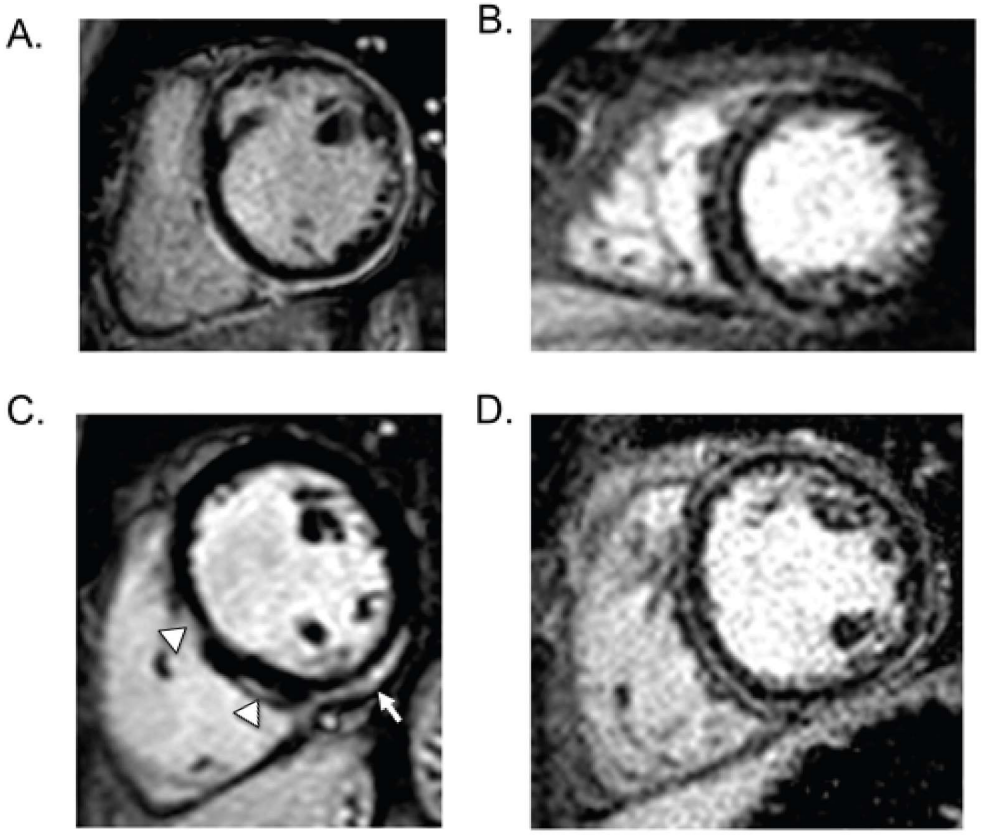
Desmoplakin Cardiomyopathy, a Fibrotic and Inflammatory Form of Cardiomyopathy Distinct from Typical Dilated or Arrhythmogenic Right Ventricular Cardiomyopathy

Supplemental Data

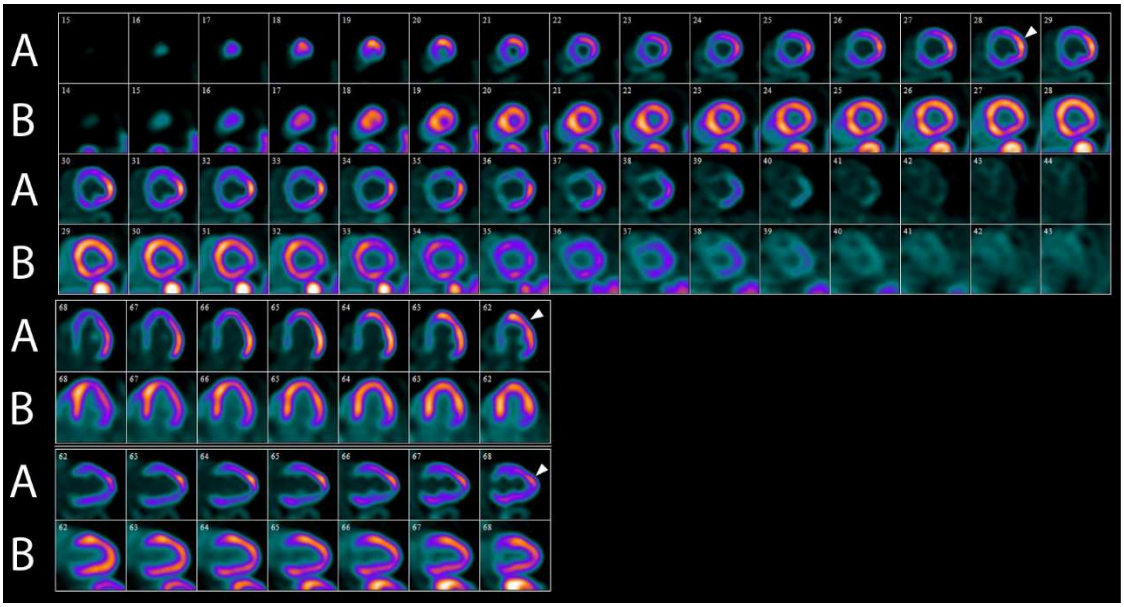
(For publication as online data supplement)

Supplemental Methods for Definition of Ventricular Involvement Subgroups:

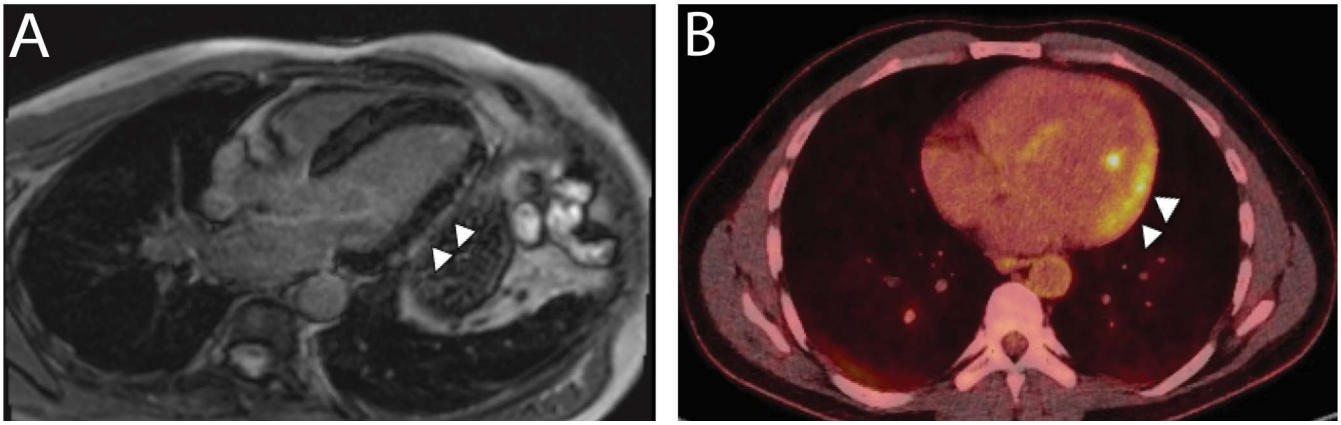
1. Normal ventricular function: defined as normal left ventricle (LV) and right ventricle (RV) size and function (LV/RV ejection fraction (EF) ≥ 50% and 45% respectively, by TTE or MRI) and absence of late gadolinium enhancement (LGE) when available.
2. Left ventricular predominant: defined as LV EF < 50% by TTE or MRI and LV EF < RV EF, or presence of LV LGE and no evidence of RV dysfunction or RV wall motionabnormalities (WMA) on MRI.
3. Right ventricular predominant: defined as RV EF ≤45% on MRI, plus RV EF < LV EF, or RV dilation on TTE or MRI using the ARVC task force criteria.



Supplemental Figure 1. Myocardial Fibrosis Patterns in *DSP* Cardiomyopathy. Late gadolinium enhanced (LGE) cardiac magnetic resonance images in the short axis plane at the mid-ventricular level are shown for four representative cases. All blinded expert-reviewed cases (N=10) exhibited non-ischemic pattern of primarily subepicardial fibrosis at the mid-ventricular level. Circumferential fibrosis was present in 2 of 10 (A, D). Inferior (arrow, C) and inferoseptal (arrowheads, C) segments were involved in all cases. Septal LGE extended on the RV surface of the septum in 7 of 10 cases (e.g. A, C) and through the mid-myocardium of the septum in 3 of 10 cases (e.g. B, D). The left ventricular ejection fractions in the cases shown here were 34% (A), 47% (B), 48% (C), and 42% (D).



Supplemental Figure 2. Acute Myocardial Inflammation in a *DSP* Cardiomyopathy Initially Diagnosed with Cardiac Sarcoidosis. Images were obtained from a 56-year-old woman with a history of frequent premature ventricular contractions, non-ischemic cardiomyopathy, chest pain, and refractory ventricular tachycardia (VT). Due to refractory VT, evaluation with cardiac ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) (A rows, long and short axis views) was obtained to evaluate for possible cardiac sarcoidosis. FDG-PET demonstrated areas of inflammation (arrow heads) detected by FDG uptake. Corollary views from rubidium PET perfusion imaging (B rows) reveals normal coronary perfusion. Based on the clinical presentation and FDG-PET evidence of acute inflammation, this patient was initially diagnosed with acute cardiac sarcoidosis and treated with prednisone, leflunomide, and methotrexate. Repeat FDG-PET after 1.5 years of immunosuppressive therapy demonstrated ongoing inflammation and anti-inflammatory therapy was minimized to low dose prednisone due to perceived lack of benefit. After the patient's nephew suddenly died at the age of 29 further evaluation for a familial cardiomyopathy was recommended and the patient was found to have a pathogenic nonsense mutation in DSP (c.1762C>T, p.Gln588*). This patient also exhibited reduced LV systolic function with an LVEF of 34%.



Supplemental Figure 3: Myocardial inflammation in *DSP* cardiomyopathy corresponds to myocardial fibrosis
Images were obtained from a 42 year old man with a DSP truncating mutation (c.5460_5472del; p.Val1821Thrfs*12) and ejection fraction of 45%. Cardiac magnetic resonance imaging (MRI) showed delayed enhancement in the septum and lateral wall (Panel A, indicated by arrows). 18F-fluorodeoxyglucose positron emission tomography also revealed uptake in the septum and lateral wall in corresponding to areas of delayed enhancement on MRI (Panel B, indicated by arrows).

Literature Reported Pathogenic Missense Variants									
Nucleotide Location	cDNA Mutation Designation	Amino Acid Mutation Designation	Consequence	Protein Domain	Gnomad Total Allele Count	Gnomad Frequency	Total Cases	# out of 100 mammals that match	References
61	c.61G>A	p.Glu21Lys	Missense	N-terminal	3	1.36E-05	1	50/100	Castelletti 2017[1]
325	c.325G>A	p.Glu109Lys	Missense	N-terminal	0	0	1	90/100	Castelletti 2017[1]
593	c.593A>C	p.Gln198Pro	Missense	N-terminal	0	0	1	82/100	Ohno 2013[2] Wada 2017[3]
616	c.616G>A	p.Ala206Thr	Missense	N-terminal	1	4.06E-06	1	40/100	Sato 2015[4]
621	c.621G>T	p.Trp207Cys	Missense	N-terminal	0	0	1	96/100	Bao 2013[5]
868	c.868G>A	p.Glu290Lys	Missense	N-Terminal	0	0	1	99/100	Castelletti 2017[1]
897	c.897C>G	p.Ser299Arg	Missense	N-terminal	0	0	27*	85/100	Rampazzo 2002[6] Bauce 2005[7] Asimaki 2009[8] Rigato 2013[9]
1124	c.1124A>T	Asn375Ile	Missense	N-terminal	0	0	1	91/100	Bauce 2011[10] Rigato 2013[9]
1203	c.1203G>T	p.Leu401Asn	Missense	N-terminal	0	0	2	98/100	Ohno 2013[2] Wada 2017[3]
1264	c.1264G>A	p.Glu422Lys	Missense	N-terminal	0	0	4*	100/100	Tan 2010[11] te Riele 2013[12] Bhonsale 2015[13] Groeneweg 2015[14]
1325	c.1325C>T	p.Ser442Phe	Missense	N-terminal	0	0	2	98/100	Castelletti 2017[1] Quarta 2011[15]
1333	c.1333A>G	p.Ile445Val	Missense	N-terminal	0	0	5*	99/100	Sen-Chowdry 2008[16] Den Haan 2009[17] Tan 2010[11] Bohnsale 2015[13] Groeneweg 2015[14]
1372	c.1372A>T	p.Asn458Tyr	Missense	N-terminal	2	7.96E-06	3	74/100	Bauce 2011[10] Rigato 2013[9]
1408	c.1408A>G	p.Lys470Glu	Missense	N-terminal	0	0	2	100/100	Rigato 2013[9]
1493	c.1493C>T	p.Pro498Leu	Missense	N-terminal	4	1.59E-05	5	99/100	Jan 2015[18]
1520	c.1520C>T	p.Ser507Phe	Missense	N-terminal	0	0	4	100/100	Sen Chowdry 2008[16] Quarta 2011[15] Castelletti 2017[1]
1544	c.1544C>T	p.Pro515Leu	Missense	N-terminal	0	0	1	99/100	Gigli 2019[19]
1678	c.1678A>T	p.Ile560Phe	Missense	N-terminal	0	0	3	99/100	Finsterer 2016[20]
1691	c.1691C>T	p.Thr564Ile	Missense	N-terminal	0	0	2	98/100	Keller 2012[21]
1748	c.1748T>C	p.Leu583Pro	Missense	N-terminal	0	0	1	98/100	Keller 2012[21]
1790	c.1790C>T	p.Ser597Leu	Missense	N-terminal	0	0	3	99/100	Chalabreysse 2011[22]
1816	c.1816C>T	p.Arg606Trp	Missense	N-terminal	6	2.39E-05	1	85/100	Gigli 2019[19]
1824		p.Ile608_609 ins30	Missense	N-terminal	0	0	1	95/100	Norgett 2006[23]
1865	c.1865T>C	p.Leu622Pro	Missense	N-terminal	0	0	1	99/100	Bitar 2016[24]
1982	c.1982A>T	p.Asn661Ile	Missense	N-terminal	0	0	1	53/100	Cox 2011[25]
3532	c.3532C>G	p.Leu1178Val	Missense	Rod	0	0	1	97/100	Castelletti 2017[1] Quarta 2010[15]
3550	c.3550C>T	p.Arg1184Trp	Missense	Rod	4	1.63E-05	7	95/100	Xue 2019[26]

3764	c.3764G>A	p.Arg1255Lys	Missense	Rod	6	2.44E-05	4	95/100	Bauce 2005[7] Rigato 2013 [9]
3774	c.3774C>A	p.Asp1258Glu	Missense	Rod	4	1.60E-05	2	84/100	Rigato 2013[9]
4043	c.4043T>G	p.Leu1348Arg	Missense	Rod	4	1.60E-06	1	92/100	Bao 2013[5]
4604	c.4604T>C	p.Leu1535Pro	Missense	Rod	1	4.08E-06		88/100	Castelletti 2017[1]
4803	c.4803G>A	p.Met1601Ile	Missense	Rod	0	0	1	83/100	Bauce 2011[10]
4915	c.4915G>A	p.Val1639Met	Missense	Rod	10	3.99E-05	1	73/100	Sato 2015[4]
4961	c.4961T>C	p.Leu1654Pro	Missense	Rod	7	2.85E-05	7	82/100	Bauce 2011[10] Rigato 2013[9]
4973	c.4973C>T	p.Ser1658Phe	Missense	Rod	1	3.99E-06	1	41/100	Rigato 2013[9]
6166	c.6166C>G	p.Gly2056Arg	Missense	Rod	1	3.99E-06	1	100/100	Christensen 2010[27]
6505	c.6505C>G	p.Gln2169Glu	Missense	C-terminal	0	0	1	67/100	Wada 2017[3]
6577	c.6577G>A	p.Glu2193Lys	Missense	C-Terminal	0	0	1	93/100	Yesudian 2014[28]
7039	c.7039V>G	p.Ile2347Val	Missense	C-terminal	3	1.19E-05	1	88/100	Rigato 2013[9]
7096	c.7096C>T	p.Arg2366Cys	Missense	C-terminal	0	0	2	98/100	Peter 2018[29]
7097	c.7097G>A	p.Arg2366His	Missense	C-terminal	1	4.06E-06	5	98/100	Al-Owain 2011[30]
7111	c.7111C>A	p.Gln2371Lys	Missense	C-terminal	0	0	2	99/100	Molho-Pressach 2015[31]
7402	c.7402G>C	p.Gly2375Arg	Missense	C-terminal	1	3.23E-05	1	99/100	Alcalai 2003[32]
7430	c.7430_7433delTGTC	p.Met2477fs8aa*	Missense	C-terminal	0	0	2	100/100	Gigli 2019[19]
7516	c.7516G>A	p.Arg2339Gln	Missense	C-terminal	0	0	1	100/100	Yu 2008[33]
7623	c.7623G>T	p.Arg2541Ser	Missense	C-terminal	0	0	1	74/100	Bao 2013[5]
8050	c.8050A>G	p.Met2684Val	Missense	C-terminal	3	1.22E-05	1	100/100	Castelletti 2017[1]
8066	c.8066A>C	p.Lys2689Thr	Missense	C-terminal	0	0	1	98/100	Bao 2013[5]
8134	c.8134G>A	p.Ala2712Thr	Missense	C-terminal	1	4.06E-06	1	100/100	Elliott 2010[34]
8269	c.8269G>C	p.Asp2757His	Missense	C-terminal	0	0	1	99/100	Ohno 2013[2]
8501	c.8501G>A	p.Arg2834His	Missense	C-terminal	0	0	1	94/100	Yang 2006[35]
Possibly Non-Pathogenic Missense Variants Reported in Literature									
88	c.88G>A	p.Val30Met	Missense	N-terminal	352	1.51E-03	11*	16/100	Yang 2006[35] Rasmussen 2013[36] Rigato 2013[9] Haas 2015[37]
269	c.269A>G	p.Gln90Arg	Missense	N-terminal	182	6.58E-04	1	100/100	Yang 2006[35]
2360	c.2360A>G	p.Tyr787Cys	Missense	N-terminal	31	1.12E-04	2	72/100	Ohno 2013[2] Wada 2017[3]
2422	c.2422C>T	p.Arg808Cys	Missense	N-terminal	77	2.70E-04	1	100/100	Haas 2015[37]
2723	c.2723G>A	p.Arg908His	Missense	N-terminal	302	1.00E-03	1	88/100	Haas 2015[37]
2815	c.2815G>A	p.Gly939Ser	Missense	N-terminal	1019	3.68E-03	1	83/100	Fressart 2010[38]
3862	c.3862A>C	p.Lys1288Gln	Missense	Rod	71	2.52E-04	1	81/100	Bao 2013[5]
4117	c.4117A>G	p.Thr1373Ala	Missense	Rod	17	6.78E-05	1	84/100	Haas 2015[37]
4372	c.4372C>G	p.Arg1458Gly	Missense	Rod	468	0.0016	1	72/100	Haas 2015[37]
4741	c.4741A>G	p.Leu1581Gly	Missense	Rod	54	2.20E-04	2	70/100	Ohno 2013[2] Wada 2017[3]
4775	c.4775A>G	p.Lys1592Arg	Missense	Rod	65	0.00023	1	96/100	Bohnsale 2015[13]
5324	c.5324G>T	p.Arg1775Ile	Missense	Rod	17	6.14E-05	4	68/100	Bauce 2005[7]
5498	c.5498A>T	p.Glu1833Val	Missense	Rod	2698	0.0095	1	97/100	Haas 2015[37]

6307	c.6307A>G	p.Lys2103Glu	Missense	C-terminal	37	1.31E-04	1	98/100	Gigli 2019[19]
6881	C.6881C>G	p.Ala2295Gly	Missense	C-terminal	221	0.00078	2	99/100	Garcia-Pavia 2011[39] Haas 2015[37]
7916	c.7916G>A	p.Arg2639Gln	Missense	C-terminal	236	8.53E-04	1	100/100	Sato 2015[4]
8455	c.8455A>C	p.Met2819Leu	Missense	C-terminal	526	1.91E-03	2	47/100	Ohno 2013[2] Wada 2017[3]
Literature Reported Pathogenic Truncating Mutations									
151	c.151C>T	p.Gln51*	Truncating	N-terminal	0	0	3*		te Riele 2013[12] Bohnsale 2015[13] Groeneweg 2015[14]
243	c.243_251delCTTGATGCG	p.Cys81*	Truncating	N-terminal		0	29		Singh 2018[40]
423	c.423-1G>A	NA	Truncating	N-Terminal	0	0	6*		Bauce 2005[7] Rigato 2013[9]
478	c.478C>T	p.Arg160*	Truncating	N-Terminal/ Rod	0	0	3*		te Riele 2013[12] Bohnsale 2015[13] Groeneweg 2015[14]
538	c.538G>A	p.Trp180*	Truncating	N-terminal	0	0	1		Protonotarios 2016[41]
699	c.699G>A	p.Trp233*	Truncating	N-terminal	0	0	1		Yang 2006[35]
808	c.808C>T	p.Arg270*	Truncating	N-terminal	0	0	3		Protonotarios 2016[41]
817	c.817C>T	p.Gln273*	Truncating	N-terminal		0	4		Rigato 2013[9]
818	c.818dupA	p.Asn274Glufs*15	Truncating	N-terminal	0	0	1		Castelletti 2017[1]
818	c.818_819insA	p.Glu274fs*288	Truncating	N-terminal	0	0	1		Quatra 2011[15]
867	c.867C>A	p.Cys298*	Truncating	N-terminal	0	0	2		Adler 2015[42]
928	c.928dupG	p.Glu310Glyfs*13	Truncating	N-terminal	0	0	1		Castelletti 2017[1]
939	c. 939+1 G>A	NA	Truncating	N-terminal	1	3.19E-05	4*		Whittock 1999[43] Sen-Chowdry 2008[16] Christensen 2010[27] Haas 2015[37]
940	c.940_946dup ATACGCA	p.Met316Asnfs*9	Truncating	N-terminal	0	0	1		Castelletti 2017[1]
946	c.946_947ins ATACGCA	p.Asn316fs*324	Truncating	N-terminal	0	0	1		Quatra 2011[15]
969	c.969_974del AAAAGA	p.Lys324_Glu325del	Truncating	N-terminal	0	0	5		Rasmussen 2013[36]
991	c.991C>T	p.Gln331*	Truncating	N-terminal	0	0	26		Armstrong 1999[44] Protonotarios 2016[41]
1218	c.1218+1G>A	NA	Splice	N-terminal	0	0	1		Asimaki 2009[8]
1339	c.1339C>T	p.Gln447*	Truncating	N-terminal	0	0	18		Lopez-Ayala 2014[45]
1755	c.1755dupA	p.His586Thrfs*9	Truncating	N-terminal	0	0	15*		Norman 2005[46] Sen-Chowdry 2008[16] Quatra 2011[15] Castelletti 2017[1]
1873	c.1873C>T	p.Gln625*	Truncating	N-terminal	0	0	2		Quarta 2011[15] Castelletti 2017[1]
1891	c.1891C>T	p.Gln631*	Truncating	N-terminal	0	0	1		Gigli 2019[19]

2130	c.2130+1G>C	NA	Truncating	N-terminal	0	0	1		Elliot 2010[34]
2131	c.2131-1G>A	Splicing defect	Truncating	N-terminal	0	0	3*		Quatra 2011[15] Haas 2015[37] Castelletti 2017[1]
2390	c.2390_2393delTCTG	p.Val797Alafs*14	Truncating	N-terminal	0	0	1		Gigli 2019[19]
2765	c.2765_2766delCA	p.Thr922Serfs*7	Truncating	N-terminal	0	0	2*		Elliot 2010[34] Castelletti 2017[1]
2821	c.2821C>T	p.Arg941*	Truncating	N-terminal	0	0	2		Quarta 2011[15] Castelletti 2017[1]
2874	c.2874del5	p.Lys959Metfs*5	Truncating	N-terminal	0	0	1		Bolling 2010[47]
2878	c.2878-1G>A	Splicing defect	Truncating	N-terminal	0	0	1		Castelletti 2017[1]
2975	c.2975C>T	p.Gln986*	Truncating	N-terminal	0	0	4		Campuzano 2013[48]
3045	c.3045delG	p.Ser1015fs*1017	Truncating	N-terminal	0	0	7*		Sen Chowdry 2008[16] Coats 2009[49] Quatra 2011[15] Castelletti 2017[1]
3133	c.3133C>T	p.Arg1045*	Truncating	N-terminal	0	0	1		Castelletti 2017[1]
3153	c.3153del5	NA	Truncating	N-terminal	1	0	2		Bolling 2010[47]
3160	c.3160_3169delAAGAACAA	p.Lys1052fs*26	Truncating	N-terminal	0	0	2		Bohnsale 2015[13] Groeneweg 2015[14]
3203	c.3203_3204delAG	p.Glu1068Valfs*19	Truncating	N-terminal	0	0	2		Rigato 2013[9]
3316	c.3316G>T	p.Glu1106*	Truncating	N-terminal	0	0	1		Haas 2015[37]
3337	c.3337C>T	p.Arg1113*	Truncating	Rod	0	0	10*		Sen-Chowdry 2008[16] Asimaki 2009[8] Rigato 2013[9] Quatra 2011[15] Cox 2011[25] Bohnsale 2015[13] Groeneweg 2015[14] Haas 2015[37] Castelletti 2017[1]
3415	c.3415_3417del TATinsG	p.Tyr1139Glyfs*10	Truncating	Rod	0	0	1		Reichl 2018[50]
3535	c.3535C>T	p.Gln1179*	Truncating	Rod	0	0	1		Castelletti 2017[1]
3784	c.3784C>T	p.Gln1262*	Truncating	Rod	0	0	2		Gigli 2019[19]
3801	c.3799C>T	p.Arg1267*	Truncating	Rod	0	0	1		Uzumcu 2006[51]
3805	c.3805C>T	p.Arg1269*	Truncating	Rod	1	4.07E-06	3		Rasmussen 2013[36]
3901	c.3901C>T	p.Gly1301*	Truncating	Rod	0	0	1		Krishnamurthy 2011[52]
3924	c.3924delG	p.His1309Thrfs*1348	Truncating	Rod	0	0	1		Molho-Pressach 2015[31]
3995	c.3995_3996del insAATCGA	p.Ala1332Glufs*15	Truncating	Rod	0	0	1		Fressart 2010[38]
4009	c.4009_4011delAGG	p.Glu1337del	Truncating	Rod	0	0	1		Protonotarios 2016[41]
4025	c.4025G>A	p.Trp1342*	Truncating	Rod	0	0	1		Haas 2015[37]
4198	c.4198C>T	p.Arg1400*	Truncating	Rod	1	4.06E-06	4		Bao 2013[5] Wada 2017[3]

4395	C.4395T>G	p.Tyr1465*	Truncating	Rod	0	0	2		Groeneweg 2015[14]
4457	c.4457T>A	p.Leu1486*	Truncating	Rod	0	0	1		Protonotarios 2016[41]
4477	c.4477G>T	p.Glu1493*	Truncating	Rod	0	0	1		Castelletti 2017[1]
4536	c.4536T>A	p.Tyr1512*	Truncating	Rod	0	0	1		Haas 2015[37]
4650	c.4650_4651delTG	p.Val155Glufs*75	Truncating	Rod		0	2		Ramoglu 2017[53] Sakamoto 2019[54]
5164	c.5164G>T	p.Glu1722*	Truncating	Rod	0	0	1		Haas 2015[37]
5208	c.5208_5209delAG	p.Gly1737fs*5	Truncating	Rod	0	0	2		Williams 2011[55]
5212	c.5212C>T	p.Arg1738*	Truncating	Rod	0	0	2		Bohnsale 2015[13] Groeneweg 2015[14]
5419	c.5419C>T	p.Gln1807*	Truncating	Rod	0	0	2		Groeneweg 2015[14]
5472	c.5472delA	p.Asp1825Thrfs*12	Truncating	Rod	0	0	2		Protonotarios 2019[56]
5596	c.5596C>T	p.Gln1866*	Truncating	Rod			4		Navarro-Manchon 2011[57]
5800	c.5800C>T	p.Arg1934*	Truncating	C-terminal	0	0	1		Fressart 2010[38] Gigli 2019[19]
5999	c.5999_6000delinsG	p.Ser2000Trpfs*33	Truncating	C-terminal	0	0	1		Fressart 2010[38]
6393	c.6393delA	p.Gly2122Valfs*2	Truncating	C-terminal	0	0	1		Gigli 2019[19]
6478	c.6478C>T	p.Arg2160*	Truncating	C-terminal	1	3.98E-06	5*		te Riele 2013[12] Bohnsale 2015[13] Groeneweg 2015[14] Gigli 2019[19]
6496	c.6496C>T	p.Arg2166*	Truncating	C-terminal	2	7.95E-06	1		Bohnsale 2015[13] Groeneweg 2015[14]
6850	c.6850C>T	p.Arg2284*	Truncating	C-terminal	0	0	1		Fressart 2010[38]
7217	c.7217C>G	p.Ser2406*	Truncating	C-terminal	0	0	1		Protonotarios 2016[41]
7567	c.7567delAAGA	p.Lys2523Glnfs*37	Truncating	C-terminal	0	0	1		Yesudian 2014[28]
7622	c.7622delG	p.Arg2541Lys	Truncating	C-terminal	5	1.77E-05	3*		Rigato 2013[9]
7780	c.7780delT	p.Ser2594Profs*8	Truncating	C-terminal	0	0	1		Rasmussen 2013[36]
7891	c.7891dupG	p.Ile2631Asnfs*13	Truncating	C-terminal	0	0	1		Gigli 2019[19]
7901	c.7901delG		Truncating	C-terminal	0	0	12		Norgett 2000[58]
7999	c.7999C>T	p.Gln2667*	Truncating	C-terminal	0	0	1		Fressart 2010[38]
8077	c.8077_8080del AAAG	p.Lys2693Profs*3	Truncating	C-terminal	0	0	1		Castelletti 2017[1]
8188	c.8188delC	p.Gln2730Serfs*16	Truncating	C-terminal	0	0	1		Castelletti 2017[1]
8195	c.8195_8195dupTC	p.Thr2733Serfs*14	Truncating	C-terminal	0	0	1		Castelletti 2017[1]
8290	c.8290_8291ins TGCT	p.Ala2765fs*2787	Truncating	C-terminal	0	0	1		Garcia-Pavia 2011[39]
Literature Reported Common Truncating Variants									
273	c.273+5G>A	NA	Splice	N-terminal	79	2.81E-04	3		Rigato 2013[9]
Literature Reported Compound Heterozygote Mutations									
88	c.88G>A c.7622G>A	p.Val30Met p.Arg2541Lys	Missense	N-terminal	352/5	1.51E03/ 1.77E-05	1		Bauce 2010[59]

478	c.478C>T c.3630T>A	p.Arg160* p.Thr1210*	Truncating	N-terminal	0	0	1		Bari 2018[60]
1990	C.1990C>T c.7096C>T	p.Gln664* Arg2366Cys	Truncating/ Missense	N-terminal/ C-terminal	0	0/0	1		Whittock 2002[61]
2019		p.Gln673* Gln1446*	Truncating	N-terminal/ Rod	0	0/0	2		Asimaki 2009[62]
2427	c.2427T>A c.861T>G	p.Cys809* Asn287Lys	Truncating/ Missense	N-terminal	0	0/0	1		Whittock 2002[61]
2516	c.2516del4 c.3971del4		Truncating	N-terminal	0	0/0	1		Tanaka 2009[63]
3564	c.3564T>A c.4395T>A	p.Tyr1188* p.Tyr1465*	Truncating	Rod	0	0/0	1		Tekin 2017[64]
4198	c.4198C>T c.6850C>T	p.Arg1400* p.Arg2284*	Truncating	Rod/ C-terminal	0	0/0	1		Antonov 2015[65]
4778	c.4778- 4790del13 c.6310delA	p.Lys1593Serf s*5 p.Thr2104Glnf s*12	Truncating	Rod	0/ 13	0/ 0.000052	1		Vahlquist 2014[66]
5800	c.5800C>T c.6370delT T	p.Arg1934*	Truncating	C-terminal	0	0/0	1		Jonkman 2005[67]
6496	c.6496C>T c.6610C>T	p.Arg2166* p.Gly2204*	Truncating	C-terminal	2	7.954E- 06	2		Kim 2017[68]
6968	c.6968T>C c.7123G>C	p.Leu2329Pro p.Gly2375Arg	Missense	C-terminal	0	0/0	2		Yermakovich 2018[69]
7096	c.7096C>T c.6721del	p.Arg2366Cys p.Ile2241Phef s*3	Missense/ Truncating	C-terminal	0/0	0/0	1		Peter 2018[29]
7964	c.7964C>A c.6310delA	p.Ala2655Asp PTC	PTC	C-terminal/ Rod	0/ 13	0/ 0.000052	1		Mahoney 2010[70]

Supplemental Table 1: Previously reported desmoplakin genetic variants from literature review

cDNA Mutation Designation	Amino Acid Mutation Designation	Consequence	Total Case Number	Total Proband Number	gNomad Frequency
c.1_8616del	p.Met1_*2872del	Truncating	1	1	0
c.268C>T	p.Q90*	Truncating	4	1	0
c.273+5G>A	NA	Truncating	4	2	0
c.478C>T	p.Arg160*	Truncating	11	4	0
c.479C>T	p.Arg160*	Truncating	2	1	0
c.491_492delins15	p.Ala164fs*23	Truncating	1	1	0
c.534_535insA	p.Gly179Argfs*4	Truncating	1	1	0
NA	p.Gln216Pro	Missense	3	1	0
c.699G>A	p.Trp233*	Truncating	1	1	0
c.712_713insA	p.Ile238fs*19	Truncating	1	0	0
c.939+1G>A	NA	Truncating	4	3	1
c.1146delT	p.Phe382fs*11	Truncating	9	2	0
c.1615C>T	p.Gln539*	Truncating	1	1	0
c.1751delA	p.Glu584Glyfs*52	Truncating	2	1	0
c.1762C>T	p.Gln588*	Truncating	3	1	0
NA	p.Glu671Serfs*9	Truncating	3	1	0
c.2547T>A	p.Tyr849*	Truncating	1	0	0
c.2593_2594dupGA	NA	Truncating	1	1	0
c.3160_3169delAAGAACAAAT	p.Lys1054fs*26	Truncating	7	1	0
C.3195C>G	p.Tyr1065*	Truncating	2	1	0
c.3474_3475insA	p.Glu1159Argfs*3	Truncating	9	1	0
c.3526delG	p.Val1176Phefs*20	Truncating	2	2	0
c.3630T>A	p.Tyr1210*	Truncating	4	1	0
c.3735_3741dupAAATCGA	p.Asp1248Lysfs*7	Truncating	1	1	1
NA	p.Gln1453Serfs*13	Truncating	2	1	0
c.4372C>T	p.Arg1458*	Truncating	1	1	1
c.4531C>T	p.Gln1511*	Truncating	7	2	5
c.4822C>T	p.Gln1608*	Truncating	2	1	0
c.4824dupA	p.Ala1609fs	Truncating	3	1	0
c.5851C>T	p.Arg1951*	Truncating	1	1	0
c.6398dupG	p.val2134cysfs*22	Truncating	2	1	0
c.6758delT	p.F2253Sfs*8	Truncating	1	1	0
c.6850C>T	p.Arg2284*	Truncating	1	1	0
c.7780dupT	NA	Truncating	2	1	0
c.8173del	p.Arg2725Alafs*21	Truncating	1	1	0
c.8384_8385insTAGA	p.Glu2795Aspfs	Truncating	1	1	0
Exon 21&24 del	NA	Truncating	1	1	0

Supplemental Table 2: Desmoplakin mutations present in study

cDNA Mutation Designation	Amino Acid Mutation Designation	Consequence	Total Case Number	Total Proband Number	gNomad Frequency
c.148_151delACAG	Thr50Serfs*61	Truncating	7	1	0
c.235C>T	p.Arg79*	Truncating	7	2	1
c.337-2A>T	Splice	Truncating	9	1	0
c368G>A	Trp123*	Truncating	1	1	0
c.489_513delCAGCGAT TACCAGTACAGCCAGAGA	His163Glnfs*19	Truncating	1	1	0
c.623delC	Thr208Lysfs*55	Truncating	1	0	0
c.772A>T	p.Lys258*	Truncating	1	1	0
c.951delG	p.His318Thrfs*2	Truncating	2	0	0
c.1034+1G>T	Splice	Truncating	2	1	0
c.1170+2T>A	Splice	Truncating	2	1	0
c.1211dup	p.Val406Serfs*4	Truncating	5	2	0
c.1237C>T	p.Arg413*	Truncating	1	0	4
c.1252delG	Ala418Profs*2	Truncating	1	0	0
c.1378+2T>A	Splice	Truncating	1	0	1
c.1613G>A	p.Trp538*	Truncating	1	1	4
c.1643delG	p.Gly548Valfs*15	Truncating	2	0	0
c.1912C>T	p.Gln638*	Truncating	1	1	2
c.1952_1955dupGAAG	p.Ser652Argfs*92	Truncating	3	1	0
c.2119C>T	p.Gln707*	Truncating	1	1	0
c.2146-1G>C	Splice	Truncating	14	4	9
c.2197_2202delinsG	p.His733Alafs*8	Truncating	3	2	6
c.2203C>T	p.Arg735*	Truncating	2	1	1
c.2489+1G>A	Splice	Truncating	8	4	8
c.2509delA	p.Ser837Valfs*94	Truncating	2	2	0
Deletion of exons 6-7	NA	Truncating	1	0	0
Deletion exons 5-7	NA	Truncating	1	1	0
Unknown deletion	NA	NA	1	0	NA

Supplemental Table 3: Plakophilin 2 mutations present in study

	Normal Ventricular Function (N=47)	Predominant RV involvement (N=32)	p-value
Female	45%	62%	0.17
Age at Evaluation (in years)	40 ± 22	36 ± 18	0.35
Palmoplantar Keratoderma and/or Curly Hair	4% (1/23)	0% (0/23)	1.0
Proband	**28%**	**66%**	**0.001**
LV Enlargement	**4.3%**	**25%**	**0.012**
LV Systolic Dysfunction	**0%**	16%	**0.009**
LVEF (%)	**62 ± 5**	**55 ± 10**	**0.001**
RV Systolic Dysfunction	**0%**	**84%**	**<0.001**
RV Focal WMA	**0% (0/24)**	**59% (16/27)**	**<0.001**
ECG T wave inversions (V1-2)	11% (5/45)	16% (5/31)	0.73
ECG T wave inversions (V1-3)	**27% (12/45)**	**84% (26/31)**	**<0.001**
ECG T wave inversions (V4-6)	11% (5/45)	39% (12/31)	<0.001
Frequent PVCs (>500/24h)	**40% (8/20)**	**83% (15/18)**	**0.009**
LV LGE	0% (0/25)	19% (5/26)	0.05
RVEDV (mL) (MRI)	**164 ± 39 (n=19)**	**207 ± 70 (n=27)**	**0.020**
LVEDV (mL) (MRI)	149 ± 32 (n=19)	160 ± 69 (n=26)	0.49
ARVC Task Force Diagnosis			<0.001
Possible	**55%** **p=0.001**	**9%** **p=0.001**	
Borderline	17% p=0.9	9% p=0.9	
Definite	**28%** **p=<0.001**	**67%** **p=<0.001**	
VT Outcome	**15%**	**53%**	**<0.001**

Supplemental Table 4. *PKP2* Cohort Clinical Characteristics Stratified by Ventricular Predominance Subgroup

LV: Left ventricle, LVEF: Left ventricle ejection fraction, RV: Right Ventricle, WMA: Wall motion abnormality, PVC: Premature ventricular contraction, LGE: Late gadolinium enhancement, EDV: End diastolic volume, MRI: Magnetic resonance imaging, VT: Ventricular tachycardia.

Gender	Male, n=33	Female, n=74	p-value
Age at evaluation	36.7 ± 17	35.6 ± 15	0.75
Proband	42%	41%	1
Hair/Skin Changes	55% (17/31)	55% (37/67)	1
Chest Pain	18%	22%	0.79
Troponin Elevation	12%	16%	0.77
Frequent PVCs (>500/24hr)	47% (8/17)	60% (24/40)	0.39
LGE	37% (7/19)	42% (16/38)	0.78
LV enlargement	33% (10/30)	37% (26/70)	0.82
LVEF (%)	46.3 ± 13 (n=31)	46.6 ± 15% n=72)	0.92
RV Systolic Dysfunction	11% (8/31)	26% (8/72)	0.059
VT Outcome	33%	26%	0.49

Supplemental Table 5. Gender Characteristics in Desmoplakin Carriers

PVC: Premature ventricular contraction, LGE: Late gadolinium enhancement, LV: Left ventricle, LVEF: Left ventricle ejection fraction, RV: Right Ventricle, VT: Ventricular tachycardia

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