cell confirmation.	Transfected cells show that the secreted truncated isoforms are not anchored in the plasma membrane ^[74] .	Unclear	(hom) Mild PPK, WH ^[75]	(hom) ACM	[<u>75</u>]	ituations more, in nenotype reducing
c.1913_1916 del	p.(Gln638Leu fs*9)	EA domain	Ρ	>PTC > NMD, no protein	Partial loss of DC2: Strong DC2 protein reduction in patient heart tissue (<10% left-WB, also IF) [74] -DSC2 mRNA was decreased in patient heart tissue (qPCR)	-Patients' explanted heart shows degradation of sarcomeres and mitochondria; widened intercellular spaces and accumulation of lipid droplets (EM); Transfected cells show that the secreted truncated isoforms are not anchored in the plasma membrane [74].	Match	n.o.	(hom) ACM		n = 7) or on factor recursor 203Cys, ated into
c.2368_2370 del	[71][73][77] p.(Gly7900el)	In hetween IA-rid ICS domains	US	>Protein expressed -MutPred- Indel> NOT pathogenic (0.4309)	Altered DC2 function: No reduction of DC2 protein levels [76]	-Slight LV dysfunction with abnormal calcium release [76]. -Mouse model > [76] Hom-mice (G790del) showed enlarged LV and a decreased	Match [<u>67</u>]	n.r.	(het) CM		runcated .nd while ortion of II induce inducing runcated lost their

ability to bind to DP ^[71] and PG ^{[71][77]}. The latter suggests a similar perturbing binding interface for GIn554*. No protein processing information is available on variant Gly790del, other than that it is expressed and translated into a transgenic mouse model. Neither the heterozygous nor homozygous mice showed structural or functional defects in the ventricles or lethal arrhythmias, and only homozygous aged mice showed slight left ventricular dysfunction. This mouse model therefore does not represent the phenotypic severity of the heterozygous Gly790del patients with ACM. In most (7/10) variants, apart from recessive variants Gln554*, Thr275Met and Ile520Thr, ACM was observed in a dominant mode of inheritance. Only recessive inheritance of variant Ser614llefs*11 caused PPK and WH, but the functional data were unclear as to whether it causes protein reduction or an altered protein function in patients [74][75]. A skin phenotype was furthermore not observed or went unreported in the other variants.

4.3. Potential Therapeutic Avenues

Whether *DSC2* variants can truly cause a cardiocutaneous phenotype remains somewhat elusive, given that only one investigated variant was associated with PPK and WH, and others that do associate with a skin phenotype were not investigated ^[75]. It seems that extreme deficiency in DC2 is well-compensated for by other desmocollins

HGVS Nomenclature (DNA)	HGVS Nomenclature (Protein)	Protein Domain	ACMG Class	In Silico Predictions	Functional mRNA and Protein Studies	Biological Effect	Prediction: Functional ^{Skin}		Heart	clusions. m native
						fractional shortening. Abnormal intracelear release, but no clear ACM phenotype. Het-mice showed no arrhythmias.				humans,
c.2553del	p.(Asp852Thr fs*4)	ICS domain DC2a only	US	-PTC > terminal exon, not NMD > protein expressed	Altered DC2a function; Truncation of the last 47 aa of the DC2a isoform ^[72] .	The mutant protein DC2a lost its ability to bind to PG (HL- 1 cells transfection) I77	Match	n.r.	(het) ACM	23,
c.2687_2688 insGA	p.(Ala897Lys fs*4)	ICS domain DC2a only	в	-PTC > terminal exon, not NMD > protein expressed	Altered DC2a function; -Premature termination of the protein [78]. -Does not exhibit defects in processing into the mature form [71].	-Cytoplasmic localization of the mutant protein (HL-1 cells transfection) [78] -This mutant protein is processed into its mature form and can be incorporated into desmosomes; impaired binding to DP and PG (COS- 1 cells transfection) [71]/	Match	n.r.	(het) ACM	4. , S.; ith ıre. Int.

- Gaul, R.T.; Nolan, D.R.; Ristori, T.; Bouten, C.V.C.; Loerakker, S.; Lally, C. Strain Mediated Enzymatic Degradation of Arterial Tissue: Insights into the Role of the Non-Collagenous Tissue Matrix and Collagen Crimp. Acta Biomater. 2018, 77, 301–310.
- 7. Getsios, S.; Huen, A.C.; Green, K.J. Working out the Strength and Flexibility of Desmosomes. Nat. Rev. Mol. Cell Biol. 2004, 5, 271–281.
- Stappenbeck, T.S.; Lamb, J.A.; Corcoran, C.M.; Green, K.J. Phosphorylation of the Desmoplakin COOH Terminus Negatively Regulates Its Interaction with Keratin Intermediate Filament Networks. J. Biol. Chem. 1994, 269, 29351–29354.
- Yang, Z.; Bowles, N.E.; Scherer, S.E.; Taylor, M.D.; Kearney, D.L.; Ge, S.; Nadvoretskiy, V.V.; DeFreitas, G.; Carabello, B.; Brandon, L.I.; et al. Desmosomal Dysfunction Due to Mutations in Desmoplakin Causes Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. Circ. Res. 2006, 99, 646–655.
- Rasmussen, T.; Hansen, J.; Nissen, P.; Palmfeldt, J.; Dalager, S.; Jensen, U.; Kim, W.; Heickendorff, L.; Mølgaard, H.; Jensen, H.; et al. Protein Expression Studies of Desmoplakin Mutations in Cardiomyopathy Patients Reveal Different Molecular Disease Mechanisms. Clin. Genet. 2013, 84, 20–30.

- Notari, M.; Hu, Y.; Sutendra, G.; Dedeić, Z.; Lu, M.; Dupays, L.; Yavari, A.; Carr, C.A.; Zhong, S.; Opel, A.; et al. IASPP, a Previously Unidentified Regulator of Desmosomes, Prevents Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)-Induced Sudden Death. Proc. Natl. Acad. Sci. USA 2015, 112, E973–E981.
- 12. Basso, C. Ultrastructural Evidence of Intercalated Disc Remodelling in Arrhythmogenic Right Ventricular Cardiomyopathy: An Electron Microscopy Investigation on Endomyocardial Biopsies. Eur. Heart J. 2006, 27, 1847–1854.
- Vermeer, M.C.S.C.; Andrei, D.; Kramer, D.; Nijenhuis, A.M.; Hoedemaekers, Y.M.; Westers, H.; Jongbloed, J.D.H.; Pas, H.H.; Berg, M.P.; Silljé, H.H.W.; et al. Functional Investigation of Two Simultaneous or Separately Segregating DSP Variants within a Single Family Supports the Theory of a Dose-dependent Disease Severity. Exp. Dermatol. 2022, 31, 970–979.
- Bliley, J.M.; Vermeer, M.C.; Duffy, R.M.; Batalov, I.; Kramer, D.; Tashman, J.W.; Shiwarski, D.J.; Lee, A.; Teplenin, A.S.; Volkers, L.; et al. Dynamic Loading of Human Engineered Heart Tissue Enhances Contractile Function and Drives a Desmosome-Linked Disease Phenotype. Sci. Transl. Med. 2021, 13, eabd1817.
- 15. Lin, X.; Ma, Y.; Cai, Z.; Wang, Q.; Wang, L.; Huo, Z.; Hu, D.; Wang, J.; Xiang, M. Next-Generation Sequencing Identified Novel Desmoplakin Frame-Shift Variant in Patients with Arrhythmogenic Cardiomyopathy. BMC Cardiovasc. Disord. 2020, 20, 74.
- Patel, D.M.; Dubash, A.D.; Kreitzer, G.; Green, K.J. Disease Mutations in Desmoplakin Inhibit Cx43 Membrane Targeting Mediated by Desmoplakin-EB1 Interactions. J. Cell Biol. 2014, 206, 779–797.
- Whittock, N.V.; Ashton, G.H.S.; Dopping-Hepenstal, P.J.C.; Gratian, M.J.; Keane, F.M.; Eady, R.A.J.; McGrath, J.A. Striate Palmoplantar Keratoderma Resulting from Desmoplakin Haploinsufficiency. J. Investig. Dermatol. 1999, 113, 940–946.
- 18. Armstrong, D. Haploinsufficiency of Desmoplakin Causes a Striate Subtype of Palmoplantar Keratoderma. Hum. Mol. Genet. 1999, 8, 143–148, Erratum in Hum. Mol. Genet. 1999, 8, 943.
- Wan, H.; Dopping-Hepenstal, P.J.C.J.C.; Gratian, M.J.J.; Stone, M.G.G.; Zhu, G.; Purkis, P.E.E.; South, A.P.P.; Keane, F.; Armstrong, D.K.B.K.B.; Buxton, R.S.S.; et al. Striate Palmoplantar Keratoderma Arising from Desmoplakin and Desmoglein 1 Mutations Is Associated with Contrasting Perturbations of Desmosomes and the Keratin Filament Network. Br. J. Dermatol. 2004, 150, 878–891.
- Ng, R.; Manring, H.; Papoutsidakis, N.; Albertelli, T.; Tsai, N.; See, C.J.; Li, X.; Park, J.; Stevens, T.L.; Bobbili, P.J.; et al. Patient Mutations Linked to Arrhythmogenic Cardiomyopathy Enhance Calpain-Mediated Desmoplakin Degradation. JCI Insight 2019, 4, e128643.

- Al-Jassar, C.; Knowles, T.; Jeeves, M.; Kami, K.; Behr, E.; Bikker, H.; Overduin, M.; Chidgey, M. The Nonlinear Structure of the Desmoplakin Plakin Domain and the Effects of Cardiomyopathy-Linked Mutations. J. Mol. Biol. 2011, 411, 1049–1061.
- Boyden, L.M.; Kam, C.Y.; Hernández-Martín, A.; Zhou, J.; Craiglow, B.G.; Sidbury, R.; Mathes, E.F.; Maguiness, S.M.; Crumrine, D.A.; Williams, M.L.; et al. Dominant de Novo DSP Mutations Cause Erythrokeratodermia-Cardiomyopathy Syndrome. Hum. Mol. Genet. 2016, 25, 348–357.
- Norman, M.; Simpson, M.; Mogensen, J.; Shaw, A.; Hughes, S.; Syrris, P.; Sen-Chowdhry, S.; Rowland, E.; Crosby, A.; McKenna, W.J. Novel Mutation in Desmoplakin Causes Arrhythmogenic Left Ventricular Cardiomyopathy. Circulation 2005, 112, 636–642.
- Uzumcu, A.; Norgett, E.E.; Dindar, A.; Uyguner, O.; Nisli, K.; Kayserili, H.; Sahin, S.E.; Dupont, E.; Severs, N.J.; Leigh, I.M.; et al. Loss of Desmoplakin Isoform I Causes Early Onset Cardiomyopathy and Heart Failure in a Naxos-like Syndrome. J. Med. Genet. 2006, 43, e5.
- 25. Impact of the DSP-H1684R Genetic Variant on Ion Channels Activity in IPSC-Derived Cardiomyocytes. Cell. Physiol. Biochem. 2020, 54, 696–706.
- Williams, T.; Machann, W.; Kühler, L.; Hamm, H.; Müller-Höcker, J.; Zimmer, M.; Ertl, G.; Ritter, O.; Beer, M.; Schönberger, J. Novel Desmoplakin Mutation: Juvenile Biventricular Cardiomyopathy with Left Ventricular Non-Compaction and Acantholytic Palmoplantar Keratoderma. Clin. Res. Cardiol. 2011, 100, 1087–1093.
- Navarro-Manchón, J.; Fernández, E.; Igual, B.; Asimaki, A.; Syrris, P.; Osca, J.; Salvador, A.; Zorio, E. Miocardiopatía Arritmogénica Con Afectación Predominante del Ventrículo Izquierdo por una Mutación Nueva «sin Sentido» En Desmoplaquina. Rev. Española Cardiol. 2011, 64, 530– 534.
- Jonkman, M.F.; Pasmooij, A.M.G.; Pasmans, S.G.M.A.; van den Berg, M.P.; Ter Horst, H.J.; Timmer, A.; Pas, H.H. Loss of Desmoplakin Tail Causes Lethal Acantholytic Epidermolysis Bullosa. Am. J. Hum. Genet. 2005, 77, 653–660.
- 29. Mohammed, F.; Odintsova, E.; Chidgey, M. Missense Mutations in Desmoplakin Plakin Repeat Domains Have Dramatic Effects on Domain Structure and Function. Int. J. Mol. Sci. 2022, 23, 529.
- Mahoney, M.G.; Sadowski, S.; Brennan, D.; Pikander, P.; Saukko, P.; Wahl, J.; Aho, H.; Heikinheimo, K.; Bruckner-Tuderman, L.; Fertala, A.; et al. Compound Heterozygous Desmoplakin Mutations Result in a Phenotype with a Combination of Myocardial, Skin, Hair, and Enamel Abnormalities. J. Investig. Dermatol. 2010, 130, 968–978.
- 31. Favre, B.; Begré, N.; Marsili, L.; van Tintelen, J.P.; Borradori, L. Desmoplakin Gene Variants and Risk for Arrhythmogenic Cardiomyopathy. Circ. Genom. Precis. Med. 2018, 11, e002241.

- Favre, B.; Begré, N.; Borradori, L. A Recessive Mutation in the DSP Gene Linked to Cardiomyopathy, Skin Fragility and Hair Defects Impairs the Binding of Desmoplakin to Epidermal Keratins and the Muscle-Specific Intermediate Filament Desmin. Br. J. Dermatol. 2018, 179, 797– 799.
- 33. Norgett, E.E. Recessive Mutation in Desmoplakin Disrupts Desmoplakin-Intermediate Filament Interactions and Causes Dilated Cardiomyopathy, Woolly Hair and Keratoderma. Hum. Mol. Genet. 2000, 9, 2761–2766.
- Huen, A.C.; Park, J.K.; Godsel, L.M.; Chen, X.; Bannon, L.J.; Amargo, E.V.; Hudson, T.Y.; Mongiu, A.K.; Leigh, I.M.; Kelsell, D.P.; et al. Intermediate Filament–Membrane Attachments Function Synergistically with Actin-Dependent Contacts to Regulate Intercellular Adhesive Strength. J. Cell Biol. 2002, 159, 1005–1017.
- Puzzi, L.; Borin, D.; Martinelli, V.; Mestroni, L.; Kelsell, D.P.; Sbaizero, O. Cellular Biomechanics Impairment in Keratinocytes Is Associated with a C-Terminal Truncated Desmoplakin: An Atomic Force Microscopy Investigation. Micron 2018, 106, 27–33.
- Martherus, R.; Jain, R.; Takagi, K.; Mendsaikhan, U.; Turdi, S.; Osinska, H.; James, J.F.; Kramer, K.; Purevjav, E.; Towbin, J.A. Accelerated Cardiac Remodeling in Desmoplakin Transgenic Mice in Response to Endurance Exercise Is Associated with Perturbed Wnt/β-Catenin Signaling. Am. J. Physiol.-Heart Circ. Physiol. 2016, 38103, H174–H187.
- Albrecht, L.V.; Zhang, L.; Shabanowitz, J.; Purevjav, E.; Towbin, J.A.; Hunt, D.F.; Green, K.J. GSK3- and PRMT-1-Dependent Modifications of Desmoplakin Control Desmoplakin-Cytoskeleton Dynamics. J. Cell Biol. 2015, 208, 597–612.
- Lapouge, K.; Fontao, L.; Champliaud, M.-F.; Jaunin, F.; Frias, M.A.; Favre, B.; Paulin, D.; Green, K.J.; Borradori, L. New Insights into the Molecular Basis of Desmoplakinand Desmin-Related Cardiomyopathies. J. Cell Sci. 2006, 119, 4974–4985.
- Dehner, C.; Rötzer, V.; Waschke, J.; Spindler, V. A Desmoplakin Point Mutation with Enhanced Keratin Association Ameliorates Pemphigus Vulgaris Autoantibody-Mediated Loss of Cell Cohesion. Am. J. Pathol. 2014, 184, 2528–2536.
- Camors, E.M.; Purevjav, E.; Jefferies, J.L.; Saffitz, J.E.; Gong, N.; Ryan, T.D.; Lucky, A.W.; Taylor, M.D.; Sullivan, L.M.; Mestroni, L.; et al. Early Lethality Due to a Novel Desmoplakin Variant Causing Infantile Epidermolysis Bullosa Simplex with Fragile Skin, Aplasia Cutis Congenita, and Arrhythmogenic Cardiomyopathy. Circ. Genom. Precis. Med. 2020, 13, e002800.
- Ian Gallicano, G.; Kouklis, P.; Bauer, C.; Yin, M.; Vasioukhin, V.; Degenstein, L.; Fuchs, E. Desmoplakin Is Required Early in Development for Assembly of Desmosomes and Cytoskeletal Linkage. J. Cell Biol. 1998, 143, 2009–2022.

- Gomes, J.; Finlay, M.; Ahmed, A.K.; Ciaccio, E.J.; Asimaki, A.; Saffitz, J.E.; Quarta, G.; Nobles, M.; Syrris, P.; Chaubey, S.; et al. Electrophysiological Abnormalities Precede Overt Structural Changes in Arrhythmogenic Right Ventricular Cardiomyopathy Due to Mutations in Desmoplakin-A Combined Murine and Human Study. Eur. Heart J. 2012, 33, 1942–1953.
- 43. Garcia-Gras, E. Suppression of Canonical Wnt/ -Catenin Signaling by Nuclear Plakoglobin Recapitulates Phenotype of Arrhythmogenic Right Ventricular Cardiomyopathy. J. Clin. Investig. 2006, 116, 2012–2021.
- Cheedipudi, S.M.; Hu, J.; Fan, S.; Yuan, P.; Karmouch, J.; Czernuszewicz, G.; Robertson, M.J.; Coarfa, C.; Hong, K.; Yao, Y.; et al. Exercise Restores Dysregulated Gene Expression in a Mouse Model of Arrhythmogenic Cardiomyopathy. Cardiovasc. Res. 2019, 116, 1199–1213.
- 45. Smith, E.A.; Fuchs, E. Defining the Interactions between Intermediate Filaments and Desmosomes. J. Cell Biol. 1998, 141, 1229–1241.
- 46. Lechler, T.; Fuchs, E. Desmoplakin: An Unexpected Regulator of Microtubule Organization in the Epidermis. J. Cell Biol. 2007, 176, 147–154.
- 47. Giuliodori, A.; Beffagna, G.; Marchetto, G.; Fornetto, C.; Vanzi, F.; Toppo, S.; Facchinello, N.; Santimaria, M.; Vettori, A.; Rizzo, S.; et al. Loss of Cardiac Wnt/β-Catenin Signalling in Desmoplakin-Deficient AC8 Zebrafish Models Is Rescuable by Genetic and Pharmacological Intervention. Cardiovasc. Res. 2018, 114, 1082–1097.
- 48. Li, D.; Zhang, W.; Liu, Y.; Haneline, L.S.; Shou, W. Lack of Plakoglobin in Epidermis Leads to Keratoderma. J. Biol. Chem. 2012, 287, 10435–10443.
- Cabral, R.M.; Liu, L.; Hogan, C.; Dopping-Hepenstal, P.J.C.; Winik, B.C.; Asial, R.A.; Dobson, R.; Mein, C.A.; Baselaga, P.A.; Mellerio, J.E.; et al. Homozygous Mutations in the 5' Region of the JUP Gene Result in Cutaneous Disease but Normal Heart Development in Children. J. Investig. Dermatol. 2010, 130, 1543–1550.
- 50. Asimaki, A.; Syrris, P.; Wichter, T.; Matthias, P.; Saffitz, J.E.; McKenna, W.J. A Novel Dominant Mutation in Plakoglobin Causes Arrhythmogenic Right Ventricular Cardiomyopathy. Am. J. Hum. Genet. 2007, 81, 964–973.
- 51. Huang, H.; Asimaki, A.; Lo, D.; McKenna, W.; Saffitz, J. Disparate Effects of Different Mutations in Plakoglobin on Cell Mechanical Behavior. Cell Motil. Cytoskelet. 2008, 65, 964–978.
- Vahidnezhad, H.; Youssefian, L.; Faghankhani, M.; Mozafari, N.; Saeidian, A.H.; Niaziorimi, F.; Abdollahimajd, F.; Sotoudeh, S.; Rajabi, F.; Mirsafaei, L.; et al. Arrhythmogenic Right Ventricular Cardiomyopathy in Patients with Biallelic JUP-Associated Skin Fragility. Sci. Rep. 2020, 10, 21622.
- 53. Groeneweg, J.A.; Ummels, A.; Mulder, M.; Bikker, H.; van der Smagt, J.J.; van Mil, A.M.; Homfray, T.; Post, J.G.; Elvan, A.; van der Heijden, J.F.; et al. Functional Assessment of Potential Splice

Site Variants in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. Heart Rhythm 2014, 11, 2010–2017.

- 54. Pigors, M.; Kiritsi, D.; Krümpelmann, S.; Wagner, N.; He, Y.; Podda, M.; Kohlhase, J.; Hausser, I.; Bruckner-Tuderman, L.; Has, C. Lack of Plakoglobin Leads to Lethal Congenital Epidermolysis Bullosa: A Novel Clinico-Genetic Entity. Hum. Mol. Genet. 2011, 20, 1811–1819.
- 55. Liu, L.; Chen, C.; Li, Y.; Yu, R. Whole-Exome Sequencing Identified a De Novo Mutation of Junction Plakoglobin (p.R577C) in a Chinese Patient with Arrhythmogenic Right Ventricular Cardiomyopathy. Biomed. Res. Int. 2019, 2019, 9103860.
- McKoy, G.; Protonotarios, N.; Crosby, A.; Tsatsopoulou, A.; Anastasakis, A.; Coonar, A.; Norman, M.; Baboonian, C.; Jeffery, S.; McKenna, W.J. Identification of a Deletion in Plakoglobin in Arrhythmogenic Right Ventricular Cardiomyopathy with Palmoplantar Keratoderma and Woolly Hair (Naxos Disease). Lancet 2000, 355, 2119–2124.
- 57. Kaplan, S.R.; Gard, J.J.; Protonotarios, N.; Tsatsopoulou, A.; Spiliopoulou, C.; Anastasakis, A.; Squarcioni, C.P.; McKenna, W.J.; Thiene, G.; Basso, C.; et al. Remodeling of Myocyte Gap Junctions in Arrhythmogenic Right Ventricular Cardiomyopathy Due to a Deletion in Plakoglobin (Naxos Disease). Heart Rhythm 2004, 1, 3–11.
- Zhang, Z.; Stroud, M.J.; Zhang, J.; Fang, X.; Ouyang, K.; Kimura, K.; Mu, Y.; Dalton, N.D.; Gu, Y.; Bradford, W.H.; et al. Normalization of Naxos Plakoglobin Levels Restores Cardiac Function in Mice. J. Clin. Investig. 2015, 125, 1708–1712.
- 59. Protonotarios, N.; Tsatsopoulou, A.; Patsourakos, P.; Alexopoulos, D.; Gezerlis, P.; Simitsis, S.; Scampardonis, G. Cardiac Abnormalities in Familial Palmoplantar Keratosis. Heart 1986, 56, 321–326.
- 60. Asimaki, A.; Kapoor, S.; Plovie, E.; Karin Arndt, A.; Adams, E.; Liu, Z.; James, C.A.; Judge, D.P.; Calkins, H.; Churko, J.; et al. Identification of a New Modulator of the Intercalated Disc in a Zebrafish Model of Arrhythmogenic Cardiomyopathy. Sci. Transl. Med. 2014, 6, 240ra74.
- 61. Bierkamp, C.; McLaughlin, K.J.; Schwarz, H.; Huber, O.; Kemler, R. Embryonic Heart and Skin Defects in Mice Lacking Plakoglobin. Dev. Biol. 1996, 180, 780–785.
- Ruiz, P.; Brinkmann, V.; Ledermann, B.; Behrend, M.; Grund, C.; Thalhammer, C.; Vogel, F.; Birchmeier, C.; Günthert, U.; Franke, W.W.; et al. Targeted Mutation of Plakoglobin in Mice Reveals Essential Functions of Desmosomes in the Embryonic Heart. J. Cell Biol. 1996, 135, 215–225.
- Li, D.; Liu, Y.; Maruyama, M.; Zhu, W.; Chen, H.; Zhang, W.; Reuter, S.; Lin, S.-F.; Haneline, L.S.; Field, L.J.; et al. Restrictive Loss of Plakoglobin in Cardiomyocytes Leads to Arrhythmogenic Cardiomyopathy. Hum. Mol. Genet. 2011, 20, 4582–4596.

- 64. Swope, D.; Li, J.; Muller, E.J.; Radice, G.L. Analysis of a Jup Hypomorphic Allele Reveals a Critical Threshold for Postnatal Viability. Genesis 2012, 50, 717–727.
- 65. Kowalczyk, A.P.; Borgwardt, J.E.; Green, K.J. Analysis of Desmosomal Cadherin–Adhesive Function and Stoichiometry of Desmosomal Cadherin-Plakoglobin Complexes. J. Investig. Dermatol. 1996, 107, 293–300.
- Christensen, A.H.; Schmitz, B.; Andersen, C.B.; Bundgaard, H.; Brand, S.-M.; Svendsen, J.H. Functional Promoter Variant in Desmocollin-2 Contributes to Arrhythmogenic Right Ventricular Cardiomyopathy. Circ. Cardiovasc. Genet. 2016, 9, 384–387.
- 67. Lin, Y.; Huang, J.; Zhu, Z.; Zhang, Z.; Xian, J.; Yang, Z.; Qin, T.; Chen, L.; Huang, J.; Huang, Y.; et al. Overlap Phenotypes of the Left Ventricular Noncompaction and Hypertrophic Cardiomyopathy with Complex Arrhythmias and Heart Failure Induced by the Novel Truncated DSC2 Mutation. Orphanet J. Rare Dis. 2021, 16, 496.
- Beffagna, G.; De Bortoli, M.; Nava, A.; Salamon, M.; Lorenzon, A.; Zaccolo, M.; Mancuso, L.; Sigalotti, L.; Bauce, B.; Occhi, G.; et al. Missense Mutations in Desmocollin-2 N-Terminus, Associated with Arrhythmogenic Right Ventricular Cardiomyopathy, Affect Intracellular Localization of Desmocollin-2 in Vitro. BMC Med. Genet. 2007, 8, 65.
- Moreau, A.; Reisqs, J.; Delanoe-Ayari, H.; Pierre, M.; Janin, A.; Deliniere, A.; Bessière, F.; Meli, A.C.; Charrabi, A.; Lafont, E.; et al. Deciphering DSC2 Arrhythmogenic Cardiomyopathy Electrical Instability: From Ion Channels to ECG and Tailored Drug Therapy. Clin. Transl. Med. 2021, 11, e319.
- 70. Reisqs, J.; Moreau, A.; Charrabi, A.; Sleiman, Y.; Meli, A.C.; Millat, G.; Briand, V.; Beauverger, P.; Richard, S.; Chevalier, P. The PPARy Pathway Determines Electrophysiological Remodelling and Arrhythmia Risks in DSC2 Arrhythmogenic Cardiomyopathy. Clin. Transl. Med. 2022, 12, e748.
- Gehmlich, K.; Syrris, P.; Peskett, E.; Evans, A.; Ehler, E.; Asimaki, A.; Anastasakis, A.; Tsatsopoulou, A.; Vouliotis, A.-I.; Stefanadis, C.; et al. Mechanistic Insights into Arrhythmogenic Right Ventricular Cardiomyopathy Caused by Desmocollin-2 Mutations. Cardiovasc. Res. 2011, 90, 77–87.
- Heuser, A.; Plovie, E.R.; Ellinor, P.T.; Grossmann, K.S.; Shin, J.T.; Wichter, T.; Basson, C.T.; Lerman, B.B.; Sasse-Klaassen, S.; Thierfelder, L.; et al. Mutant Desmocollin-2 Causes Arrhythmogenic Right Ventricular Cardiomyopathy. Am. J. Hum. Genet. 2006, 79, 1081–1088.
- Gerull, B.; Kirchner, F.; Chong, J.X.; Tagoe, J.; Chandrasekharan, K.; Strohm, O.; Waggoner, D.; Ober, C.; Duff, H.J. Homozygous Founder Mutation in Desmocollin-2 (DSC2) Causes Arrhythmogenic Cardiomyopathy in the Hutterite Population. Circ. Cardiovasc. Genet. 2013, 6, 327–336.

- 74. Brodehl, A.; Weiss, J.; Debus, J.D.; Stanasiuk, C.; Klauke, B.; Deutsch, M.A.; Fox, H.; Bax, J.; Ebbinghaus, H.; Gärtner, A.; et al. A Homozygous DSC2 Deletion Associated with Arrhythmogenic Cardiomyopathy Is Caused by Uniparental Isodisomy. J. Mol. Cell. Cardiol. 2020, 141, 17–29.
- Simpson, M.A.; Mansour, S.; Ahnood, D.; Kalidas, K.; Patton, M.A.; McKenna, W.J.; Behr, E.R.; Crosby, A.H. Homozygous Mutation of Desmocollin-2 in Arrhythmogenic Right Ventricular Cardiomyopathy with Mild Palmoplantar Keratoderma and Woolly Hair. Cardiology 2009, 113, 28– 34.
- 76. Hamada, Y.; Yamamoto, T.; Nakamura, Y.; Sufu-Shimizu, Y.; Nanno, T.; Fukuda, M.; Ono, M.; Oda, T.; Okuda, S.; Ueyama, T.; et al. G790del Mutation in DSC2 Alone Is Insufficient to Develop the Pathogenesis of ARVC in a Mouse Model. Biochem. Biophys. Rep. 2020, 21, 100711.
- 77. Gehmlich, K.; Lambiase, P.D.; Asimaki, A.; Ciaccio, E.J.; Ehler, E.; Syrris, P.; Saffitz, J.E.; McKenna, W.J. A Novel Desmocollin-2 Mutation Reveals Insights into the Molecular Link between Desmosomes and Gap Junctions. Heart Rhythm 2011, 8, 711–718.
- 78. De Bortoli, M.; Beffagna, G.; Bauce, B.; Lorenzon, A.; Smaniotto, G.; Rigato, I.; Calore, M.; Li Mura, I.E.A.; Basso, C.; Thiene, G.; et al. The p.A897KfsX4 Frameshift Variation in Desmocollin-2 Is Not a Causative Mutation in Arrhythmogenic Right Ventricular Cardiomyopathy. Eur. J. Hum. Genet. 2010, 18, 776–782.
- 79. Rimpler, U. Funktionelle Charakterisierung von Desmocollin 2 Während Der Embryonalentwicklung und im Adulten Herzen in Der Maus. Ph.D. Thesis, Humboldt-Universität zu Berlin, Berlin, Germany, 2014.
- Brodehl, A.; Belke, D.D.; Garnett, L.; Martens, K.; Abdelfatah, N.; Rodriguez, M.; Diao, C.; Chen, Y.-X.; Gordon, P.M.K.; Nygren, A.; et al. Transgenic Mice Overexpressing Desmocollin-2 (DSC2) Develop Cardiomyopathy Associated with Myocardial Inflammation and Fibrotic Remodeling. PLoS ONE 2017, 12, e0174019.

Retrieved from https://encyclopedia.pub/entry/history/show/72222