Supplemental Material

Table S1. Results of genetic testing in 168 patients with arrhythmogenic cardiomyopathy.

Mutation	Individuals, n (%)	Families, n (%)
No identified mutation	*36 (21.4)*	*36 (39.6)*
c.2145+2T>A (seq: NM_004572.3) intron 10 in PKP2	55 (32.7)	18 (19.8)
c.2197C>G, c.2198_2202delACACC (seq: NM_004572.3) exon 11 in PKP2	29 (17.3)	8 (8.8)
Deletion of Promoter, exon 1 and exon 2 in PKP2	15 (8.9)	2 (2.2)
c.1952_1955dupGAAG (seq: NM_004572.3) exon 9 in PKP2	4 (2.4)	4 (4.4)
c.3059_3062delAGAG (seq: NM_001943.3) exon 15 in DSG2	4 (2.4)	3 (3.3)
R46Q (c.137G>A, seq: NM_001943.3) exon 3 in DSG2	4 (2.4)	1 (1.1)
c.2300-1G>A (seq: NM_004572.3) intron 11 in PKP2	2 (1.2)	1 (1.1)
R425X (c.1273C>T, seq: NM_004415.2) exon 11 in DSP	2 (1.2)	1 (1.1)
c.198delG (seq: NM_004572.3) exon 1 in PKP2	1 (0.6)	1 (1.1)
A2294G (c.6881C>G, seq: NM_004415.2) exon 24 in DSP	1 (0.6)	1 (1.1)
c.223+2T>C ((seq: NM_004572.3) intron 1 in PKP2	1 (0.6)	1 (1.1)
c.1597dup (seq: NM_004572.3) exon 7 in PKP2	1 (0.6)	1 (1.1)
c.2463_2464insAC (seq: NM_004415.2) exon 18 in DSP	1 (0.6)	1 (1.1)
c.2489+1G>A (seq: NM_004572.3) intron 12 in PKP2	1 (0.6)	1 (1.1)
c.3203_3204delAG (seq: NM_004415.2) exon 23 of DSP	1 (0.6)	1 (1.1)
c.5764delA (seq: NM_004415.2) exon 24 in DSP	1 (0.6)	1 (1.1)
c.6310delA (seq: NM_004415.2) exon 24 in DSP	1 (0.6)	1 (1.1)
D407N (c.1219G>A, seq: NM_001792) exon 9 in CDH2	1 (0.6)	1 (1.1)
G48D (c.143G>A, seq: NM_004572.3) exon 1 in PKP2	1 (0.6)	1 (1.1)
E1345A (c.4034A>C, seq: NM_004415.2) exon 23 in DSP	1 (0.6)	1 (1.1)
G509E (c.1526G>A, seq: NM_004415.2) exon 12 in DSP	1 (0.6)	1 (1.1)
c.148_151delACAG (seq: NM_004572.3) exon 1 in PKP2	1 (0.6)	1 (1.1)
S140F (c. 419C>T, seq: NM_004572.3) exon 3 in PKP2	1 (0.6)	1 (1.1)
T335A (c.1003A>G, seq: NM_001943.3) exon 8 in DSG2	1 (0.6)	1 (1.1)
V392I (c.1174G>A, seq: NM_001943.3) exon 9 in DSG2	1 (0.6)	1 (1.1)

CDH2 = Cadherin 2-gene, DSG2 = Desmoglein 2-gene, DSP = Desmoplakin-gene, PKP2 = Plakophillin 2-gene.

Table S2. Relationship between exercise exposure, pathogenic mutations in desmoplakin gene and left ventricular function during long-term follow-up with 628 echocardiographic exams in 146 patients with arrhythmogenic cardiomyopathy and known exercise habits at presentation

	Beta	95% CI	p
GLS (constant), n=584 (93%)	-19.3	-20.0 to -18.6	
Time (years)	0.06	0.01 to 0.11	0.03
Exercise dose (5 METhrs/week)	0.09	0.01 to 0.17	0.02
Interaction: Time*Exercise dose	0.003	-0.003 to 0.008	0.33
DSP mutation	0.11	-2.03 to 2.25	0.92
Interaction: Time*DSP mutation	0.22	0.02 to 0.42	0.03
EF (constant), n=616 (98%)	58	56 to 60	
Time (years)	0.06	-0.07 to 0.18	0.37
Exercise dose (5 METhrs/week)	-0.19	-0.37 to -0.01	0.04
Interaction: Time*Exercise dose	0.002	-0.012 to 0.016	0.76
DSP mutation	-1.4	-6.3 to 3.6	0.58
Interaction: Time*DSP mutation	-0.8	-1.3 to -0.3	0.004

Values are regression coefficients with 95% confidence intervals. P-values by linear mixed model regression with exchangeable covariance structure and random effects by families and individuals. CI = confidence interval, DSP = desmoplakin, EF = ejection fraction, GLS = global longitudinal strain, METhrs/week = metabolic equivalents of task multiplied by hours per week.

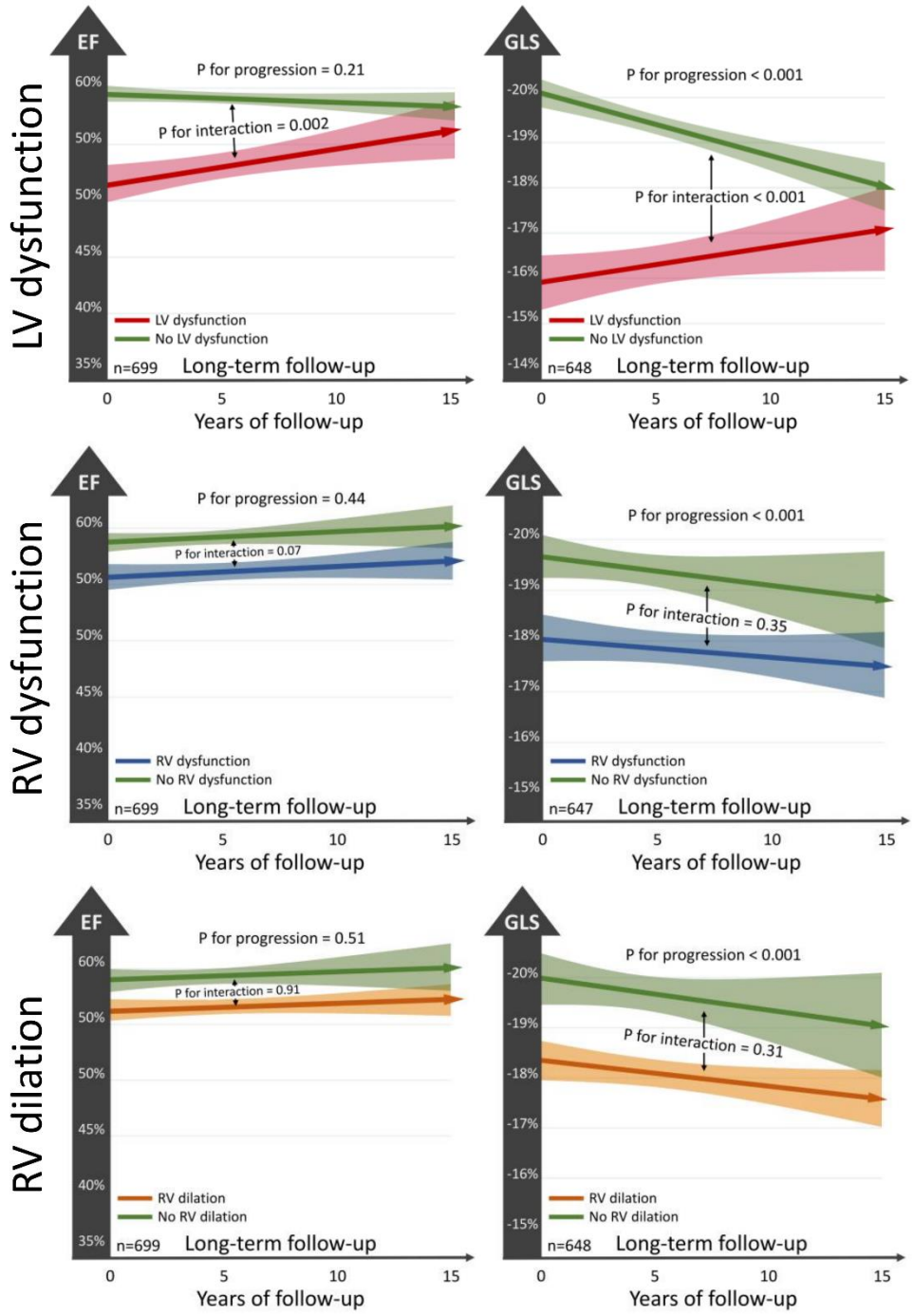
Table S3. Prediction of impending ventricular tachyarrhythmia in 168 patients (total population) and 102 patients without previous events (primary prevention), adjusted for genetic basis of disease.

	Odds ratio	95% CI	p
Total population - EF (n=699/168)			
Time (1 year)	1.06	1.00 to 1.13	0.06
Previous event	6.50	2.84 to 14.86	<0.001
EF (-5%)	1.13	0.91 to 1.41	0.27
PKP2 mutation	1.02	0.39 to 2.66	0.96
DSG2 mutation	0.28	0.04 to 2.02	0.21
DSP mutation	0.68	0.14 to 2.93	0.64
CDH2 mutation	-	-	-
Total population - GLS (n=648/166)			
Time (1 year)	1.06	0.99 to 1.13	0.08
Previous event	5.84	2.42 to 14.10	<0.001
GLS (1%)	1.13	1.00 to 1.27	0.04
PKP2 mutation	1.10	0.40 to 3.03	0.85
DSG2 mutation	0.22	0.03 to 1.85	0.17
DSP mutation	0.94	0.20 to 4.31	0.94
CDH2 mutation	-	-	-
Primary prevention - EF (n=418/102)			
Time (1 year)	1.14	1.04 to 1.24	0.003
EF (-5%)	1.52	1.04 to 2.22	0.03
PKP2 mutation	0.44	0.12 to 1.68	0.23

DSG2 mutation	-	-	-
DSP mutation	-	-	-
CDH2 mutation	-	-	-
Primary prevention - GLS (n=402/101)			
Time (1 year)	1.14	1.05 to 1.25	0.003
GLS (1%)	1.38	1.17 to 1.64	<0.001
PKP2 mutation	0.38	0.10 to 1.43	0.15
DSG2 mutation	-	-	-
DSP mutation	-	-	-
CDH2 mutation	-	-	-

Values are odds ratios with 95% confidence intervals, calculated by multivariable generalized estimating equations with binomial family, logit link and independent covariance structure, adjusted for patient relatedness. DSP and DSG mutations were omitted from analyses in the primary prevention subgroups due to lack of events in these patients. CI = confidence interval, CDH2 = Cadherin 2, DSG2 = desmoglein 2, DSP = desmoplakin, EF = ejection fraction, GLS = global longitudinal strain, PKP2 = plakophilin 2.

Figure S1. Left ventricular functional deterioration during follow-up of 168 patients with arrhythmogenic cardiomyopathy with and without functional or structural abnormalities at presentation.



Slopes are fitted mean linear response with 95% confidence intervals for patients with and without LV dysfunction (upper panel), RV dysfunction (mid panel) and RV dilation (lower panel) at presentation. P-values for progression and interaction by linear mixed model regression with random effects for families and individuals and exchangeable covariance structure. EF = ejection fraction, GLS = global longitudinal strain, LV = left ventricle, RV = right ventricle.