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Prognostic Prediction of Genotype vs Phenotype in Genetic Cardiomyopathies

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ABSTRACT

BACKGROUND Diverse genetic backgrounds often lead to phenotypic heterogeneity in cardiomyopathies (CMPs). Previous genotype-phenotype studies have primarily focused on the analysis of a single phenotype, and the diagnostic and prognostic features of the CMP genotype across different phenotypic expressions remain poorly understood.

OBJECTIVES We sought to define differences in outcome prediction when stratifying patients based on phenotype at presentation compared with genotype in a large cohort of patients with CMPs and positive genetic testing.

METHODS Dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy, left-dominant arrhythmogenic cardiomyopathy, and biventricular arrhythmogenic cardiomyopathy were examined in this study. A total of 281 patients (80% DCM) with pathogenic or likely pathogenic variants were included. The primary and secondary outcomes were: 1) all-cause mortality (D)/heart transplant (HT); 2) sudden cardiac death/major ventricular arrhythmias (SCD/MVA); and 3) heart failure–related death (DHF)/HT/left ventricular assist device implantation (LVAD).

RESULTS Survival analysis revealed that SCD/MVA events occurred more frequently in patients without a DCM phenotype and in carriers of *DSP*, *PKP2*, *LMNA*, and *FLNC* variants. However, after adjustment for age and sex, genotype-based classification, but not phenotype-based classification, was predictive of SCD/MVA. *LMNA* showed the worst trends in terms of D/HT and DHF/HT/LVAD.

CONCLUSIONS Genotypes were associated with significant phenotypic heterogeneity in genetic cardiomyopathies. Nevertheless, in our study, genotypic-based classification showed higher precision in predicting the outcome of patients with CMP than phenotype-based classification. These findings add to our current understanding of inherited CMPs and contribute to the risk stratification of patients with positive genetic testing. (J Am Coll Cardiol 2022;80:1981–1994)

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ABBREVIATIONS AND ACRONYMS

ACM = arrhythmogenic cardiomyopathy

ALVC = left-dominant arrhythmogenic cardiomyopathy

ARVC = arrhythmogenic right ventricular cardiomyopathy

BiV = biventricular arrhythmogenic cardiomyopathy

DCM = dilated cardiomyopathy

LP = likely pathogenic variants

MVA = major ventricular arrhythmias

P = pathogenic variants

SCD = sudden cardiac death

Cardiomyopathies (CMPs) are a heterogeneous group of primary heart diseases characterized by structural and electrical abnormalities that are frequently associated with mutations in disease-related genes.[1] Currently, CMPs are classified clinically based on observed phenotypic expression as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricle cardiomyopathy (ARVC), restrictive cardiomyopathy, and other rare forms, each with specific guidelines for treatment.[1-3] In the last few years, however, a deeper understanding of the clinical characteristics of these conditions has revealed a more complex scenario. Although HCM represents a distinct disease in terms of pathophysiology, therapeutic treatment, and prognostic assessment,[2] DCM and ARVC frequently present overlapping aspects that challenge the conventional classification, leading to the proposal of a single definition, arrhythmogenic cardiomyopathy (ACM), which incorporates ARVC, left-dominant arrhythmogenic cardiomyopathy (ALVC), and biventricular ACM (BiV).[4] In DCM and ACM, variability in phenotypic expression can be found within the same family or the same patient over time,[5] and several factors, including individual genetic background and exposure to environmental factors, can influence the presenting phenotype and progression of the disease.[6]

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Next-generation sequencing technologies allow the identification of the underlying causative monogenic variant in approximately 30% to 45% of cases of DCM and ACM.[7] The correlation between genetic mutations and disease expression is helpful for early diagnosis, improving survival, and reducing morbidity.[7] Although genetic substrates do not always predict the same phenotypic disease expression, literature data suggest that specific genes can lead to distinct outcomes, particularly concerning the risks of progressive heart failure (HF), sudden cardiac death (SCD), and arrhythmias.[8-13] Previous genotype-phenotype studies have primarily focused on the analysis of a single phenotype, and the diagnostic and prognostic features of CMP genotypes across different phenotypic expressions remain poorly understood.

In this study, we assessed the prognostic prediction of an initial clinical phenotype-based classification vs applying a genotype-based classification in a large cohort of patients with nonhypertrophic CMP phenotypes (DCM, ARVC, ALVC, or BiV) carrying pathogenic/likely pathogenic variants (P/LP) in CMP genes.[14,15]

METHODS

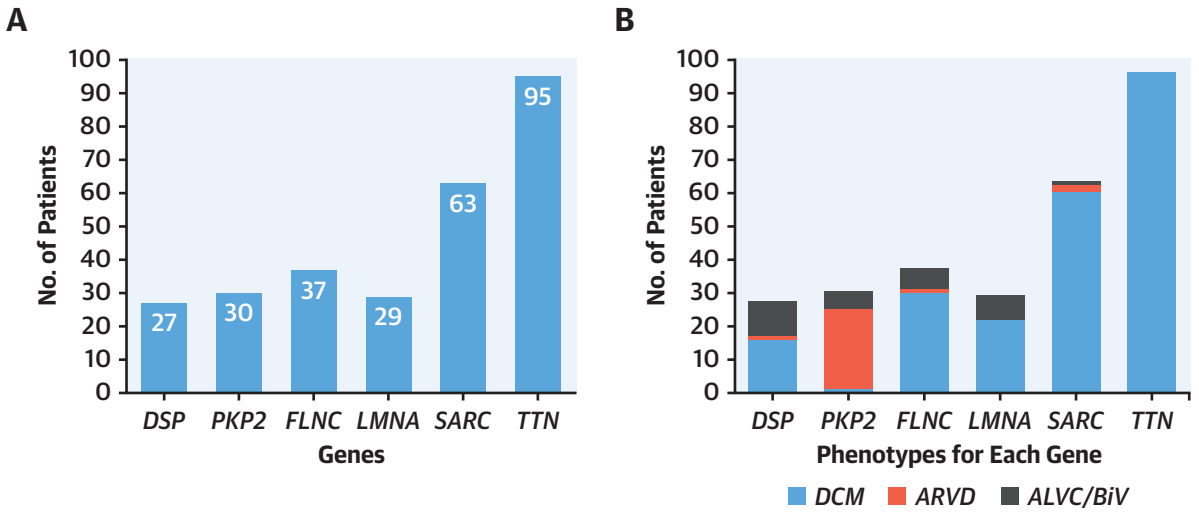
STUDY POPULATION AND CLINICAL CHARACTERIZATIONS.

We included patients with DCM, ARVC, ALVC, and BiV who underwent genetic testing between January 1, 2016, and December 31, 2019, in the Familial Cardiomyopathy Registry, which is a multicenter (Cardiovascular Department, University of Trieste, Italy, and Cardiovascular Institute, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA) ongoing project studying hereditary human cardiomyopathies. Our study received the proper ethical oversight (CERU N.O. 43/2009, 211/2014/Em).

DCM was defined as the presence of impaired left ventricular ejection fraction (LVEF) (<50%) after careful exclusion of secondary causative etiologies.[1] ARVC phenotype was defined according to the 2010 Task Force Criteria[16]; ALVC phenotype was defined as DCM presentation not fulfilling Task Force Criteria for ARVC and with ≥1 of the following criteria at baseline: SCD/major ventricular arrhythmias (MVAs) (defined as resuscitated cardiac arrest, sustained ventricular tachycardia [VT], appropriate implantable cardioverter-defibrillator [ICD] interventions), unexplained syncope, ≥1,000 premature ventricular contractions (PVCs)/24 hours, and ≥50 couplets/24 hours at electrocardiogram (ECG) monitoring[4,17]; BiV was defined as "definite" ARVC plus LVEF <50%.[4]

Demographic and clinical data, including HF symptoms (New York Heart Association functional class), previous myocardial injury events, and competitive sport activity levels, were collected at the baseline evaluation. Myocardial injury was defined as chest pain, serum cardiac troponin elevation, and the absence of obstructive coronary disease on coronary angiogram.[11] Intense exercise (>60 minutes, >3 times/wk and beyond aerobic threshold) participation was classified as participation in competitive sport.[11] Detailed information on family history of CMPs and SCD, with a ≥3 generation pedigree, were recorded. Data from 12-lead ECGs and Holter ECG monitoring including ventricular arrhythmias (nonsustained ventricular tachycardia [NSVT]), atrial fibrillation (AF)/atrial flutter, and atrioventricular (AV) blocks were recorded. Echocardiographic left ventricular (LV) and right ventricular (RV) dimensions and systolic function were assessed at transthoracic echocardiography following international guidelines.[18] LV and RV systolic dysfunction were defined by

FIGURE 1 Gene Variants and Phenotypic Distribution of the Study Population



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	DCM	ARVD	ALVC/BiV
DSP (27)	16 (59%)	1 (4%)	10 (37%)
PKP2 (30)	1 (3%)	24 (80%)	5 (17%)
FLNC (37)	30 (81%)	1 (3%)	6 (16%)
LMNA (29)	22 (76%)	0 (0%)	7 (24%)
SARC (63)	60 (95%)	2 (3%)	1 (2%)
TTN (95)	95 (100%)	0 (0%)	0 (0%)
Total (281)	224 (80%)	28 (10%)	29 (10%)

A brief description our final study population elucidating the number of patients enrolled with pathogenic/likely pathogenic variants (P/LP) in the selected genes and their phenotypes at enrollment. **(A)** Histograms showing the number of patient carriers of P/LP variants in each gene or gene-group of our study population. **(B)** The same histograms with **(C)** annexed table, reporting the phenotypic distribution of patient carriers of P/LP variants in each gene or gene-group. ALVC = left dominant arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; BiV = biventricular arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; DSP = desmoplakin; FLNC = filamin C; LMNA = lamin; PKP2 = plakophilin 2; SARC = sarcomeric genes; TTN = titin.

LVEF <50% and RV fractional area change <35%, respectively.[18] Severity of mitral regurgitation was quantified according to current recommendations.[19]

MOLECULAR GENETICS AND DEFINITION OF GENETIC VARIANTS. Genetic testing was performed by next generation DNA sequencing of multigene panels, as previously reported.[20,21] Gene variants were classified as P/LP according to the American College of Medical Genetics and Genomics criteria (ACMG).[22] Only carriers (probands and affected relatives) of P/LP variants in genes with robust disease association[14,15,23] were considered eligible for the purposes of this study. Inside the cohort of P/LP carriers, patients were separately grouped by gene or cluster. Sarcomeric genes (*SARC*) were grouped in a "gene-cluster," with a functionally homogeneous background, including *TNNT2, MYH7, TNNC1,* and *ACTC1*, according to recent evidence[15] and as previously reported.[20] To obtain statistically meaningful comparisons, genes represented by fewer than 10 patients

TABLE 1 Baseline Characteristics of Total Population, According to Phenotype (DCM, ARVC, ALVC/BiV)

	Total Population (N = 281)	DCM (n = 224 [80%])	ARVC (n = 28 [10%])	ALVC/BiV (n = 29 [10%])	*P* Value
Age, y	42 (31-52)	44 (40-45)	39 (36-50)	41 (34-45)	0.308
Gene variants					
DSP	27 (10)	16 (7)	1 (4)	10 (34)	<0.001[a,b,c]
PKP2	30 (11)	1 (0.4)	24 (86)	5 (17)	
FLNC	37 (13)	30 (13)	1 (4)	6 (21)	
LMNA	29 (10)	22 (10)	0 (0)	7 (24)	
SARC	63 (22)	60 (27)	2 (7)	1 (3)	
TTN	95 (34)	95 (42)	0 (0)	0 (0)	
Caucasian	276 (98)	219 (98)	28 (100)	29 (100)	0.523
Male	197 (70)	161 (72)	18 (64)	18 (62)	0.432
NYHA functional class					
I	148 (53)	106 (47)	23 (82)	19 (65)	0.028
II	84 (30)	72 (32)	4 (14)	8 (27)	
III	46 (16)	43 (19)	1 (4)	2 (7)	
IV	3 (1)	3 (1)	0 (0)	0 (0)	
Family history of CMP	170 (60)	132 (59)	18 (64)	20 (67)	0.507
Family history of SCD	71 (25)	46 (20)	11 (39)	14 (48)	0.006[b]
Hypertension	42 (15)	36 (16)	5 (18)	2 (7)	0.064
Myocardial injury	12 (4)	10 (5)	0 (0)	2 (7)	0.351
Competitive sport	19 (7)	5 (2)	7 (25)	7 (24)	<0.001[a,b]
LBBB	38 (13)	38 (17)	0 (0)	0 (0)	0.004[a,b]
LVEF ≤35%	138 (49)	138 (62)	0 (0)	0 (0)	<0.001[a,b]
LVEF, %	43 (35-52)	32 (30-34)	62 (58-66)	49 (46-54)	<0.001[a,b,c]
RV dysfunction	60 (21)	36 (16)	12 (43)	12 (41)	0.254
LVEDd, mm	61 (51-70)	64 (62-66)	49 (46-51)	51 (48-54)	<0.001[a,b]
MR moderate-severe	51 (18)	46 (20)	2 (7)	3 (10)	<0.001[a,b]
Atrial fibrillation	47 (17)	35 (16)	4 (14)	8 (27)	0.301
NSVT	75 (27)	54 (24)	7 (25)	14 (48)	0.001[b]
AV blocks					
I	25 (9)	20 (9)	3 (10)	2(7)	0.581
II - Mobitz type I	4 (1)	4 (2)	0 (0)	0.461	0.461
II - Mobitz type II	1 (0.3)	1 (0.4)	0 (0)	0.828	0.828
III	3 (1)	3 (1)	0 (0)	0.686	0.686
RAAS-I	193 (69)	177 (79)	6 (21)	10 (34)	<0.001[a,b]
Beta-blockers	212 (76)	183 (83)	12 (43)	19 (65)	<0.001[a,b]
ICD implantation (at follow-up)	136 (48)	103 (46)	16 (57)	17 (58)	0.327
CRTD implantation/upgrading (at follow-up)	37 (13)	37 (16)	0 (0)	0 (0)	0.004[a,b]

Values are median (IQR) or n (%). Main clinical and instrumental characteristics of study population based on phenotype. [a]$P < 0.02$ dilated cardiomyopathy (DCM) vs arrhythmogenic right ventricular cardiomyopathy (ARVC). [b]$P < 0.02$ DCM vs left dominant arrhythmogenic cardiomyopathy (ALVC)/ biventricular arrhythmogenic right ventricular cardiomyopathy (BiV). [c]$P < 0.02$ ARVC vs ALVC/BiV.

AV = atrioventricular; CMP = cardiomyopathy; CRTD = cardiac resynchronization therapy defibrillator; DSP = desmoplakin; FLNC = filamin C; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LMNA = lamin; LVEDd = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PKP = plakophilin; RAAS-I = renin angiotensin aldosterone system inhibitors (ie, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers); RV = right ventricle; SARC = sarcomeric genes; SCD = sudden cardiac death; TTN = titin.

were excluded from the analysis of clinical characterization and prognostic assessment. The complete list of carriers and genes are in the Supplemental Appendix. To validate the predictivity of genotype and phenotype in a larger population of non-hypertrophic CMPs, a cohort of patients in whom next-generation sequencing tested negative for P/LP variants (P/LP variant-negative cohort) and available follow-up data was considered.

STUDY ENDPOINTS. The combined study endpoints were as follows: 1) primary outcome: all-cause mortality (D)/heart transplantation (HT); 2) arrhythmic secondary outcome: SCD/MVA; and 3) HF secondary outcome: heart failure-related death (DHF)/HT/left ventricular assist device (LVAD). MVA included ventricular fibrillation, sustained VT (lasting >30 seconds or with hemodynamic instability), and appropriate ICD interventions (shock or

TABLE 2 Baseline Characteristics of Study Population, According to Genotype Distribution

	DSP (n = 27 [10%])	*PKP2* (n = 30 [11%])	*FLNC* (n = 37 [13%])	*LMNA* (n = 29 [10%])	*SARC* (n = 63 [22%])	*TTN* (n = 95 [34%])	*P* Value
Age, y	41 (28-54)	39 (28-52)	39 (31-51)	40 (33-53)	42 (32-55)	47 (37-59)	0.088
Disease							
DCM	16 (59)	1 (3)	30 (81)	22 (76)	60 (95)	95 (100)	<0.001[a,b,c,d,e,f,g,h]
ARVC	1 (4)	24 (80)	1 (3)	0 (0)	2 (3)	0 (0)	
ALVC/BiV	10 (37)	5 (17)	6 (16)	7 (24)	1 (2)	0 (0)	
Caucasian	27 (100)	30 (100)	37 (100)	29 (100)	59 (94)	94 (99)	0.074
Sex	14 (52)	20 (67)	27 (73)	20 (69)	46 (73)	70 (74)	0.362
NYHA functional class							
I	16 (59)	24 (80)	23 (62)	13 (45)	28 (44)	44 (46)	0.140
II	9 (33)	5 (17)	10 (27)	10 (35)	19 (30)	31 (32)	
III	2 (7)	1 (3)	4 (11)	5 (17)	15 (24)	19 (20)	
IV	0 (0)	0 (0)	0 (0)	1 (3)	1 (2)	1 (1)	
Family history of CMP	14 (52)	18 (60)	26 (70)	17 (59)	40 (63)	55 (58)	0.710
Family history of SCD	8 (30)	9 (30)	21 (57)	7 (24)	6 (9)	20 (21)	<0.001[d,f,i]
Hypertension	4 (15)	5 (17)	4 (11)	3 (10)	7 (11)	19 (29)	0.348
Myocardial injury	2 (7)	0 (0)	2 (5)	1 (3)	0 (0)	7 (7)	0.260
Competitive sport	2 (7)	8 (27)	4 (10)	2 (7)	1 (2)	2 (2)	0.048[j]
LBBB	2 (7)	0 (0)	3 (9)	10 (35)	9 (15)	14 (15)	0.005[e]
LVEF ≤35%	10 (37)	0 (0)	12 (32)	14 (48)	39 (62)	63 (66)	<0.001[a,d,e,f,k,j]
LVEF, %	40 (29-48)	61 (56-65)	42 (30-49)	33 (26-47)	30 (21-43)	32 (23-40)	<0.001[a,d,e,k,j]
RV dysfunction	6 (22)	13 (43)	7 (19)	5 (17)	10 (16)	19 (20)	0.047[d,e,k]
LVEDd, mm	57 (54-61)	48 (46-50)	59 (57-62)	60 (56-65)	63 (60-65)	66 (63-68)	<0.001[a,c,d,e,j,k]
MR moderate-severe	5 (18)	2 (3)	6 (16)	4 (14)	9 (14)	25 (26)	<0.001[a,d,e,j,k]
Atrial fibrillation	2 (7)	2 (7)	4 (11)	9 (31)	7 (11)	23(24)	0.003[e,g,l,m]
NSVT	10 (37)	7 (23)	12 (32)	10 (34)	8 (13)	28 (29)	0.003[b]
AV blocks							
I	0 (0)	3 (10)	5 (13)	6 (21)	3 (5)	8 (8)	0.021[g,h,l,n]
II - Mobitz type I	0 (0)	0 (0)	0 (0)	3 (10)	0 (0)	1 (1)	<0.001[l,n,m,h]
II - Mobitz type II	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0.031
III	1 (4)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)	0.401
RAAS-I	17 (62)	8 (27)	23 (62)	20 (69)	44 (68)	81 (85)	<0.001[a,d,e,j,k]
Beta-blockers	22 (81)	12 (40)	28 (75)	24 (82)	46 (73)	80 (84)	<0.001[a,d,e,j,k]
ICD implantation (at follow-up)	17 (63)	17 (57)	15 (41)	17 (59)	24 (38)	46 (48)	0.174
CRTD implantation/upgrading (at follow-up)	4 (15)	0 (0)	1 (3)	8 (28)	10 (16)	14 (15)	0.017[e]

Values are median (IQR) or n (%). Main clinical and instrumental characteristics of study population based on genotype. [a]$P < 0.0034$ DSP vs PKP2. [b]$P < 0.0034$ DSP vs SARC. [c]$P < 0.0034$ DSP vs TTN. [d]$P < 0.0034$ PKP2 vs FLNC. [e]$P < 0.0034$ PKP2 vs LMNA. [f]$P < 0.0034$ FLNC vs TTN. [g]$P < 0.0034$ LMNA vs SARC. [h]$P < 0.0034$ LMNA vs TTN. [i]$P < 0.0034$ FLNC vs SARC. [j]$P < 0.0034$ PKP2 vs TTN. [k]$P < 0.0034$ PKP2 vs SARC. [l]$P < 0.0034$ DSP vs LMNA. [m]$P < 0.0034$ FLNC vs LMNA.

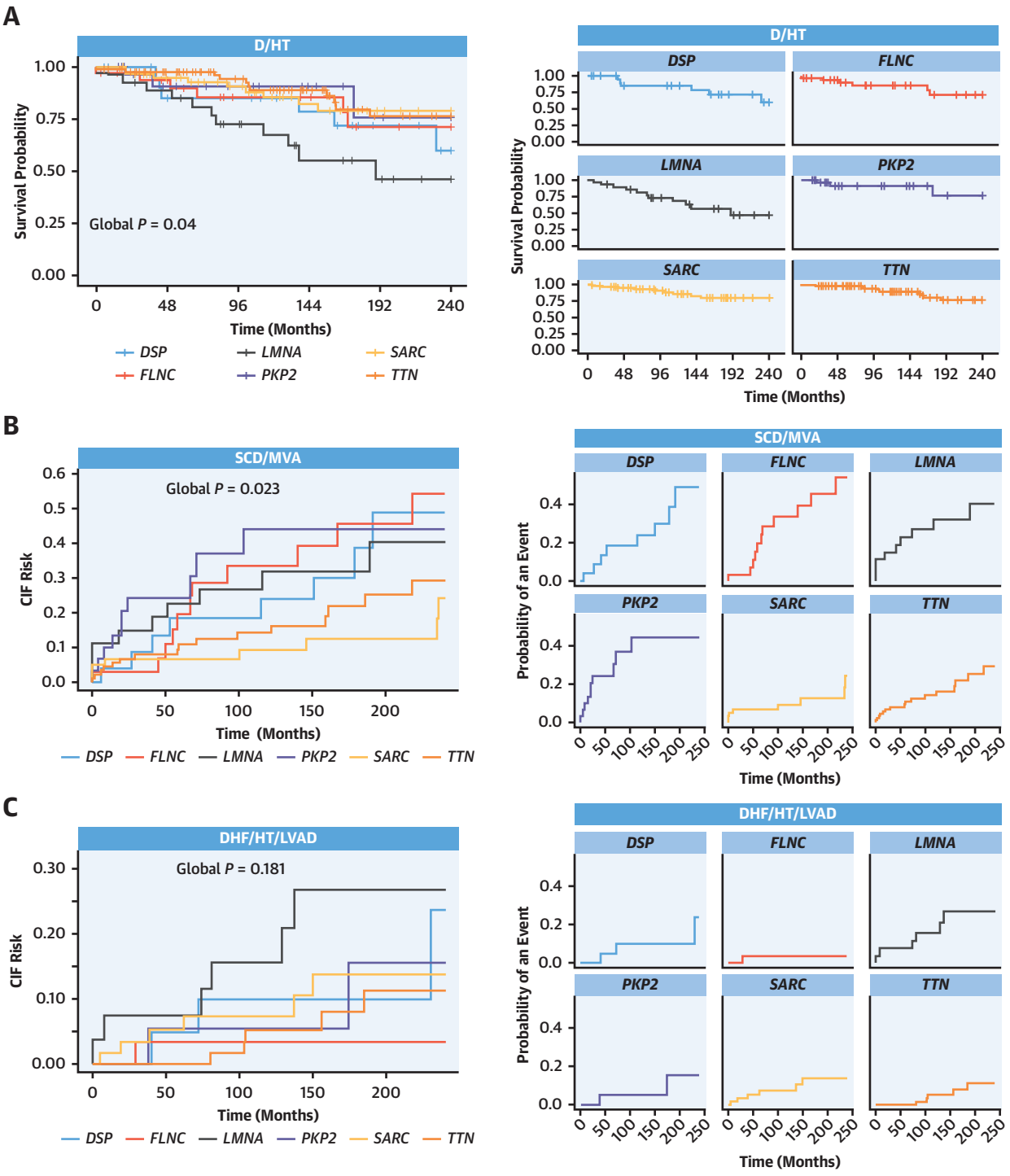
Abbreviations as in Table 1.

antitachycardia pacing on ventricular fibrillation or sustained VT). SCD was defined as witnessed SCD with or without documented ventricular fibrillation, death within 1 hour of acute symptoms, or nocturnal death with no antecedent history of immediate worsening symptoms. The follow-up date for analysis ended at the date of the first endpoint or at the last available contact with the patient.

To assess the performance of the 2 different classifications of patients (phenotype and genotype based) for the clinical categorization and endpoint prediction, patients were differentially grouped according to 3 phenotypes at presentation (DCM, ARVC, and ALVC/BiV) and into genotype categories (as explained in the "Molecular genetics and definition of genetic variants" section).

STATISTICAL ANALYSIS. Variables were expressed as median (IQR) or counts (%), as appropriate. Comparisons between groups were made by the analysis of variance test on continuous variables using the Brown-Forsythe statistic when the assumption of equal variances did not hold or the nonparametric Mann-Whitney test; the chi-square test or the Fisher exact test were calculated for discrete variables. Kaplan-Meier curves for primary endpoint (log-rank test) and cumulative incidence function for the

FIGURE 2 Survival Analysis of the Study Population Based on Genotype



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	DSP (27)	*PKP2* (30)	*FLNC* (37)	*LMNA* (29)	*SARC* (63)	*TTN* (95)	*P* Value
D/HT	6 (23%)	3 (10%)	6 (18%)	11 (41%)	9 (15%)	11 (12%)	0.04
SCD/MVA	8 (31%)	10 (33%)	11 (33%)	9 (33%)	8 (13%)	16 (18%)	0.023
DHF/HT/LVAD	3 (12%)	3 (7%)	1 (3%)	6 (22%)	6 (10%)	5 (6%)	0.181

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2 secondary endpoints (Gray's test) were compared in the first instance for phenotype manifestation. Multivariate analysis was performed using Cox regression models with cause-specific hazard function. As some patients were family members, family was included in the model as clustering factor. A P value <0.05 was considered statistically significant. Statistical analyses were performed in R version 4.1.1 (R Foundation for Statistical Computing) with packages "survival"[24] and "cmprisk."[25]

RESULTS

DESCRIPTION OF STUDY POPULATION. In the selected period, a total of 834 patients affected by DCM (n = 690; 83%), ARVC (n = 70; 8%), and ALVC/BiV (n = 74; 9%) were subjected to genetic testing in our centers. Of these patients, 315 (38%) were carriers of P/LP variants, including 253 DCM (DCM genetic yield: 37%), 30 ARVC (ARVC genetic yield: 43%), and 32 ALVC/BiV (ALVC/BiV genetic yield: 43%). A total of 9 genes (*PLN, BAG3, RMB20, SCN5A, DMD, DES, DSG2, DSC2,* and *NEXN*), counting <7 carriers each, were excluded from further analysis (Supplemental Table 1). The final population included 281 patients (218 probands [78%]; 63 affected relatives [22%] belonging to 33 families) (Supplemental Figure 1). In total, 6 gene/gene cluster groups were identified: *TTN* (n = 95; 34%), *SARC* (n = 63; 22%), *FLNC* (n = 37; 13%), *PKP2* (n = 30; 11%), *LMNA* (n = 29; 10%), and *DSP* (n = 27; 10%) (**Figure 1A,** Supplemental Table 2). The median age at enrollment was 42 years (IQR: 31-52 years), and 70% of the patients were men. The phenotypic distribution at presentation was characterized predominantly by DCM (n = 224; 80%), followed by ARVC (n = 28; 10%) and ALVC/BiV (n = 29; 10%). Over a median follow-up of 118 months (IQR: 50-188 months), 46 D/HT, 23 DHF/HT/LVAD, and 62 SCD/MVA events were recorded.

SPECTRUM OF CMPs PHENOTYPES AT ONSET. Table 1 shows the baseline characteristics of the study population according to phenotype. The adopted diagnostic criteria clearly distinguished the phenotypes between the different CMPs. Patients with DCM showed more prominent LV dilatation and LV systolic dysfunction (LVEF ≤35%) (ARVC, n = 0; ALVC/BiV, n = 0; DCM, n = 138 [62%]; $P < 0.001$), more frequently with left bundle branch block (LBBB) (ARVC, n = 0; ALVC/BiV, n = 0; DCM, n = 38 [17%]; $P < 0.001$), and were more likely to have moderate-severe mitral regurgitation (ARVC, n = 2 [7%]; ALVC/BiV, n = 3 [10%]; DCM, n = 46 [20%]; $P < 0.001$). Patients with ARVC and ALVC/BiV had a family history of SCD (ARVC, n = 11 [39%]; ALVC/BiV, n = 14 [48%]; DCM, n = 46 [20%]; $P = 0.006$), reported engaging in competitive sports (ARVC n = 7 [25%]; ALVC/BiV n = 7 [24%]; DCM n = 5 [2%]; $P < 0.001$), or had RV dysfunction (ARVC, n = 12 [43%]; ALVC/BiV, n = 12 [41%]; DCM, n = 36 [16%]; $P < 0.001$). Moreover, NSVT was more frequently detected on Holter ECG monitoring in patients with ALVC/BiV than in patients with ARVC and DCM (ALVC/BiV, n = 14 [48%]; ARVC, n = 7 [25%]; DCM, n = 54 [24%]; $P = 0.001$).

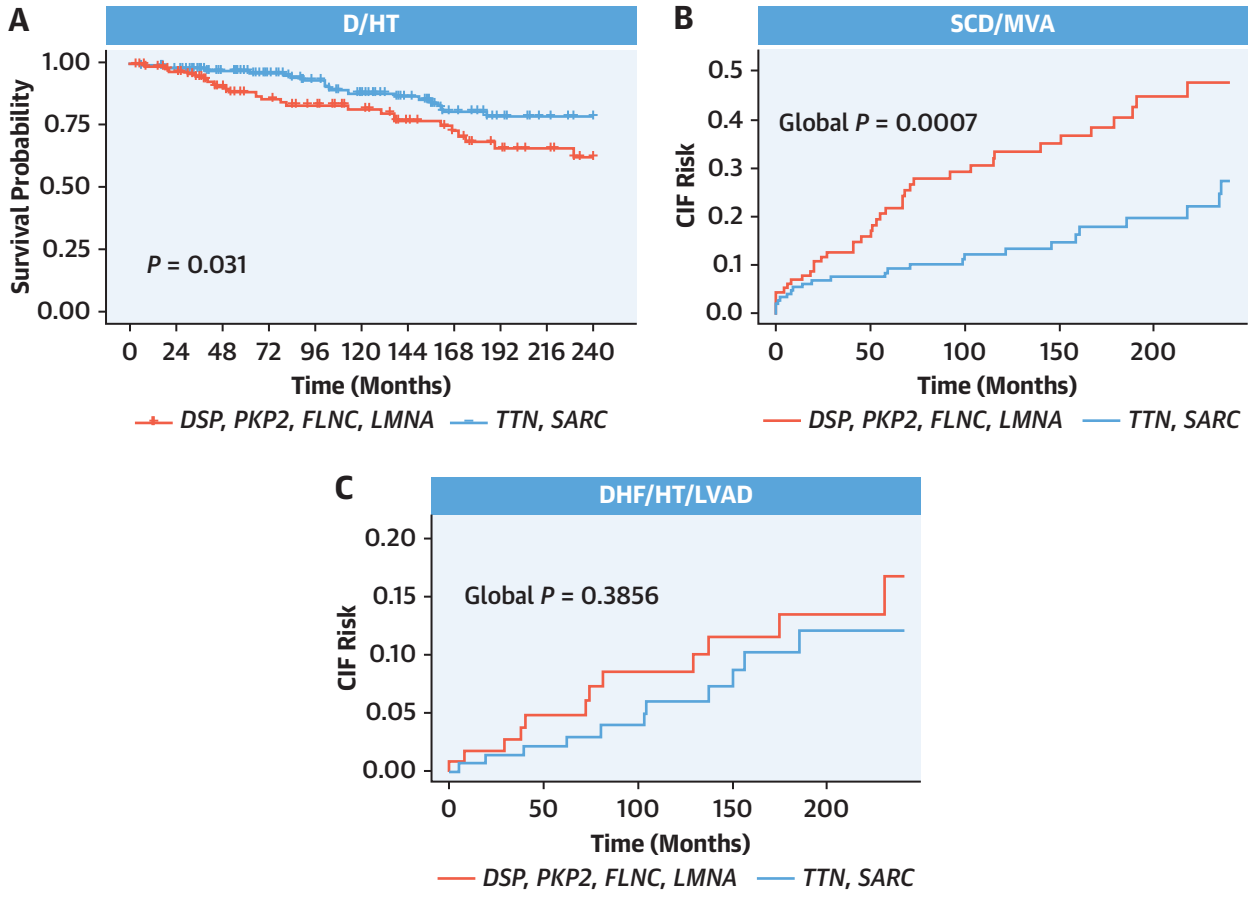
Each phenotype was associated with multiple causative genes. The largest genetic heterogeneity was identified for DCM (6 genes), followed by ALVC/BiV (5 genes) and ARVC (4 genes). Notably, at the end of the follow-up period, 39 patients with DCM (17% of the DCM cohort) met the criteria for ALVC/BiV diagnosis. In particular, *TTN* (17%), *DSP* (15%), *LMNA* (21%), and *FLNC* (22%) carriers initially affected by DCM tended to convert their phenotypes (Supplemental Figure 2).

SPECTRUM OF GENOTYPE-PHENOTYPE ASSOCIATIONS. Gene-based characterization is reported in **Table 2**, which shows the baseline characteristics of the study population according to gene/gene cluster groups. *TTN* and *SARC* variants were mostly associated with the DCM phenotype (*TTN*: n = 95 DCM [100%]; *SARC*: n = 60 [95%]), whereas *PKP2* variants were mostly associated with ARVC or ALVC/BiV (n = 24 ARVC [80%]; n = 5 ALVC/BiV [17%]) (**Figures 1B and 1C**). A more heterogeneous phenotypic distribution was detected for 3 genes: *DSP* (n = 16 patients with DCM [59%]), *LMNA* (n = 22 DCM [76%]), and *FLNC* (n = 30 DCM [81%]). Notably, *TTN*, *SARC*, and *LMNA* variant carriers were more frequently affected by severe (LVEF ≤35%) LV dysfunction at enrollment. *PKP2* carriers showed isolated RV dysfunction more frequently. LBBB was not present among our carriers

FIGURE 2 Continued

Gene-specific survival curves for each outcome, showing *LMNA* carriers at the highest risk of D/HT and *DSP*, *PKP2*, *FLNC*, and *LMNA* with higher and comparable sudden cardiac death (SCD)/major ventricular arrhythmia (MVA) risks. **(A) (Left)** Kaplan-Meier curves for D/HT endpoint. **(Right)** The same curves split singularly for each gene/gene group. **(B)** CIF curves for the SCD/MVA endpoint. **(Right)** The same curves split singularly for each gene/gene group. **(C)** CIF curves for the DHF/HT/LVAD endpoint. **(Right)** The same curves split singularly for each gene/gene group. **(D)** Table reporting the counts of each endpoint for each gene/gene group. D = all-cause mortality; DHF = heart failure-related death; CIF = cumulative incident fraction; HT = heart transplantation; LVAD = left ventricular assist device; other abbreviations as in **Figure 1**.

FIGURE 3 Survival Analysis of "Arrhythmic Genes" Compared With *TTN* and *SARC*



D

	DSP, PKP2, FLNC, LMNA (123)	*TTN, SARC* (158)	*P* Value
D/HT	26 (22%)	20 (13%)	0.031
SCD/MVA	42 (36%)	30 (20%)	< 0.001
DHF/HT/LVAD	13 (11%)	13 (9%)	0.385

Patient carriers of "arrhythmic genes" variants (*DSP*, *FLNC*, *LMNA*, and *PKP2*), were associated with a significantly higher risk of D/HT ($P = 0.031$) and SCD/MVA ($P < 0.001$) compared with carriers of *TTN* and *SARC* variants. **(A)** Kaplan-Meier curves for the primary endpoint (D/HT). **(B)** CIF curves for the SCD/MVA secondary outcome. **(C)** CIF curves for the DHF/HT/LVAD outcome. **(D)** Table reporting the counts of each endpoint. Abbreviations as in Figures 1 and 2.

of *DSP*, *PKP2*, and *FLNC* variants but was particularly enriched in *LMNA* carriers. Moreover, *LMNA* carriers showed a higher prevalence of AF and second-degree AV block.

PROGNOSTIC PREDICTION OF PHENOTYPE- VS GENOTYPE-BASED CLASSIFICATION. Because patients with ARVC and ALVC/BiV showed a comparable number of events (Supplemental Figure 3), they were grouped into the ACM category[4] for phenotype-based prognostic analyses. Patients with ACM had a higher number of SCD/MVA events than patients with DCM (ACM, n = 21 [37%]; DCM, n = 41 [18%]; $P = 0.001$), but no differences in D/HT and DHT/HT/LVAD outcomes were detected (Supplemental Figure 4). The 6 gene groups differed with respect to D/HT and SCD/MVA

outcomes (Figure 2A) (D/HT: *LMNA* n = 11 [41%]; *DSP* n = 6 [23%]; *PKP2* n = 3 [10%]; *FLNC* n = 6 [18%]; *SARC* n = 9 [15%]; *TTN* n = 11 [12%]; *P* = 0.04) (Figure 2B) (SCD/MVA: *LMNA* n = 9 [33%]; *DSP* n = 8 [31%]; *PKP2* n = 10 [33%]; *FLNC* n = 11 [33%]; *SARC* n = 8 [13%]; *TTN* n = 16 [18%]; *P* = 0.023), whereas no significant differences were observed in the risk of DHT/HT/LVAD (Figure 2C, Supplemental Figure 5 with age in the X-axis). *LMNA* carriers were at the highest risk of developing D/HT and DHF/HT/LVAD. *DSP*, *PKP2*, *FLNC*, and *LMNA* showed a higher and more comparable number of SCD/MVA events; these 4 genes, if grouped together ("arrhythmic genes"), were associated with a significantly higher risk of D/HT (*P* = 0.031) and SCD/MVA (*P* < 0.001) compared with *TTN* and *SARC* variants (Figure 3). To properly identify the predictive value of genotype (considered as a carrier of a P/LP variant in one of the "arrhythmic genes") and phenotype (considered as the presence of DCM vs ACM at presentation) in our cohort, we performed a multivariable analysis, adjusting for familial forms, sex, age, and LVEF at baseline (Table 3). With respect to the primary outcome (D/HT), both genotype-based and phenotype-based classifications, together with LVEF at baseline, were predictive (Table 3), although carriers of arrhythmic gene variants showed the strongest association. Conversely, genotype-based classification was associated with the risk of SCD/MVA among the candidate risk predictors (HR: 2.22; 95% CI: 1.26-3.93), whereas phenotype-based classification did not significantly predict this risk (Table 3). Accordingly, the incidence of SCD/MVA in DCM and ACM phenotypes was similar for patients carrying P/LP variants in *DSP*, *LMNA*, and *FLNC* genes (*DSP*: MVA 35% in DCM vs 36% in ACM; *LMNA*: MVA 27% in DCM vs 33% in ACM; *FLNC*: MVA 38% in DCM and 42% in ACM). The results for DHF/HT/LVAD are reported in Table 3, showing that neither genotype nor phenotype were predictive of this outcome. Finally, when a cohort of 370 patients who were P/LP variant-negative (300 DCM [81%]; 34 ARVC [9%]; 36 ALVC/BiV [10%]) (Supplemental Table 3) was included in the multivariable model to test the predictivity of genotype-based classification in a larger population, the arrhythmic genes were still significantly predictive of the risk of the primary outcome (Supplemental Table 4A: HR: 2.69; 95% CI: 1.52-4.76; and Supplemental Table 4B for SCD/MVA risk: HR: 2.14; 95% CI: 1.30-3.54). P/LP variant-negative status was also mildly associated with the primary outcome (HR: 1.77; 95% CI: 1.10-2.85) (Supplemental Table 4A). In this model, the DCM phenotype, compared with the ACM phenotype, showed a weak association with a lower risk of SCD/MVA (see Supplemental Table 4C for the prediction of DHF/HT/LVAD).

TABLE 3 Multivariable Outcome Analysis of the Study Population

	HR	95% CI	*P* Value
D/HT			
Sex	0.65	0.36-1.16	0.15
Age	0.98	0.96-1.01	0.091
LVEF	0.93	0.90-0.96	<0.001
Phenotype (DCM)	0.28	0.11-0.76	0.012
Genotype (AG)	2.45	1.25-4.79	0.009
SCD/MVA			
Sex	2.28	1.15-4.51	0.018
Age	1.02	1.01-1.04	0.018
LVEF	0.99	0.97-1.01	0.3
Phenotype (DCM)	0.53	0.25-1.14	0.11
Genotype (AG)	2.22	1.26-3.93	0.004
DHF/HT/LVAD			
Sex	0.42	0.19-0.90	0.026
Age	0.99	0.96-1.02	0.6
LVEF	0.95	0.91-0.99	0.015
Phenotype (DCM)	0.28	0.06-1.29	0.10
Genotype (AG)	1.53	0.57-4.07	0.4

Predictive modeling of phenotype (reference DCM) and genotype (reference TTN/SARC) for the expected outcomes were adjusted for sex (male), age, and left ventricular ejection fraction (LVEF) at baseline. Primary outcome (all-cause mortality [D]/heart transplantation [HT]), arrhythmic secondary outcome (SCD/major ventricular arrhythmia [MVA]), and heart failure secondary outcome (heart failure related death [DHF]/HT/left ventricular assist device [LVAD]).

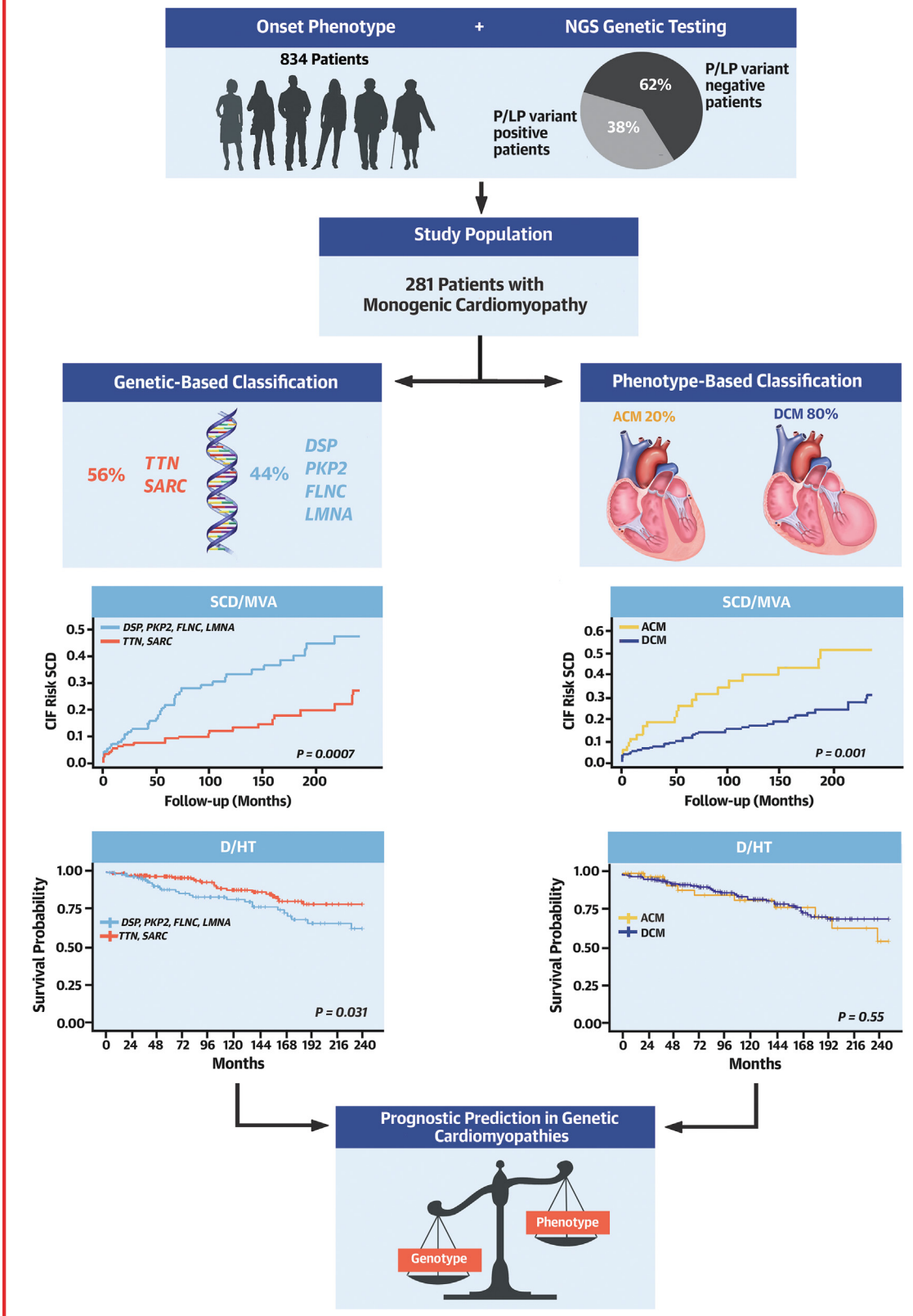
AG = arrhythmic genes; DCM = dilated cardiomyopathy; other abbreviations as in Table 1.

DISCUSSION

MAIN FINDINGS. In the present study, the phenotype- and genotype-based CMP classifications were compared in a large cohort of 281 monogenetically determined nonhypertrophic CMPs (DCM, ARVC, ALVC, and BiV) to test their efficiency in predicting outcomes. To our knowledge, this is the first study to encompass multiple phenotypes in a CMP population with P/LP variant genotype.

The key findings of our study include the following: 1) a genotype-based classification provides a different but efficient prognostic prediction of genetic CMPs initially classified according to phenotype; 2) the genotype-based classification was found to be particularly effective in predicting the risk of SCD/MVA, whereas the phenotype-based classification was not predictive of this risk; and 3) among the tested genes, *LMNA* variants were associated with worse outcomes in terms of D/HT and DHF/HT/LVAD compared with other genotypes (Central Illustration).

CENTRAL ILLUSTRATION **Toward Genotype-Based Classification of Nonhypertrophic Cardiomyopathies for Precise Risk Prediction**



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ROLE OF PHENOTYPE-BASED AND GENOTYPE-BASED CLASSIFICATION. Even if the commonly adopted phenotype-based CMP classification provides a universally applicable diagnostic approach, the overlap of some phenotypes, especially among DCM, ALVC, and BiV, is frequent. This renders the phenotype-only classification challenging. Furthermore, clinical diagnostic criteria are rapidly evolving to become multiparametric and thus, potentially complex to apply to a single patient by a clinician.[20] Finally, the phenotype might be insufficiently accurate for prognostic stratification of CMPs caused by a specific genetic background.[26]

In our cohort, the appropriateness of the phenotype-based classification was demonstrated to distinguish the typical clinical features of genetic CMPs. However, the application of stringent phenotypic criteria determined the need to modify the classification for almost 20% of patients in the follow-up period (switch from DCM to ALVC/BiV), primarily in carriers of *FLNC, LMNA, TTN*, and *DSP* variants. The subsequent application of a genotype-based classification in the same cohort highlighted gene-specific clinical features relevant for future therapeutic management: eg, AV blocks and LBBB were strongly associated with *LMNA*, as well as AF with *LMNA* and *TTN*, and isolated RV dysfunction with *PKP2*.

Therefore, we consider the genotype-based classification of CMPs to be very informative and to significantly improve the phenotype-based classification. Furthermore, grouping CMPs per causative gene may provide a basis for the implementation of disease-specific research in precision medicine.[26]

In our cohort, significant phenotypic heterogeneity was confirmed, mostly in the subset of nonsarcomeric genes (*DSP*, *FLNC*, and *LMNA*), possibly reflecting different pathogenetic processes. The same consideration applies to other genes in which the association with phenotype seems more constant (*PKP2*, mostly ARVC, and *TTN* and *SARC*, mostly DCM). Furthermore, current consensus documents recommend targeted genetic testing once the patient's phenotype has been classified.[27,28] However, according to our results, genetic testing contributes to define the diagnosis and should be always considered during the classification process.

OUTCOME PREDICTION AND PROGNOSTIC FEATURES OF SPECIFIC GENES. Both phenotype- and genotype-based classifications were able to identify patients at higher risk of MVAs during follow-up in our large cohort of genetic CMPs. However, genotype-based classification has proven to be more accurate for SCD/MVA prediction. Most notably, according to this classification, only "arrhythmic genes'' were predictive for this outcome upon multivariable analysis, whereas phenotype was not. This finding has a clinical impact, because it implies that when genetic data are available and informative, they allow a better prognostic prediction for SCD/MVA risk than phenotype alone. Consistently, genes that were classified as "arrhythmic" presented the highest phenotypic heterogeneity, and we found no correlation between LVEF and SCD/MVA, as previously shown in some specific genetic form of CMPs.[10,11,29] Our results can be considered confirmatory in a more general population of CMPs with available genetic testing and further support recent trends in current guideline recommendations[4,30] to consider genotype-positivity for high-risk genes (*LMNA, FLNC, DSP,* and *PKP2*) to prompt evaluation for ICD implantation independent of the severity of LV dysfunction.

Furthermore, in our study, both genotype-based and phenotype-based classifications showed a significant correlation with overall mortality (D/HT). This result, according to the genotype-based classification, might be partially related to a faster and worse disease progression in *LMNA* variant carriers, also clearly showing the DHF/HT/LVAD outcome (**Figure 2**). Our *LMNA* population was characterized by a high prevalence of AV blocks, AF, LBBB, and NSVT, and we confirmed a high risk of SCD/MVA, even without LV systolic dysfunction, as already described.[12,29,31] In our study, however, the worst

CENTRAL ILLUSTRATION Continued

Approximately one-third of patients with nonhypertrophic cardiomyopathies are found to be carriers of monogenic disease-causing variants. If patients are grouped according to phenotype or genotype, a different risk prediction is obtained. *PKP2, FLNC, DSP,* and *LMNA* (arrhythmic genes) are associated with a higher risk of D/HT and SCD/MVA with respect to *TTN*/SARC genes, regardless of phenotypic presentation. ACM = arrhythmogenic cardiomyopathy; ALVC = left dominant arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; B = basal evaluation; BiV = biventricular arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; D/HT = all-cause mortality/heart transplantation; DSP = desmoplakin; F = follow-up evaluation; FLNC = filamin C; LMNA = lamin; PKP2 = plakophilin 2; P/LP = pathogenic/likely pathogenic SARC = sarcomeric genes; TTN = titin; SCD/MVA = sudden cardiac death/major ventricular arrhythmias.

global prognosis of *LMNA* variants, also compared with the other "arrhythmic genes," was mostly caused by a higher incidence of adverse nonarrhythmic events over follow-up, equally present in all *LMNA* phenotypes. Finally, *TTN* and *SARC* variants were the most represented gene mutations in our study population. Variants in these genes were almost exclusively associated with the DCM phenotype at baseline. Few conflicting reports on DCM related to *SARC* variants and their outcomes are currently available.[32-34] These mutations have been identified in almost 25% of DCM cases and 10% of familial DCM forms, showing a mild disease course and little tendency toward progression.[32] However, presentation early in life (from infancy to adolescence)[33] and some specific variants[34] appear to be characterized by more severe outcomes. In addition, for *TTN* truncating variants (*TTNtv*), inconsistent prognostic data regarding MVA[35] and response to optimal medical therapy have been reported in previous studies.[36] A recent report highlighted a relevant *TTNtv* arrhythmic burden mainly associated with severe LV systolic dysfunction.[13] Our study supports a relatively benign role, in terms of D/HT and SCD/MVA, of *TTNtv* and *SARC* variants presenting with the DCM phenotype compared with mutations in other genes.

Finally, the predictivity of genotype for D/HT and SCD/MVA was further strengthened when a cohort of P/LP variant-negative patients was included in the study. In this larger population, P/LP variant-negative status was associated only with the primary outcome, whereas the DCM phenotype, compared with the ACM phenotype, was mildly protective for SCD/MVA.

The available statements by the principal cardiological societies provide phenotypically oriented recommendations.[4,27,29,37] Our data, conversely, suggest that an approach in which patients with CMPs are firstly classified according to the underlying genotype (eg, *TTN*-CMP, *FLNC*-CMP, *DSP*-CMP) may further improve their clinical management and prognostic stratification.

STUDY LIMITATIONS. This was a retrospective study obtained from 2 referral centers for CMPs, mostly dedicated to DCM, which represented 80% of our population. Patients with BiV and ALVC were grouped together because of the limited number of patients in each group. It was a predominantly male population (70%) of mostly White or Caucasian ethnicities.

Due to the statistically insufficient number of individuals, carriers of P/LP variants in rare genes were excluded from the analysis of outcomes, further reducing the spectrum of clinical and prognostic characterization of a larger genetic DCM and ACM population. To contribute to the same effect, a single technology was used for sequencing, leading to the exclusion of falsely negative patients from this analysis because of the intrinsic error rate. Although phenotypic classification seems to be accurate, magnetic resonance imaging data were not considered in this analysis, and there is the potential for unrecognized arrhythmic events that were experienced by patients but not captured by any phenotypic measures, leading to misclassification of some ACM into DCM.

In summary, these results need to be validated in larger, multicenter studies, possibly associated with the availability of magnetic resonance imaging data and multiple genotyping techniques, to further optimize phenotyping and genotyping of the entire cohort.

CONCLUSIONS

Our study demonstrates that predicting key clinical outcomes based on the presence of a specific mutated gene is superior to phenotype-based classification in a heterogenous genetic nonhypertrophic CMP population. Independent of the phenotype (ARVC, ALVC, BiV, or DCM), *DSP*, *FLNC*, *LMNA,* and *PKP2* predicted a higher rate of SCD/MVA than *TTN* and *SARC* P/LP variants, whereas *LMNA* showed the worst prognosis in terms of nonarrhythmic events. These findings should prompt the inclusion of genotypes, in addition to phenotypes, in the evaluation and management of CMPs.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with genetically determined, monogenic, nonhypertrophic cardiomyopathy, genotype-based classification improves risk stratification compared with phenotypic characteristics alone.

COMPETENCY IN MEDICAL KNOWLEDGE: The *LMNA*, *FLNC*, *DSP*, and *PKP2* genotypes are associated with a high risk of arrhythmic events regardless of the severity of LV dysfunction, whereas the *LMNA* genotype is associated with the highest risk of nonarrhythmic adverse events.

TRANSLATIONAL OUTLOOK: The pathogenic mechanisms mediating the associations between specific genotypes with adverse outcomes in patients with cardiomyopathies requires further investigation.

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KEY WORDS ALVC, ARVC, DCM, genotype, pathogenic/likely pathogenic variants, phenotype

APPENDIX For supplemental tables and figures, please see the online version of this paper.