PLACE 2026
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

CONGRESSO
ROMA, 25 - 27 Giugno 2026

Cardiomiopatia aritmogena: what's new?

Espressione clinica dei pazienti con cardiomiopatia aritmogena portatori di mutazione del gene Desmogleina2

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Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited cardiomyopathy characterized by fibro-fatty replacement of the ventricular myocardium, right ventricular (RV) dysfunction, and life-threatening ventricular arrhythmias.[1,2] Refinement of the ARVC/D diagnostic criteria[3] coupled with better understanding of the pathogenesis and clinical manifestations has led to both improved recognition and appropriate use of therapies to prevent sudden death in this population.[4]

Arrhythmogenic cardiomyopathy (ACM) is a genetically determined myocardial disease characterized by myocyte necrosis and fibro-fatty replacement, which leads to ventricular dysfunction and the onset of life-threatening ventricular arrhythmias (LTAs).[1,2]

Introduction

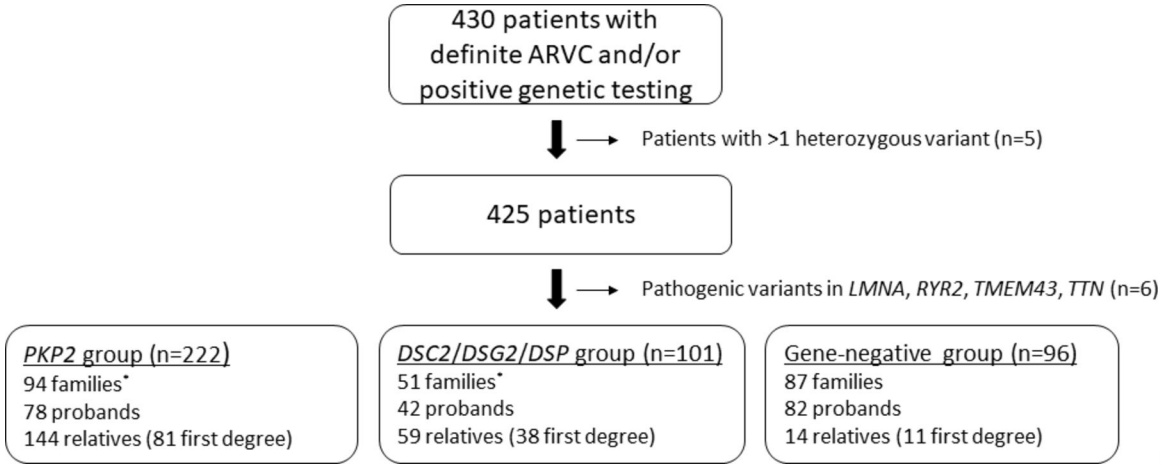
Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited cardiomyopathy characterized by progressive fibro-fatty myocardial replacement, mostly involving the right ventricle, leading to right ventricular dysfunction and ventricular arrhythmias (VA), causing sudden death.[1−3] The first clinical description was reported in 1982,[1] and the estimated prevalence in the general population ranges from 1 in 1000 to 1 in 5000.[2,3] Clinical diagnosis is often difficult at early stages and in mild forms due to a broad spectrum of clinical manifestations and a long period of concealed cardiac expression. Diagnosis is currently based on a diagnostic score using revised task force criteria.[4]

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is predominantly a genetically determined heart muscle disease, pathologically characterized by progressive cardiomyocyte loss and fibrofatty replacement, with a predominant involvement of the right ventricle (RV) (1,2). A broader phenotypic spectrum has been recognized, with the identification of biventricular and left-dominant subtypes (3,4).

Introduction

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy characterized by ventricular arrhythmias, predominantly right ventricular dysfunction, and an increased risk of sudden cardiac death (SCD).[1,2] Over the last decade, pathogenic mutations have been identified in desmosomal genes: plakoglobin (*JUP*),[3] plakophilin-2 (*PKP2*),[4] desmoplakin (*DSP*),[5] desmoglein-2 (*DSG2*),[6] and desmocollin-2 (*DSC2*).[7] Mutations in several non-desmosomal genes including *PLN*-encoding phospholamban[8] and *TMEM43*-encoding transmembrane protein 43[9] have also been reported to cause ARVD/C. While evidence suggests that genotype may influence risk of both life-threatening arrhythmia and heart failure,[10] previous genotype−phenotype studies were largely limited by population size. The objective of this study was to (i) define the long-term clinical course among a large cohort of ARVD/C mutation carriers, (ii) investigate the prognostic influence of genotype, including impact of multiple mutations, and (iii) ascertain the association of sex with phenotypic expression.

Desmosomal mutations are identified in approximately two-thirds of patients with Arrhythmogenic Cardiomyopathy



Alex Hørby Christensen et al. J Med Genet 2022;59:858-864

Index patients

Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance.[227–231,237,238]	I	B

ESC Cardiomyopathy Guidelines 2023 (Arbelo et al., Eur Heart J 2023)

Age at diagnosis

29

Age at which the patient fulfilled ARVC diagnosis as per 2010 Task Force Criteria (Marcus et al. 2010)

Sex

○Male ◉Female

Cardiac syncope (<6 months)

○Yes ◉No

Syncope suspected to be caused by cardiac arrhythmia within 6 months prior to diagnosis.

Number of inverted T-waves

5

Total number of precordial and inferior leads with inverted T-waves on standard 12-lead ECG.

Maximum 24 hours PVC count

4714

Maximum number of PVCs in 24 hours registered by continuous ECG monitoring (e.g. Holter)

History of non-sustained VT

◉Yes ○No

Specified as a recorded ventricular tachycardia (>100bpm) ending spontaneously within 30 seconds.

Right ventricular ejection fraction

44

As measured by cardiac MRI.

PATIENTS WITHOUT PRIOR SUSTAINED VA

I.e. primary prevention

OPTIONAL: programmed ventricular stimulation (PVS)

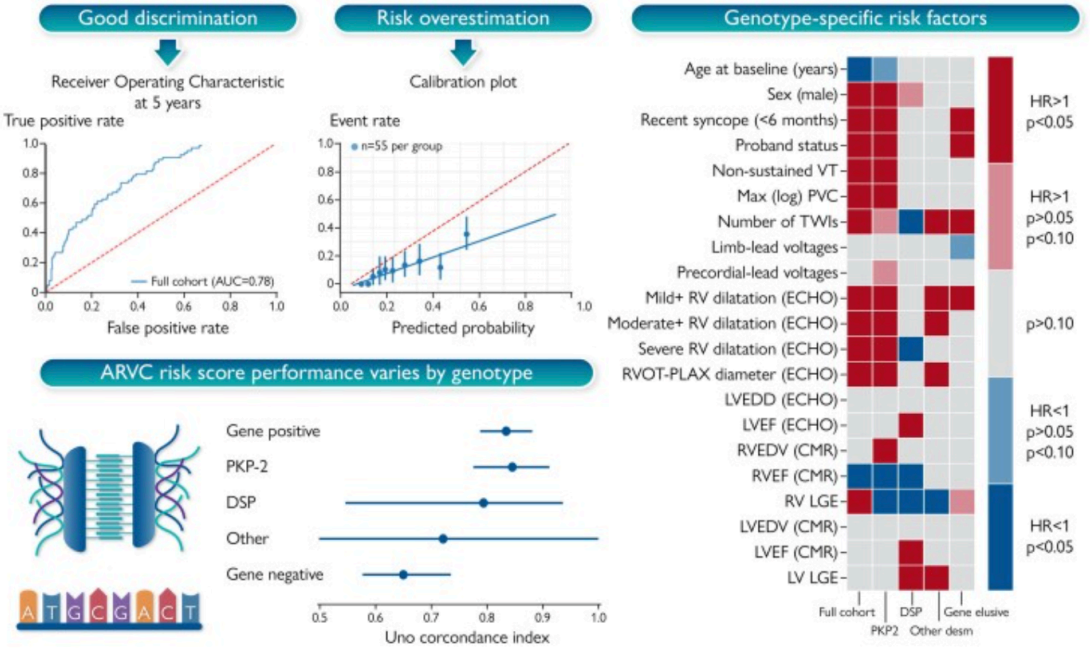
◉N/A ○Positive ○Negative

Positive if induction of sustained monomorphic VT lasting >30s or with hemodynamic compromise

Risk of first sustained VA (any type), within:

◉5 years ○2 years ○1 year

40.1%



Eur Heart J. 2022 Jun 29;43(32):3053–3067. doi: 10.1093/eurheartj/ehac235

Circulation

ORIGINAL RESEARCH ARTICLE

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

ESC European Society of Cardiology
European Heart Journal (2025) **46**, 362–376
https://doi.org/10.1093/eurheartj/ehae571

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Clinical features and outcomes in carriers of pathogenic desmoplakin variants

> Heart Rhythm. 2026 Apr 27:S1547-5271(26)02305-2. doi: 10.1016/j.hrthm.2026.04.038. Online ahead of print.

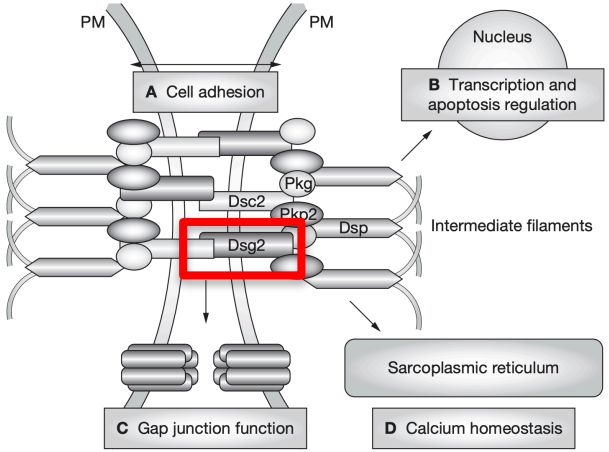
External validation of the DSP-risk score for prediction of clinically significant ventricular arrhythmias in primary prevention patients with desmoplakin cardiomyopathy-associated genetic variants

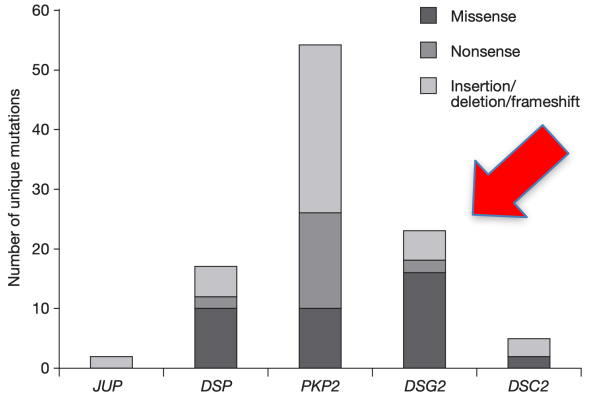
Circulation
Volume 113, Issue 9, 7 March 2006; Pages 1171-1179
https://doi.org/10.1161/CIRCULATIONAHA.105.583674

ARRHYTHMIA/ELECTROPHYSIOLOGY

Mutations in Desmoglein-2 Gene Are Associated With Arrhythmogenic Right Ventricular Cardiomyopathy

Kalliopi Pilichou, BSc, Andrea Nava, MD, Cristina Basso, MD, PhD, Giorgia Beffagna, BSc, PhD, Barbara Bauce, MD, PhD, Alessandra Lorenzon, BSc, Gianfranco Frigo, MD, PhD, Andrea Vettori, BSc, PhD, Marialuisa Valente, MD, Jeffrey Towbin, MD, Gaetano Thiene, MD, Gian Antonio Danieli, BSc, and Alessandra Rampazzo, BSc, PhD

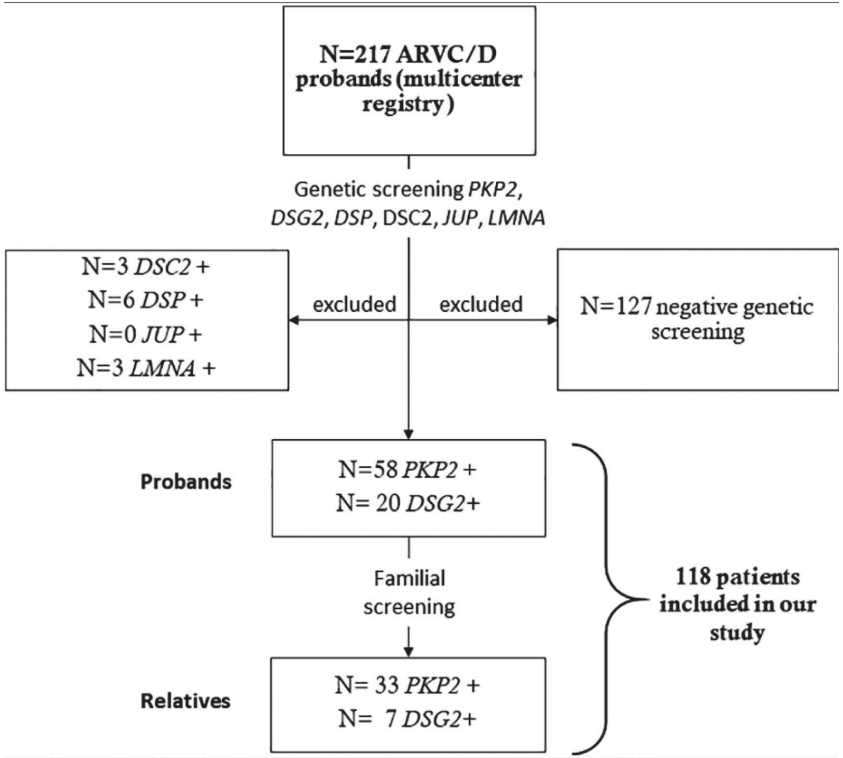




Awad et al., *Nat Clin Pract Cardiovasc Med*, 2008

ESC European Society of Cardiology
European Journal of Heart Failure (2019) 21, 792–800
doi:10.1002/ejhf.1423

RESEARCH ARTICLE



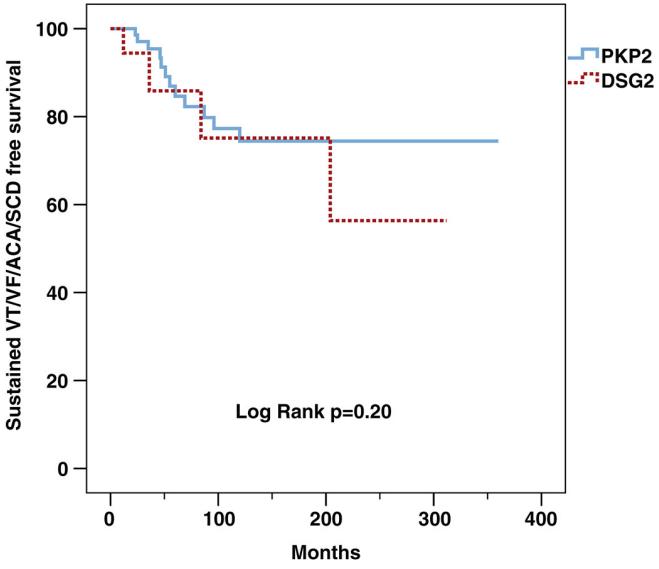
High risk of heart failure associated with desmoglein-2 mutations compared to plakophilin-2 mutations in arrhythmogenic right ventricular cardiomyopathy/dysplasia

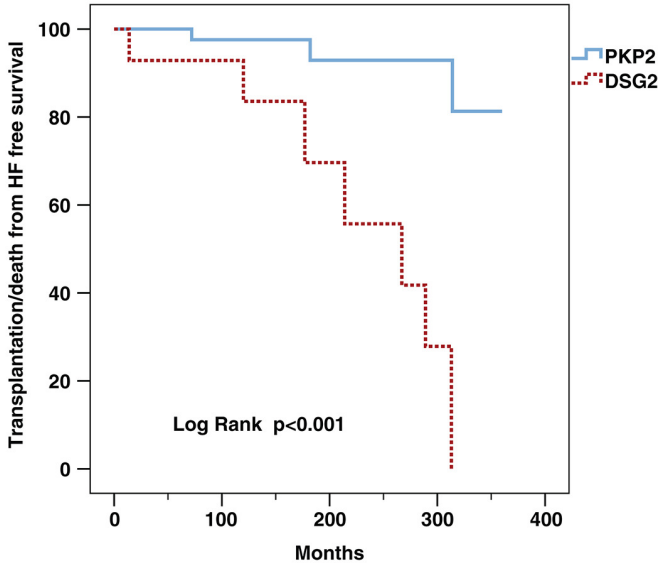
Alexis Hermida[1,2,3]*, Véronique Fressart[1,2], Francoise Hidden-Lucet[1,2], Erwan Donal[4], Vincent Probst[5†], Jean-Claude Deharo[6], Philippe Chevalier[7†], Didier Klug[8], Nicolas Mansencal[9], Etienne Delacretaz[10], Pierre Cosnay[11], Patrice Scanu[12], Fabrice Extramiana[1,13], Dagmar I. Keller[14], Stephanie Rouanet[15], Philippe Charron[1,9†], and Estelle Gandibakhch[1,2†]

Table 1 **Clinical data of desmoglein-2 vs. plakophilin-2 mutation carriers at diagnosis**

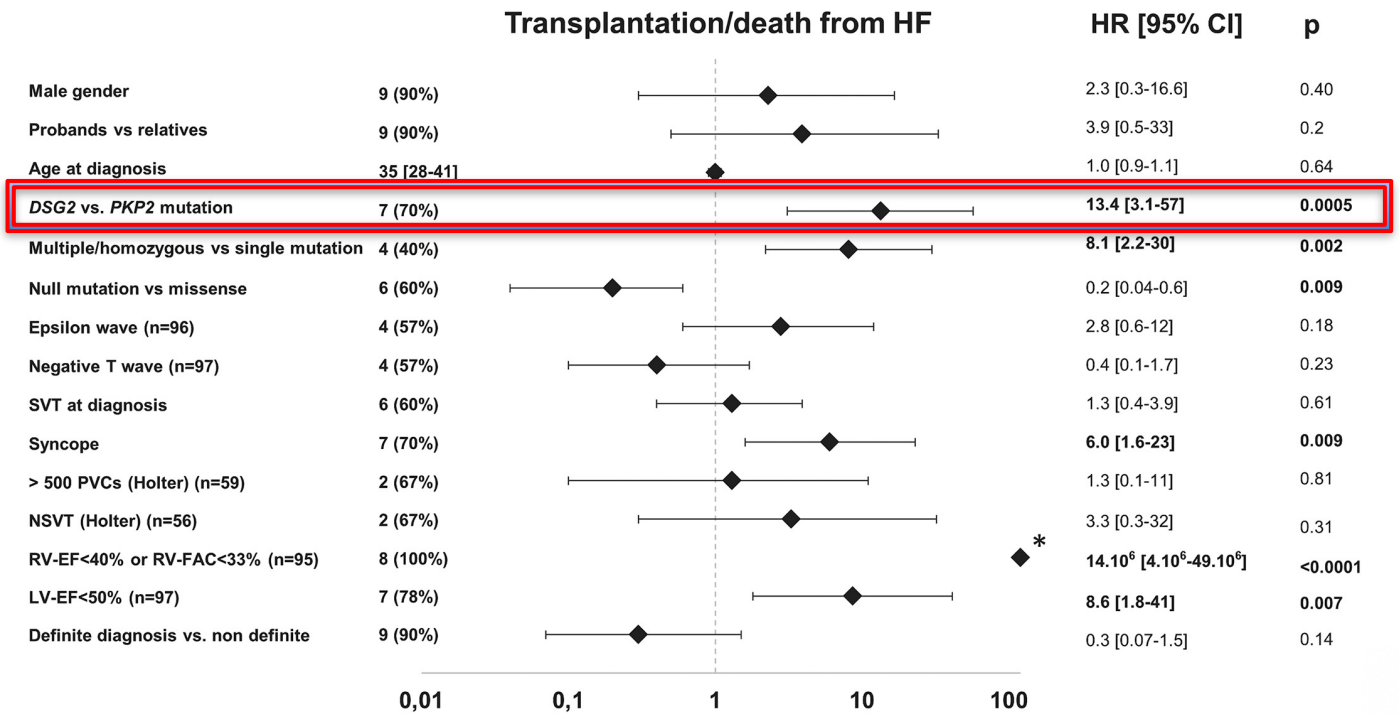
Baseline characteristics	Total ($n = 118$)	*DSG2* ($n = 27$)	*PKP2* ($n = 91$)	*P*-value
Male sex	86 (73)	18 (67)	68 (75)	0.46
Proband	78 (66)	20 (74)	58 (64)	0.36
Caucasian origin	106 (90)	22 (81)	84 (92)	0.14
Family history of sudden death ($n = 102$)	26 (25)	5 (24)	21 (26)	1
Age at the diagnosis				
Mean ± SD	36 ± 14	36 ± 15	36 ± 14	0.91
Median (Q1–Q3)	35 (25–47)	35 (24–50)	35 (25–47)	0.89
Diagnosis mode				
Asymptomatic	56 (47)	13 (48)	43 (47)	0.56
Syncope	8 (7)	3 (11)	5 (5)	
SVT/VF/ACA/SCD	54 (46)	11 (41)	43 (47)	
ECG/Holter/EPS				
Epsilon wave ($n = 111$)	24 (22)	9 (37)	15 (17)	**0.048**
Negative T-wave V1–V3 ($n = 112$)	82 (73)	14 (58)	68 (77)	0.07
Negative T-wave V4–V6 ($n = 86$)	14 (16)	4 (25)	10 (14)	0.28
Low QRS voltages lead ($n = 86$)	4.2 ± 3	4.6 ± 4	4.2 ± 2	0.61
> 500 PVCs (Holter) ($n = 59$)	31 (52)	4 (57)	27 (52)	1
NSVT (Holter) ($n = 56$)	17 (30)	2 (33)	15 (30)	1
Positive EPS ($n = 33$)	24 (73)	3 (43)	21 (81)	0.07
Imaging				
RVEF < 40% (MRI) or RVFAC < 33% (TTE) ($n = 101$)	51 (50)	15 (65)	35 (45)	0.10
LVEF < 50% (TTE) ($n = 113$)	23 (20)	14 (54)	9 (10)	**<0.001**
Diagnosis according to task force criteria				
Possible	8 (7)	1 (4)	7 (8)	0.15
Borderline	14 (12)	6 (22)	8 (9)	
Definite	96 (81)	20 (74)	76 (83)	
ICD implantation	43 (36)	11 (41)	32 (35)	0.65

Values are displayed as *n* (%), mean ± SD, or median (Q1–Q3). Percentages are of the total population, unless mentioned otherwise.
ACA, aborted cardiac arrest; DSG2, desmoglein-2; ECG, electrocardiogram; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PKP2, plakophilin-2; PVC, premature ventricular complexes; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; SCD, sudden cardiac death; SD, standard deviation; TTE, transthoracic echocardiography; VT, ventricular tachycardia.





European J of Heart Fail, Volume: 21, Issue: 6, Pages: 792-800, First published: 21 February 2019, DOI: (10.1002/ejhf.1423)



European J of Heart Fail, Volume: 21, Issue: 6, Pages: 792-800, First published: 21 February 2019, DOI: (10.1002/ejhf.1423)

Multicenter study,

11 centers across 5 countries:

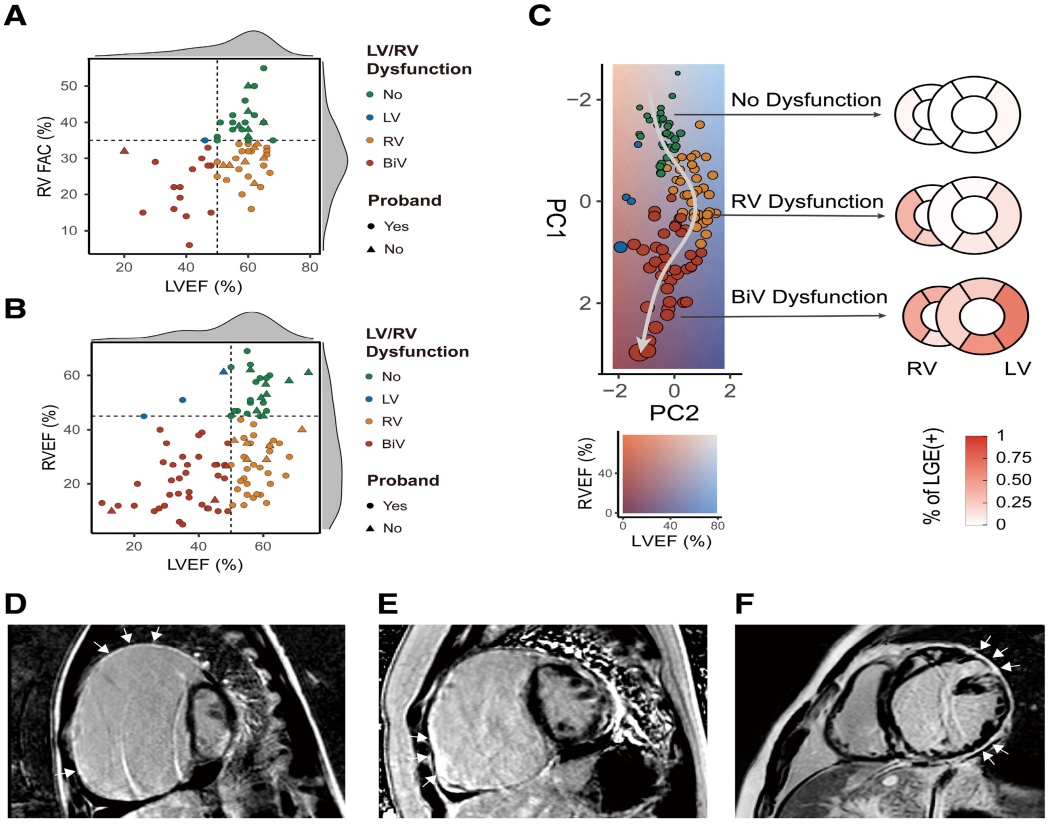
- 193 single variant status
- 78 multiple variant status

Circulation

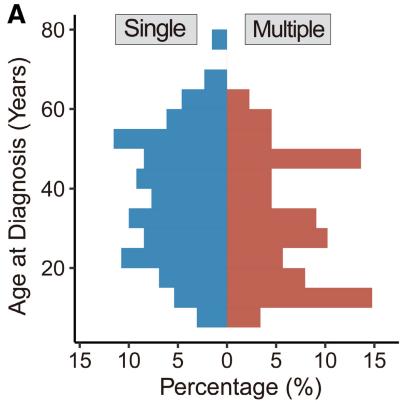
ORIGINAL RESEARCH ARTICLE

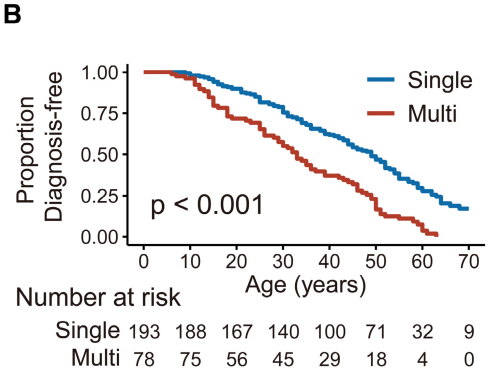
Natural History and Clinical Outcomes of Patients With *DSG2/DSC2* Variant-Related Arrhythmogenic Right Ventricular Cardiomyopathy

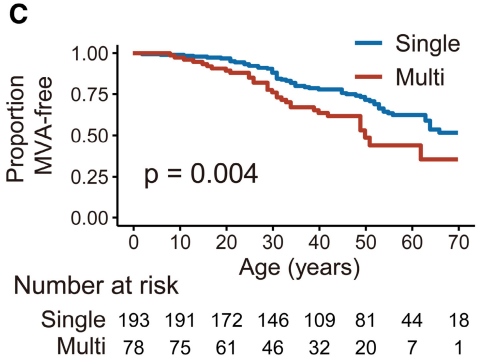
Liang Chen, MD, PhD*; Yuxiao Hu, MD*; Ardan M. Saguner, MD*; Barbara Bauce, MD, PhD*; Yaxin Liu, MD, PhD*; Anteng Shi, MD; Fu Guan, MD; Zhongli Chen, MD, PhD; Maria Bueno Marinas, PhD; Lingmin Wu, MD, PhD; Deborah Foltran, MD; Alexis Hermida, MD; Veronique Fressart, MD; Serena Pinci, MD; Rudy Celeghin, PhD; Zixian Chen, MD; Baowei Zhang, MD; Lin Yubi, MD, PhD; Xiaorui Liu, MD; Marco Cason, PhD; Marika Martini, MD; Ilaria Rigato, MD, PhD; Corinna Brunckhorst, MD; Ruth Biller, MD; Cristina Basso, MD, PhD; Bing Yang, MD, PhD; Xiaoyan Zhao, MD, PhD; Julia Cadrin-Tourigny, MD; Alessio Gasperetti, MD; Cynthia A. James, PhD; Xianliang Zhou, MD; Estelle Gandjbakhch, MD, PhD; Kalliopi Pilichou, PhD; Firat Duru, MD; Shengshou Hu, MD

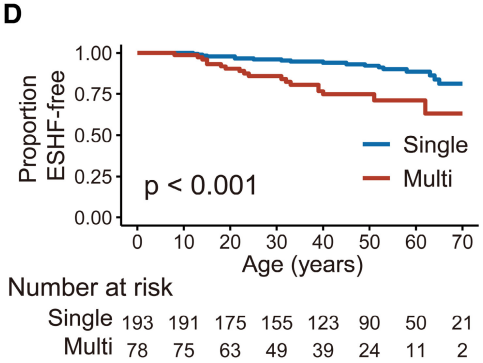


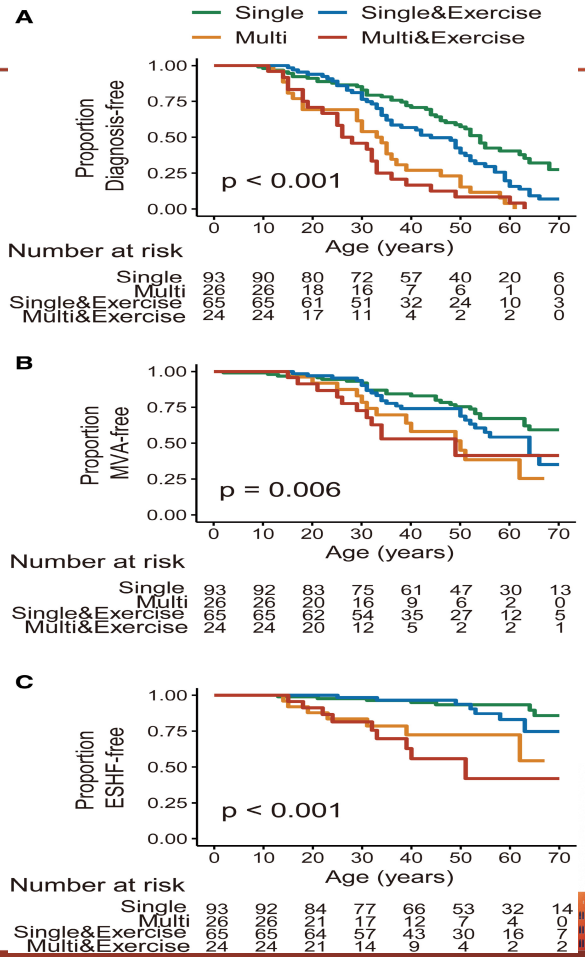
Liang Chen. Circulation. Natural History and Clinical Outcomes of Patients With DSG2/DSC2 Variant-Related Arrhythmogenic Right Ventricular Cardiomyopathy, Volume: 151, Issue: 17, Pages: 1213-1230, DOI: (10.1161/CIRCULATIONAHA.124.072226)


A
Single
Multiple
Age at Diagnosis (Years)
80
60
40
20
15 10 5 0 5 10 15
Percentage (%)


B
Proportion Diagnosis-free
1.00
0.75
0.50
0.25
0.00
p < 0.001
Single
Multi
0 10 20 30 40 50 60 70
Age (years)
Number at risk
Single 193 188 167 140 100 71 32 9
Multi 78 75 56 45 29 18 4 0


C
Proportion MVA-free
1.00
0.75
0.50
0.25
0.00
p = 0.004
Single
Multi
0 10 20 30 40 50 60 70
Age (years)
Number at risk
Single 193 191 172 146 109 81 44 18
Multi 78 75 61 46 32 20 7 1


D
Proportion ESHF-free
1.00
0.75
0.50
0.25
0.00
p < 0.001
Single
Multi
0 10 20 30 40 50 60 70
Age (years)
Number at risk
Single 193 191 175 155 123 90 50 21
Multi 78 75 63 49 39 24 11 2

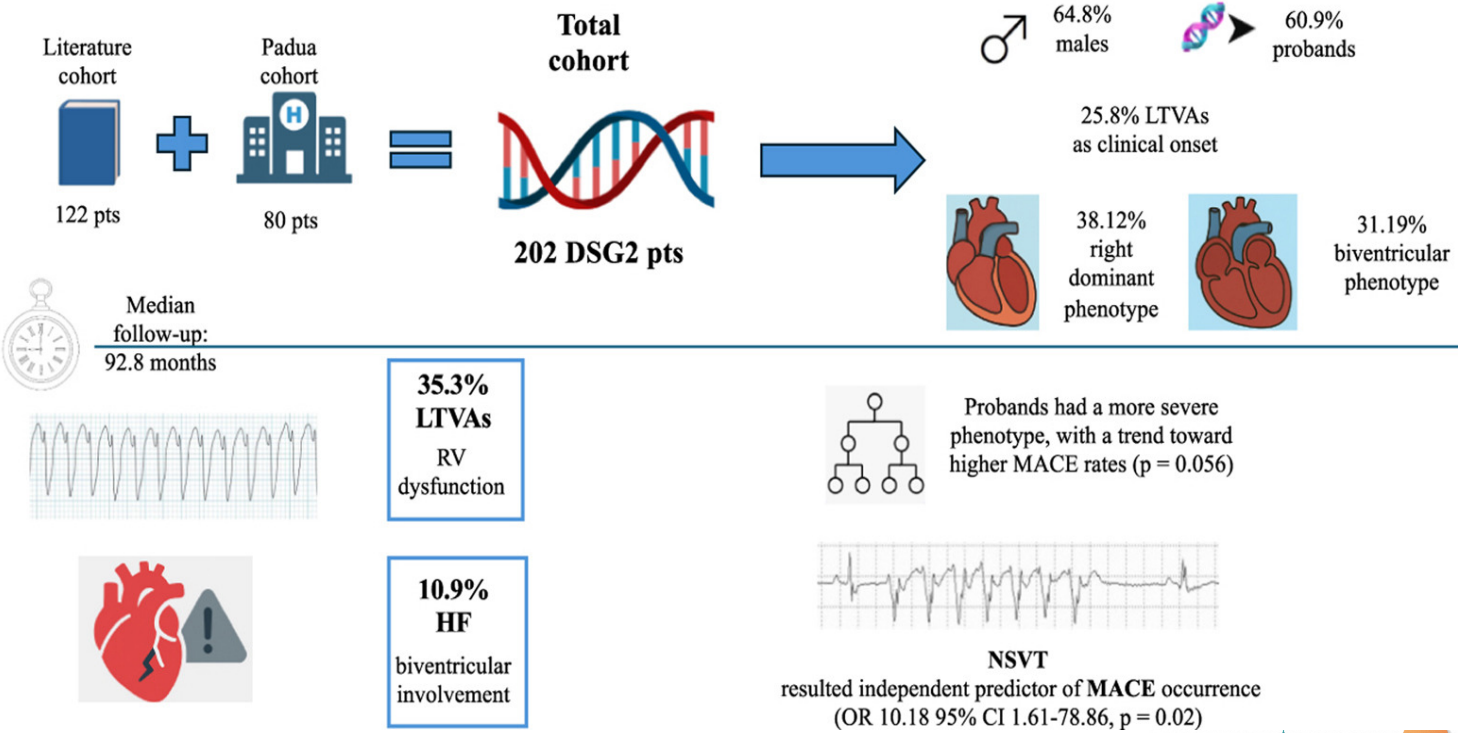

A
Single
Single&Exercise
Multi
Multi&Exercise
Proportion Diagnosis-free
1.00
0.75
0.50
0.25
0.00
p < 0.001
0 10 20 30 40 50 60 70
Age (years)
Number at risk
Single 93 90 80 72 57 40 20 6
Multi 26 26 18 16 7 6 1 0
Single&Exercise 65 65 61 51 32 24 10 3
Multi&Exercise 24 24 17 11 4 2 2 0
B
Proportion MVA-free
1.00
0.75
0.50
0.25
0.00
p = 0.006
0 10 20 30 40 50 60 70
Age (years)
Number at risk
Single 93 92 83 75 61 47 30 13
Multi 26 26 20 16 9 6 2 0
Single&Exercise 65 65 62 54 35 27 12 5
Multi&Exercise 24 24 20 12 5 2 2 1
C
Proportion ESHF-free
1.00
0.75
0.50
0.25
0.00
p < 0.001
0 10 20 30 40 50 60 70
Age (years)
Number at risk
Single 93 92 84 77 66 53 32 14
Multi 26 26 21 17 12 7 4 0
Single&Exercise 65 65 64 57 43 30 16 7
Multi&Exercise 24 24 21 14 9 4 2 2

Supplemental Tables

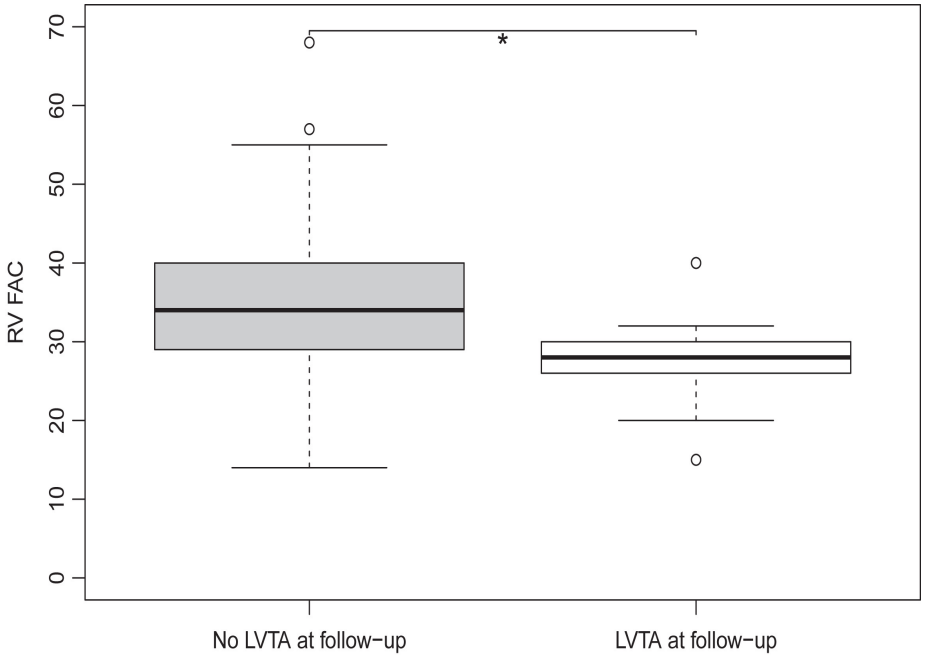
Table S1. Baseline clinical characteristics according to country

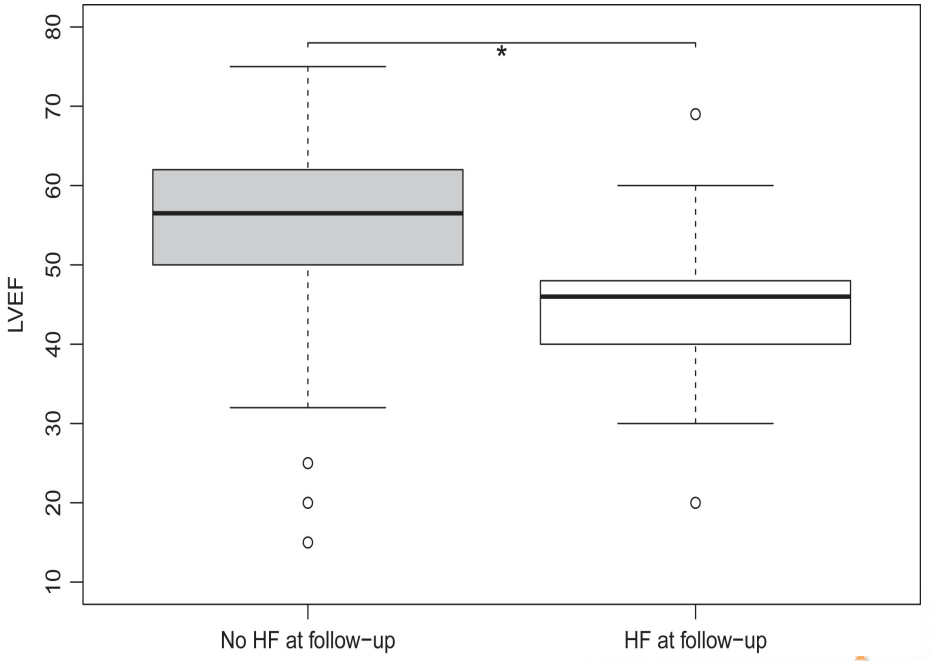
Characteristics	China (n = 140)	Switzerland and Germany (n = 32)	France (n = 61)	Italy (n = 38)
Male sex, n (%)	88 (62.9%)	20 (62.5%)	37 (60.7%)	25 (65.8%)
Proband, n (%)	89 (63.6%)	20 (62.5%)	27 (44.3%)	29 (76.3%)
Intense Exercise, n (%)	25 (27.2%)	16 (50.0%)	36 (75.0%)	12 (33.3%)
Missense Variant, n (%)	128 (91.4%)	6 (18.8%)	30 (49.2%)	17 (44.7%)
Multiple Variant, n (%)	75 (53.6%)	4 (12.5%)	10 (16.4%)	3 (7.9%)
Age at Diagnosis, years	38 (21, 51)	46 (31, 57)	36 (28, 50)	41 (25, 50)
Sustained VT/VF, n (%)	36 (29.3%)	13 (43.3%)	15 (33.3%)	4 (10.8%)
NYHA III/IV, n (%)	30 (30.6%)	4 (13.3%)	4 (9.1%)	0 (0.0%)
TWI in V1-V3, n (%)	68 (60.2%)	17 (58.6%)	7 (14.9%)	21 (58.3%)
Numbers of Precordial TWI Leads	4 (0, 5)	1 (0, 4)	2 (1, 6)	1 (0, 4)
ECG depolarization criteria*, n (%)	38 (33.9%)	11 (36.7%)	14 (29.8%)	1 (2.8%)
PVC/24h	1,318 (345, 3,574)	271 (18, 1,211)	307 (4, 1,973)	702 (262, 1,866)
> 500 PVCs, n (%)	53 (71.6%)	9 (47.4%)	13 (48.1%)	20 (74.1%)
NSVT, n (%)	47 (56.0%)	1 (5.3%)	13 (29.5%)	4 (14.8%)
LVEF, %	58 (44, 64)	56 (49, 61)	57 (45, 60)	59 (55, 65)
LVEF<50%, n (%)	37 (32.5%)	5 (25.0%)	15 (33.3%)	4 (12.1%)
RV Dilatation, n (%)	85 (64.9%)	16 (59.3%)	31 (72.1%)	23 (67.6%)
RV Dyskinesia, n (%)	73 (55.7%)	16 (59.3%)	28 (66.7%)	24 (70.6%)
LV Dilatation, n (%)	37 (29.1%)	7 (25.9%)	9 (20.9%)	6 (17.6%)
LV Dyskinesia, n (%)	39 (30.7%)	7 (24.1%)	14 (29.8%)	8 (23.5%)
ICD Implantation, n (%)	20 (21.5%)	16 (53.3%)	18 (39.1%)	16 (48.5%)
VA Ablation, n (%)	29 (32.2%)	2 (6.7%)	12 (27.3%)	0 (0.0%)
HTx, n (%)	20 (15.9%)	1 (3.2%)	6 (12.5%)	2 (5.7%)

Phenotypic Spectrum and Prognostic Stratification in Desmoglein-2-Associated Arrhythmogenic Cardiomyopathy: Results from a Pooled Analysis



Martini et al. *Heart rhythm* vol. 23,2 (2026): e162-e171.

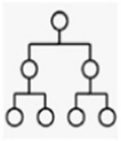




Heart Rhythm 2026 23e162-e171DOI: (10.1016/j.hrthm.2025.09.046

Table 3 Comparison of clinical characteristics and outcomes between probands and affected first-degree relatives with DSG2 variants

Baseline characteristics	Probands (n = 123) N	Probands (n = 123) NA	First degree relatives (n = 79) N	First degree relatives (n = 79) NA	*P*-value
Anamnesis					
Padua cohort	55 (44.7)	0	25 (31.6)	0	.088
Male sex	80 (66.7)	3	49 (62)	0	.604
Caucasian origin	93 (78.2)	4	69 (88.5)	1	.097
Family history of SCD	19 (17)	11	20 (29.4)	11	.075
Age at presentation	36 [21–46]	6	37 [24–52.75]	1	.187
Presentation symptom					
Asymptomatic	22 (19.6)	11	42 (60)	9	<.001
LTVA	39 (34.8)	11	8 (11.4)	9	.001
Palpitations	23 (20.5)	11	14 (20)	9	1
Syncope	25 (22.3)	11	6 (8.6)	9	.028
Dyspnea	11 (9.8)	11	1 (1.4)	9	.031
HF	6 (5.4)	11	0 (0)	9	.084
Chest pain	9 (7.8)	8	2 (2.9)	9	.212
ECG/Holter					
Abnormal ECG	91 (79.8)	9	41 (56.2)	6	.001
AF	2 (2)	23	1 (2)	30	1
LBBB	3 (3)	23	1 (1.8)	24	1
RBBB	17 (16.8)	22	3 (5.2)	21	.059
Epsilon Waves	13 (12.1)	16	4 (6.7)	19	.391
TWI V1-V3	72 (66.1)	14	21 (30)	9	<.001
TWI V4-V6	38 (37.6)	22	10 (15.6)	15	.004
Low QRS precordial leads	19 (23.8)	43	3 (9.1)	46	.126
Holter >500 PVC	60 (82.2)	50	1 (32.3)	67	<.001
Holter NSVT	30 (42.9)	53	10 (16.7)	19	.002
Echocardiography					
LV dilatation	27 (34.6)	45	6 (17.1)	44	.096
LVEF	54 [47.75–60]	47	57.5 [52–62]	51	.142
LVEDD	51.9 ± 8.32	88	48.9 ± 8.77	59	.199
RV dilatation	65 (75.9)	38	21 (45)	37	.005
RV akinesia/dyskinesia	55 (74.3)	49	19 (51.4)	42	.027
RV FAC	32 [28–40]	66	35 [30.25–41.5]	57	.151
Cardiac magnetic resonance					
LVEF	50 [42.75–57]	71	57.5 [49.75–61]	55	.008
RVEF	42.3 ± 13.22	72	52 ± 12.07	51	.062
Fatty infiltration	31 (62)	73	11 (57.9)	60	.971
LGE	45 (81.8)	68	14 (63.6)	57	.16
Follow-up					
ICD implantation	49 (51)	27	10 (29.4)	45	.048
Any LTVA	31 (38.8)	43	5 (22.7)	57	.254
SCD	15 (18.8)	43	2 (9.1)	57	.352
sVT/VF	14 (17.5)	43	1 (4.5)	57	.181
ICD intervention	3 (3.8)	43	2 (9.1)	57	.294
HF	11 (13.9)	44	0 (0)	57	.115
HTx	6 (7.6)	44	0 (0)	57	.335
Death	17 (20.5)	40	2 (9.1)	57	.351
Any MACE	41 (48.2)	38	5 (22.7)	57	.056



Probands had a more severe phenotype, with a trend toward higher MACE rates (p = 0.056)

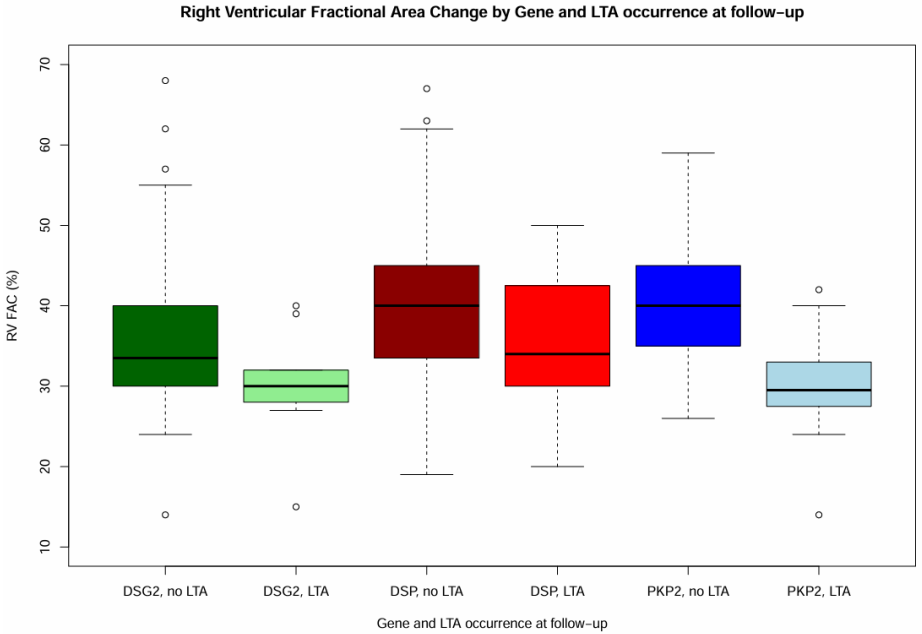
Variables Associated with Major Adverse Cardiovascular Events

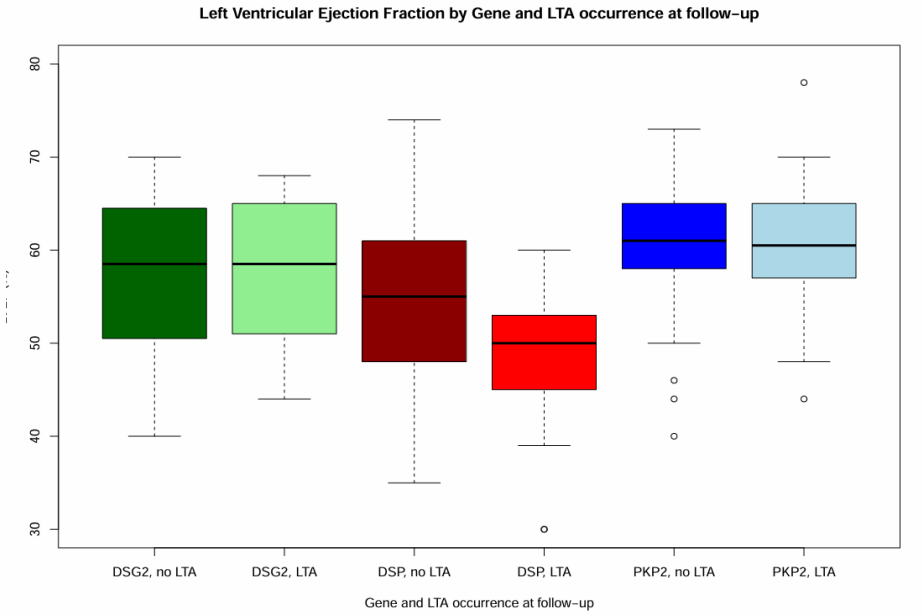
Variable	OR (95% CI)	p
Proband status	3.17 (1.14–10.34)	0.05
LTVA at presentation	5.46 (2.19–14.75)	<0.001
NSVT on Holter	3.89 (1.22–12.85)	0.04
Reduced RV FAC	0.89 (0.81–0.97)	0.02
Reduced LVEF (Echo)	0.93 (0.88–0.97)	0.006
Reduced LVEF (CMR)	0.91 (0.86–0.98)	0.008

NSVT on 24-hour Holter

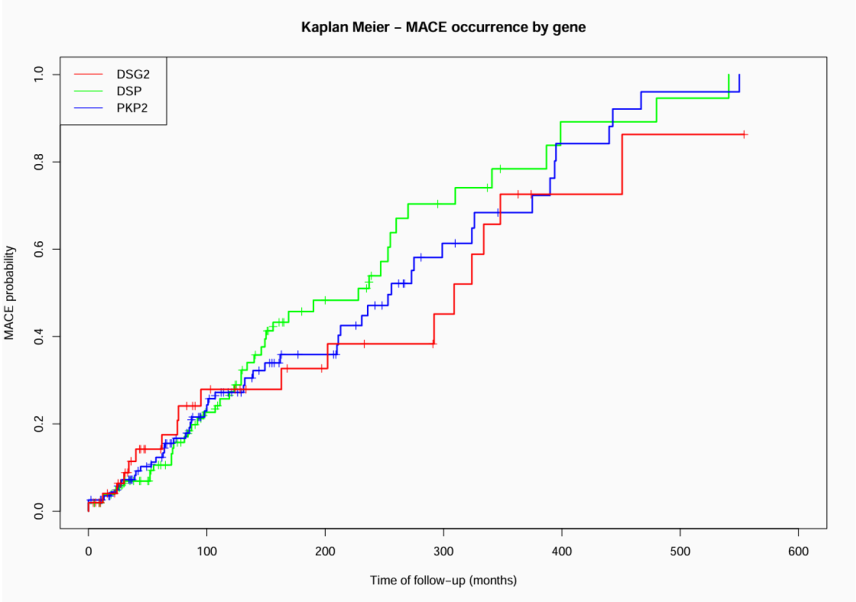
OR 10.18
95% CI 1.61–78.86
p = 0.02

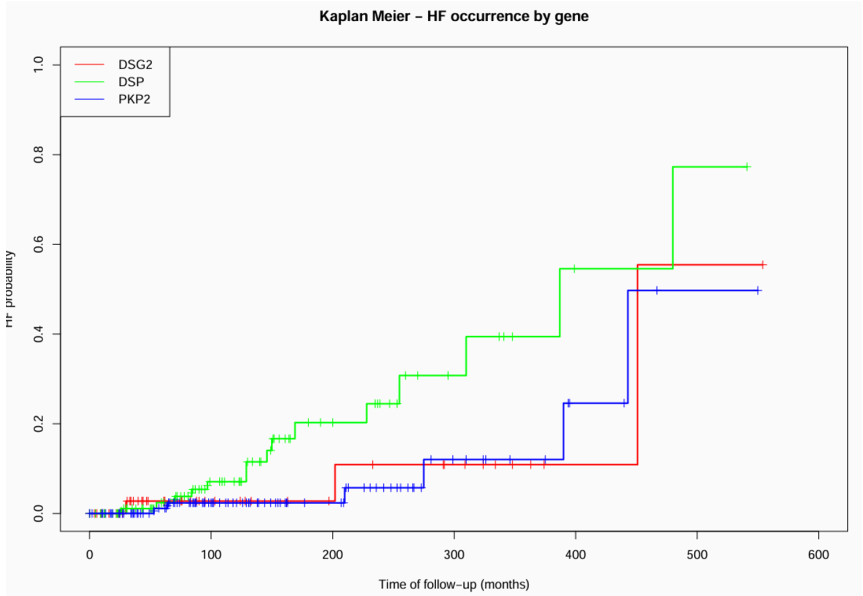
In multivariable regression analysis, NSVT was the only variable independently associated with MACE.





Martini et al. Unpublished data (under review)





Martini et al. Unpublished data (under review)

- *DSG2* is one of the most prevalent desmosomal genes in Arrhythmogenic Cardiomyopathy.
- *DSG2*-related ACM predominantly exhibits a right-dominant or biventricular phenotype, whereas isolated left-dominant disease is uncommon.
- Ventricular arrhythmias represent the main clinical manifestation, often occurring at disease presentation and throughout follow-up.
- Heart failure is less frequent but is strongly associated with left ventricular involvement and biventricular disease progression.

Grazie per l'attenzione