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Penetrance of Dilated Cardiomyopathy in Genotype-Positive Relatives

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ABSTRACT

BACKGROUND Disease penetrance in genotype-positive (G+) relatives of families with dilated cardiomyopathy (DCM) and the characteristics associated with DCM onset in these individuals are unknown.

OBJECTIVES This study sought to determine the penetrance of new DCM diagnosis in G+ relatives and to identify factors associated with DCM development.

METHODS The authors evaluated 779 G+ patients (age 35.8 ± 17.3 years; 459 [59%] females; 367 [47%] with variants in *TTN*) without DCM followed at 25 Spanish centers.

RESULTS After a median follow-up of 37.1 months (Q1-Q3: 16.3-63.8 months), 85 individuals (10.9%) developed DCM (incidence rate of 2.9 per 100 person-years; 95% CI: 2.3-3.5 per 100 person-years). DCM penetrance and age at DCM onset was different according to underlying gene group (log-rank $P = 0.015$ and $P < 0.01$, respectively). In a multivariable model excluding CMR parameters, independent predictors of DCM development were: older age (HR per 1-year increase: 1.02; 95% CI: 1.0-1.04), an abnormal electrocardiogram (HR: 2.13; 95% CI: 1.38-3.29); presence of variants in motor sarcomeric genes (HR: 1.92; 95% CI: 1.05-3.50); lower left ventricular ejection fraction (HR per 1% increase: 0.86; 95% CI: 0.82-0.90) and larger left ventricular end-diastolic diameter (HR per 1-mm increase: 1.10; 95% CI: 1.06-1.13). Multivariable analysis in individuals with cardiac magnetic resonance and late gadolinium enhancement assessment (n = 360, 45%) identified late gadolinium enhancement as an additional independent predictor of DCM development (HR: 2.52; 95% CI: 1.43-4.45).

CONCLUSIONS Following a first negative screening, approximately 11% of G+ relatives developed DCM during a median follow-up of 3 years. Older age, an abnormal electrocardiogram, lower left ventricular ejection fraction, increased left ventricular end-diastolic diameter, motor sarcomeric genetic variants, and late gadolinium enhancement are associated with a higher risk of developing DCM. (J Am Coll Cardiol 2024;83:1640-1651) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Advances in family screening and genetic testing sequencing techniques have increased the prevalence of dilated cardiomyopathy (DCM) known to be of genetic (familial) origin.[1-3] Genetic testing with next-generation sequencing technology has improved the diagnostic yield in cardiomyopathies progressively and, currently, a pathogenic (P) variant in DCM-related genes can be identified in approximately 30% to 40% of patients with DCM.[4-6]

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Once a DCM-causing variant is identified in a DCM patient, it is possible to screen his/her relatives to identify who has inherited the genetic variant.[7-9] This strategy has been proven to be cost-effective compared with clinical screening with electrocardiogram (ECG) and echocardiogram in all relatives, as it allows stopping regular evaluations in noncarriers of the genetic variant who are not at risk of developing the familial disease.[10]

Conversely, identification of genotype-positive (G+) relatives who do not display signs of DCM at initial evaluation leads to lifelong surveillance at regular time intervals, irrespective of clinical and genetic characteristics according to current recommendations.[7-9] However, the evidence to support this strategy is relatively weak,[11-14] and might lead also to a potentially unsustainable burden on health care providers and individuals.

Despite their clinical relevance, data on DCM penetrance, age at DCM onset, and clinical characteristics associated with DCM development in G+ relatives without DCM are scarce. The aim of the present study was to determine the penetrance of new DCM diagnosis in G+ relatives without DCM at initial evaluation and to evaluate predictors of DCM development during follow-up.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CMR = cardiac magnetic resonance

DCM = dilated cardiomyopathy

ECG = electrocardiogram

G+ = genotype-positive

ICD = implantable cardioverter-defibrillator

LP = likely pathogenic

LV = left ventricle

LVED = left ventricular end-diastolic

LVEDD = left ventricular end-diastolic diameter

LVEF = left ventricular ejection fraction

P = pathogenic

SCD = sudden cardiac death

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TABLE 1 Characteristics of Relatives Without DCM at the Initial Evaluation

	Entire Cohort (N = 779)	Individuals With CMR (n = 362)
Median follow-up time, mo	37.12 (16.3-63.77)	43.6 (23.5-76.3)
Mean follow-up time, mo	45.9 ± 37.1	52.5 (48.7-56.4)
Female	459 (59)	194 (53.6)
Mean age at first evaluation, y	36.7 (35.5-37.9)	36.5 ± 15.4
Clinical features		
Hypertension	90 (11.5)	37 (10.2)
Diabetes	31 (4.0)	7 (2)
Dyslipidemia	80 (10.3)	35 (9.7)
Smoker	94 (12.1)	50 (13.9)
Devices (at baseline)		
Pacemaker	7 (0.9)	0 (0)
ICD	8 (1.0)	0 (0)
History of previous arrhythmias		
SVT	18 (2.3)	9 (2.5)
Atrial fibrillation or flutter	31 (4.0)	14 (3.9)
Environmental modifiers		
Intense exercise	78 (10.1)	51 (14.2)
Alcohol abuse	10 (1.3)	3 (0.8)
Chemotherapy	11 (1.4)	3 (0.8)
Gene group		
TTN	367 (47.1)	105 (29)
Cytoskeleton/Z-disk	100 (12.8)	72 (19.9)
Desmosomal	88 (11.3)	71 (19.6)
Nuclear envelope	129 (16.6)	66 (18.2)
Motor sarcomeric	50 (6.4)	22 (6.1)
Others	45 (5.8)	26 (7.2)
First-degree relative of a DCM patient	473 (60.1)	219 (61)
ECG		
Sinus rhythm	766 (98.3)	356 (98.3)
RBBB	20 (2.6)	9 (2.5)
LBBB	17 (2.2)	9 (2.5)
Negative T-wave	133 (17.1)	77 (21.3)
Precordial leads	45 (33.8)	27 (35.1)
Limb leads	88 (66.2)	50 (64.9)
Abnormal ECG[a]	170 (21.8)	92 (25.4)
Echocardiogram		
LVEDD, mm	46.2 (45.8-46.6)	47.3 (41.8-51.8)
LVEF, %	60.7 (60.3-61.1)	60.0 (54.3-65.7)
Abnormal LV filling pattern[b]	103 (13.2)	44 (12.8)
Left atrial diameter, mm	32.2 (31.6-32.8)	31.7 (24.1-38.5)
CMR (n = 362)		
LVEDV, mL	144.8 (106-183.6)	144.8 (106-183.6)
LVEF, %	57.4 (56.6-58.2)	57.4 (56.6-58.2)
Noncompaction	20 (5.5)	20 (5.5)
LGE[c]	71 (19.6)	71 (19.6)
Subepicardial	30 (41.4)	30 (41.4)
Intramyocardial	27 (38.6)	27 (38.6)
Other	14 (20.0)	14 (20.0)

Values are median (Q1-Q3), mean ± SD, or n (%). [a]Abnormal ECG: negative T waves in two consecutive leads, bundle branch block, atrial fibrillation, atrial flutter, second-degree atrioventricular block or history of previous atrial fibrillation or atrial flutter. [b]Abnormal LV filling pattern: impaired relaxation, pseudonormal or restrictive filling patterns. [c]Two individuals did not have LGE assessment.

DCM = dilated cardiomyopathy; ICD = implantable cardioverter defibrillator; CMR = cardiac magnetic resonance; ECG = electrocardiogram; SVT = supraventricular tachycardia; RBBB = right bundle branch block; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LGE = late gadolinium enhancement.

METHODS

STUDY POPULATION. This retrospective study included a cohort of consecutive adult and pediatric relatives of patients with DCM with P or likely P (LP) variants identified during family screening who did not fulfill diagnostic criteria for DCM at first clinical evaluation. Twenty-five Spanish centers participated in the study.

All relatives were evaluated between 2002 and 2022 at participating institutions and underwent standard ECG and echocardiography and/or cardiac magnetic resonance (CMR) at 1- to 3-year time intervals. During the initial visit, a family pedigree was drawn after a structured interview. Most of the centers had inherited cardiac diseases programs and followed the recommendations of the Spanish Society of Cardiology.[15]

The study was approved by the Hospital Universitario Puerta de Hierro ethics committee and conformed to the principles of the Declaration of Helsinki. The authors from each participating center guarantee the integrity of data.

STUDY ENDPOINT AND DEFINITIONS. The primary endpoint was a new diagnosis of DCM, defined as new onset of left ventricle (LV) or biventricular systolic dysfunction and/or LV dilatation not explained solely by loading conditions or coronary artery disease.[16,17] Systolic dysfunction was defined as a LV ejection fraction (LVEF) of <50%, and LV dilatation was defined by LV end-diastolic (LVED) volumes or LV diameter of ≥2 standard deviations from those predicted according to body surface area and sex.[17]

The time of onset of the primary endpoint was defined as the earliest time a patient fulfilled the diagnostic criteria for DCM. Patients who did not reach the primary endpoint were censored at the time of their last evaluation or death.

Follow-up was calculated from the date of first evaluation at participating centers to the occurrence of the study endpoint, death from another cause, or the date of the most recent evaluation.

Clinical outcomes collected during follow-up were heart failure hospitalization, implantable cardioverter-defibrillator (ICD) insertion or death (cardiovascular and noncardiovascular).

CANDIDATE PREDICTOR VARIABLES. Demographic, clinical, ECG, echocardiographic, and CMR data at initial evaluation were obtained from clinical records at the participating centers, using uniform methods, and were compiled in a common database. Information about other potential risk factors such as intense

sports activity, alcohol abuse, or the need for previous chemotherapy treatment was also gathered.

Intense sport activity was defined as sports that have either a high sustained static component (>50% of maximal voluntary contraction) or a very high resistance dynamic component (>70% maximal oxygen uptake) for ≥6 hours in a typical week during at least the previous 2 years.[18,19] Alcohol abuse was defined as a daily intake of 80 g of alcohol during ≥5 years.[20] Previous chemotherapy was defined as having received chemotherapy agents with known cardiac toxicity (ie, anthracyclines).

A prespecified set of clinical, ECG, and echocardiographic candidate variables that are easy to obtain during the first evaluation of a G+ individual were selected to evaluate their association with DCM development during follow-up. For the purpose of the evaluation of candidate variables associated with DCM development, an individual was considered to have an abnormal ECG if the baseline ECG showed negative T waves in ≥2 contiguous leads, bundle branch block, atrial fibrillation (AF), atrial flutter, second-degree atrioventricular block or the patient had a previous history of AF or atrial flutter.

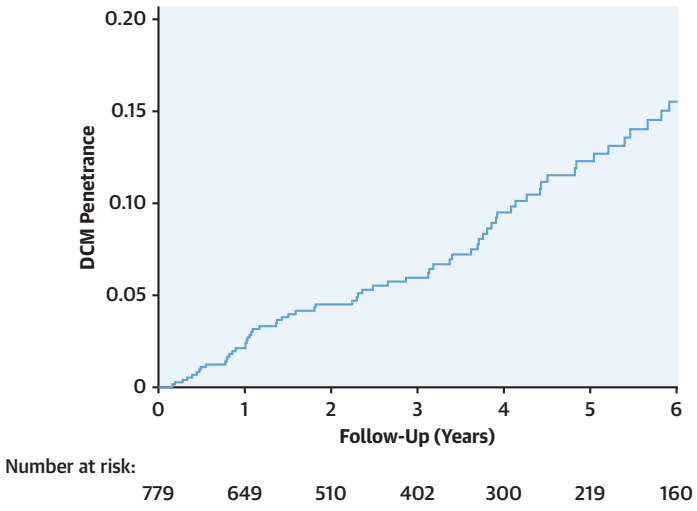
We also classified individuals according to the presence of severe disease traits in the index cases in their families. Accordingly, "high-risk probands" were defined as those probands who had history of sudden cardiac death (SCD), heart transplantation, and/or a LVEF of <30% at DCM diagnosis.

GENETIC ANALYSIS AND VARIANT INTERPRETATION. Genetic testing was performed at participating centers or at accredited genetic laboratories. DCM probands were tested using next-generation sequencing, including ≥50 DCM-related genes. Relatives underwent genetic testing for variants identified in index cases using Sanger sequencing.

Genetic variant interpretation was centrally curated by a cardiologist expert in cardiovascular genetics (J.P.O.), following modified American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines, as described in the Supplemental Methods. Variants were classified as P, LP, or variants of unknown significance.

Genes were clustered into functional gene groups based on similar common functions, involvement in biological processes, localization to subcellular compartments, and other shared properties based on scientific evidence from the literature and available biological databases as previously described.[4,21] Functional gene groups included: 1) *TTN*; 2) structural cytoskeleton/Z-disk (*DES*, *DMD*, and *FLNC*); 3) desmosomal (*DGS2*, *DSP*, and *PKP2*); 4) nuclear envelope (*LMNA* and *TMEM43*); 5) motor sarcomeric (*MYH7*, *TNNI3*, *TNNT2*, and *TPM1*); and 6) other genes (*BAG3*, *RBM20*, and *NKX2-5*).

FIGURE 1 Penetrance of DCM in the Study Cohort



Kaplan-Meier curves of DCM penetrance in 779 individuals with DCM-associated variants and without DCM at initial evaluation. DCM = dilated cardiomyopathy.

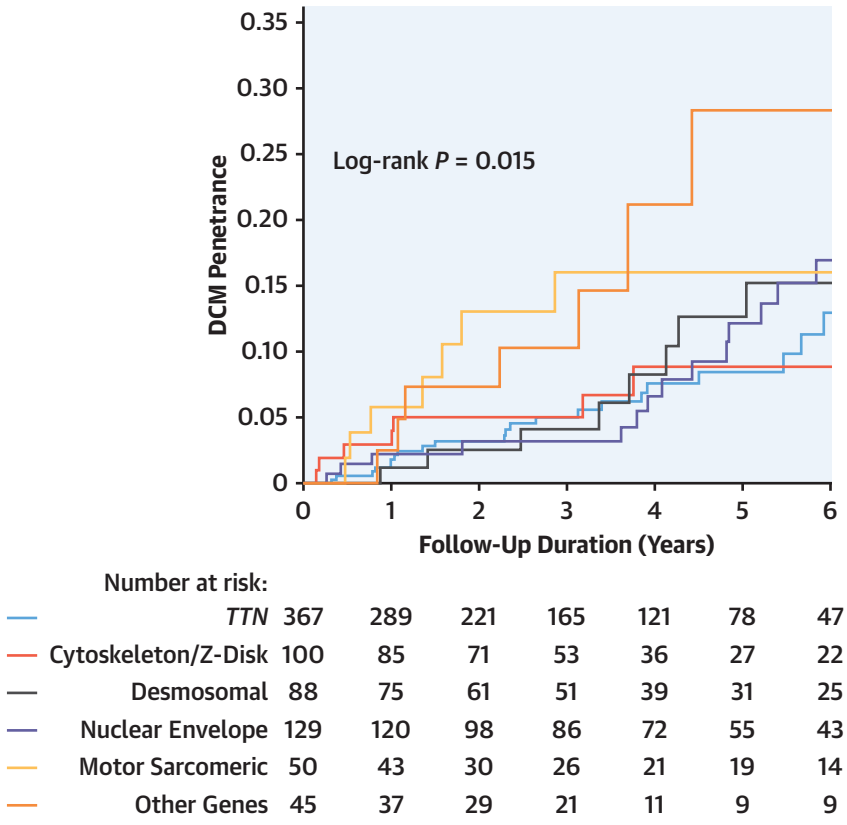
STATISTICAL ANALYSIS. For descriptive statistics, variables are expressed as median (Q1-Q3) or counts (%), as appropriate. The frequency of categorical variables was compared with the chi-square or Fisher exact test and continuous variables were compared using Student's *t*-test or Mann-Whitney *U* test and Kruskal-Wallis test for >2 samples. Time to DCM development was estimated using the Kaplan-Meier method and groups were compared using the log-rank test. HRs of variables associated with DCM development were obtained by univariable and multivariable analyses using Cox proportional hazards regression models. The proportional hazards assumption was investigated using Schoenfeld residuals.

Variables with *P* values of <0.05 in univariable analysis were selected for inclusion in a multivariable Cox regression analysis using an automatic backward selection strategy with a threshold of 0.05.

After completing analysis of the entire cohort of G+ relatives, an identical approach was followed with the smaller cohort of G+ relatives with CMR available.

STATA software version 16.1 (StataCorp) was used for statistical analysis. A 2-tailed *P* value of <0.05 was considered statistically significant.

FIGURE 2 Penetrance of DCM According to Gene Group



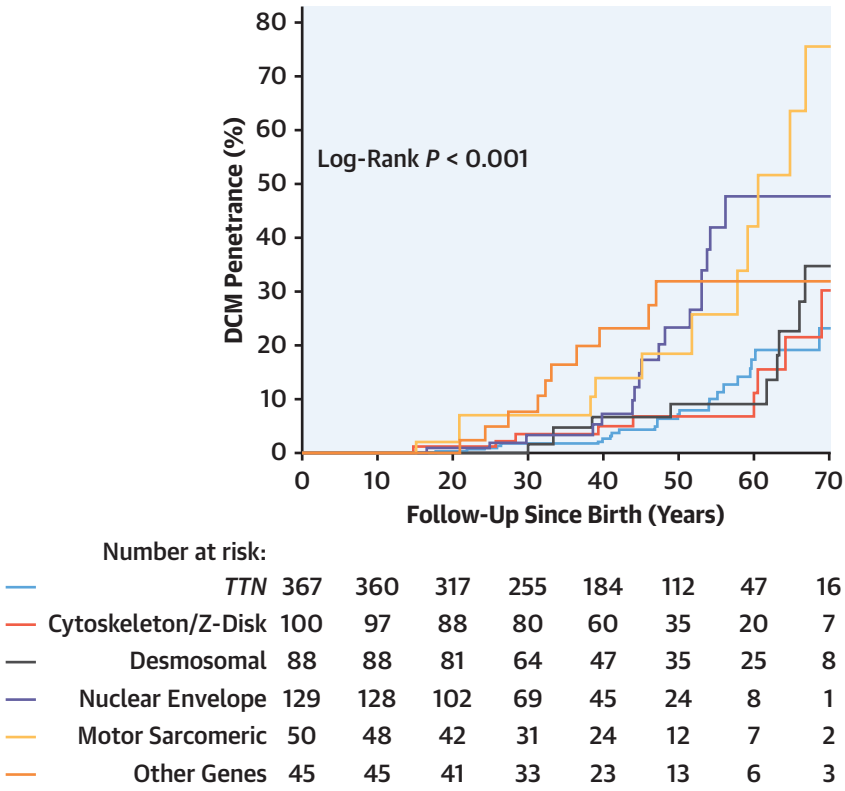
Kaplan-Meier curves of DCM penetrance in 779 individuals with DCM-associated variants and without DCM at initial evaluation according to gene group. DCM = dilated cardiomyopathy.

RESULTS

BASELINE CHARACTERISTICS. Initially, 923 G+ variant carriers from 340 families were included in the study. Upon central review of genetic variants, 144 relatives (15.6%) were reclassified as carriers of variants of unknown significance and were removed from the analysis. Therefore, the final study cohort comprised 779 individuals with P/LP DCM-causing variants who did not fulfill diagnostic criteria for DCM at first evaluation, from 300 families. The baseline clinical characteristics are shown in **Table 1** and genetic variants along with their pathogenicity classification criteria are presented in the Supplemental Appendix. A total of 459 patients (59.0%) were female and the median age at first evaluation was 36.7 years (Q1-Q3: 23.2-49.3 years); 362 patients (45.2%) had a baseline CMR and 118 (15.1%) were <18 years at first evaluation. The mean LVEF by echocardiogram at baseline was 60.7% (Q1-Q3: 60.3%-61.1%) and 170 individuals (21.8%) exhibited abnormalities on ECG. Of note, at initial evaluation at participating centers 8 patients (1.0%) had an ICD implanted owing to high-risk genetics (*LMNA* and *TMEM43*) and a family history of sudden death (5 individuals), high-risk genetics (*LMNA*) and conduction disease, or high-risk genetics (*LMNA*) or a family history of SCD (*TTN*) (1 each).

By genes affected, the greatest number of individuals had *TTN* variants (n = 367, 47.1%), followed by those with variants in nuclear envelope genes (n = 129 [16.6%]), cytoskeleton/Z-disk genes (n = 100 [12.8%]), desmosomal genes (n = 88 [11.3%]), motor sarcomeric genes (n = 50 [6.4%]), and other genes (n = 45 [5.8%]). The baseline clinical characteristics according to genes' groups and

FIGURE 3 DCM Penetrance According to Age by Gene Group



Kaplan-Meier curves of DCM penetrance in 779 individuals with DCM-associated variants and without DCM at initial evaluation by age according to gene group. DCM = dilated cardiomyopathy.

distribution of genes affected are shown in Supplemental Tables 1 and 2.

PENETRANCE OF DCM. After a median follow-up of 37.1 months (Q1-Q3: 16.3-63.8 months), 85 individuals (10.9%) developed DCM, which corresponds with an incidence rate of 2.9 per 100 person-years (95% CI: 2.3-3.5 per 100 person-years). Overall, DCM penetrance at 1, 3, and 5 years of follow-up was 2.4% (95% CI: 1.5%-3.8%), 5.9% (95% CI: 4.3%-8.2%), and 12.3% (95% CI: 9.5%-15.9%), respectively (**Figure 1**).

However, DCM penetrance was different according to the underlying gene group (log-rank 0.015) (**Figure 2**). Individuals with variants in sarcomeric genes and in the other genes group exhibited the highest penetrance at 5 years (17.2% [95% CI: 8.5%-33.2%] and 30.5% [95% CI: 14.3%-57.4%], respectively), whereas for those harboring variants in *TTN*, cytoskeleton/Z-disk, nuclear envelope, and desmosomal genes it was lower (9.1% [95% CI: 5.7%-14.3%], 9.5% [95% CI: 4.4%-19.8%], 13.1% [95% CI: 7.3%-22.8%], and 13.5% [95% CI: 6.5%-26.8%], respectively). Data on DCM penetrance according to gene groups from 1 to 6 years of follow-up are displayed in Supplemental Table 3. Interestingly, age at DCM onset also differed according to gene groups ($P < 0.001$), with the highest penetrance in the motor sarcomeric and the other genes group <40 years of age and penetrance increasing after this age for individuals with variants in nuclear envelope genes (**Figure 3**).

CHARACTERISTICS ASSOCIATED WITH DCM DEVELOPMENT. Characteristics associated with DCM development are shown in **Table 2**. Patients who developed DCM during follow-up were significantly older than those who did not develop DCM (age

TABLE 2 Characteristics of Individuals Without DCM At Initial Evaluation According to DCM Onset During Follow-Up

	Did Not Develop DCM (n = 694)	Developed DCM (n = 85)	*P* Value
Median follow-up time, mo	36.8 (17.1-63.7)	43.4 (12.9-69.9)	0.641
Mean follow-up time, mo	45.4 ± 36.5	49.3 ± 41.4	0.367
Female	418 (60.2)	41 (48.2)	**0.034**
Mean age at first evaluation, y	36.1 (34.8-37.4)	41.4 (37.8-45.0)	**0.008**
Clinical features			
Hypertension	75 (10.8)	15 (17.7)	0.063
Diabetes	24 (3.5)	7 (8.3)	**0.032**
Dyslipidemia	65 (9.4)	15 (17.7)	**0.016**
Smoker	81 (11.7)	13 (15.3)	0.346
Devices (at baseline)			
Pacemaker	5 (0.7)	2 (2.3)	0.129
ICD	6 (0.9)	2 (2.4)	0.199
History of previous arrhythmias			
SVT	15 (2.1)	3 (3.5)	0.432
Atrial fibrillation or flutter	19 (2.74)	12 (14.1)	**<0.001**
Environmental modifiers			
Intense exercise	62 (9.0)	16 (18.8)	**0.004**
Alcohol abuse	6 (0.8)	4 (4.7)	**0.003**
Chemotherapy	11 (1.5)	0 (0)	0.242
Gene group			**<0.001**
TTN	341 (49.1)	26 (30.6)	
Cytoskeleton/Z-disk	91 (13.1)	9 (10.6)	
Desmosomal	78 (11.2)	10 (11.8)	
Nuclear envelope	112 (16.1)	17 (20.0)	
Motor sarcomeric	37 (5.3)	13 (15.3)	
Others	35 (5.0)	110 (11.8)	
First-degree relative of a DCM patient	412 (59.4)	61 (71.7)	**0.016**
ECG			
Sinus rhythm	688 (99.1)	78 (91.8)	**<0.001**
RBBB	16 (2.3)	4 (4.7)	0.244
LBBB	10 (1.4)	7 (8.2)	0.244
Negative T-wave	110 (16.0)	23 (27.1)	**0.010**
Precordial leads	37 (5.3)	8 (9.4)	0.916
Limb leads	73 (10.5)	15 (17.6)	0.916
Abnormal ECG[a]	145 (21.0)	33 (38.8)	**<0.001**
Echocardiogram			
LVEDD, mm	45.8 (45.4-46.2)	49.9 (48.8-51.0)	**<0.001**
LVEF, %	61.1 (60.7-61.5)	57.0 (55.7-58.2)	**<0.001**
Abnormal LV filling pattern[b]	87 (13.0)	16(18.8)	0.114
Left atrial diameter, mm	32.1 (31.5-32.7)	33.1 (30.5-35.6)	0.2983
CMR (n = 362)	n = 294	n = 68	
LVEDV, mL	140.7 (136.6-144.8)	161.8 (149.8-173.9)	**<0.001**
LVEF, %	59.3 (58.7-59.9)	53.2 (52.1-54.3)	**<0.001**
Noncompaction	13 (4.5)	10 (14.7)	**0.008**
LGE[c]	43 (14.6)	28 (41.1)	**<0.001**
Subepicardial	21 (47.6)	9 (32.1)	0.424
Intramyocardial	15 (35.7)	12 (42.9)	0.424
Other	7 (1.6)	7 (25.0)	0.424

Values are median (Q1-Q3), mean ± SD, or n (%). *P* value is for overall comparison. Bold indicates *P* values <0.05. [a]Abnormal ECG: negative T waves in two consecutive leads, bundle branch block, atrial fibrillation, atrial flutter, second-degree atrioventricular block or history of previous atrial fibrillation or atrial flutter. [b]Abnormal LV filling pattern: impaired relaxation, pseudonormal or restrictive filling patterns. [c]2 individuals did not have LGE assessment.

Abbreviations as in Table 1.

41.4 ± 3.6 years vs 36.1 ± 1.3 years; $P = 0.008$) and were more likely to have history of AF or flutter (14.1% vs 2.7%; $P < 0.001$). Patients who developed DCM also showed inverted T waves more frequently (27.1% vs 16.0%; $P = 0.010$) and exhibited a lower mean LVEF (57.0% ± 1.3% vs 61.1% ± 1.4%; $P < 0.001$) and larger left ventricular end-diastolic diameter (LVEDD) (49.9 ± 1.1 mm vs 45.8 ± 0.4 mm; $P < 0.001$), although within considered normal cut-off values.

Among the 362 patients who had a CMR, those who developed DCM showed a larger LV end-diastolic volume (161.8 ± 12.1 mL vs 140.7 ± 4.1 mL; $P = 0.04$) and a lower LVEF (53.2% ± 1.1% vs 59.3% ± 0.6%; $P < 0.001$). LGE was also more frequent among those who developed DCM during follow-up (41.1% vs 14.1%; $P < 0.001$).

UNIVARIABLE AND MULTIVARIABLE ANALYSES. The exploratory univariable analyses are shown in Table 3. Based on their statistical significance the following 9 candidate variables were included in the multivariable Cox regression model, because they attained statistical significance in univariable analysis: age at initial evaluation, sex, presence of cardiovascular risk factors (hypertension, diabetes, smoking history, hypercholesterolemia), environmental phenotype modifiers (intense sport, alcohol abuse, and chemotherapy), abnormal ECG, other genes group, motor sarcomeric genes group, LVEDD, abnormal LV filling pattern, and LVEF. CMR parameters were not included in the multivariable analysis because less than one-half of the cohort had a CMR performed.

After running the automatic backward strategy, final multivariable Cox regression model identified the following 5 variables independently associated with DCM development: age (per 1-year increase), abnormal ECG, LVEDD (per 1-mm increase) and LVEF (per 1% decrease), and motor sarcomeric genes group (Table 3).

LGE AS A PREDICTOR OF DCM DEVELOPMENT. Among the 362 individuals with a CMR available (median age, 36.5 years [Q1-Q3: 34.9-38.1 years], 194 [53%] were female, and 105 [29%] had variants in *TTN*), 70 (19.3%) developed DCM after a median follow-up of 43.6 months (Q1-Q3: 23.5-76.3 months). The baseline clinical characteristics of the entire cohort of G+ relatives with CMR data and according to LGE presence are shown in Tables 1 and 4.

Overall, DCM penetrance at 1, 3, and 5 years of follow-up in G+ relatives with CMR data was 4.0% (95% CI: 2.4%-6.6%), 9.8% (95% CI: 7.0%-13.6%), and 18.2% (95% CI: 13.8%-23.7%), respectively.

The univariable and multivariable analyses of predictors associated with DCM onset in the CMR cohort are shown in Table 5.

The following 7 variables were included in the multivariable analysis, because they attained statistical significance in univariable analysis: age, environmental factors, cardiovascular risk factors, history of AF/flutter, LV end-diastolic volume and LVEF (both measured by CMR), and presence of LGE. Likewise, echocardiographic variables were not included owing to their redundancy with the CMR parameters.

Multivariable Cox regression analysis of the CMR cohort initially identified the following 4 variables independently associated with DCM development: age at baseline evaluation, environmental factors, LVEF, and LGE (Table 5).

CLINICAL OUTCOMES. Four cases of noncardiovascular death were documented before DCM onset in the entire cohort, all of them due to cancer and in individuals ≥70 years old. No cases of SCD or cardiovascular deaths were recorded in individuals who did not fulfill the DCM criteria. Four individuals (0.5% of the total cohort) experienced heart failure as a debut of DCM. Apart from the 8 individuals who had an ICD at the initial evaluation, 20 additional patients (2.6%) received an ICD before the diagnosis of DCM during follow-up: 2 of them (*LMNA* variants) because of nonsustained ventricular tachycardia, 1 (*DGS2*) after having a sustained ventricular tachycardia, 1 (*FLNC*) because of nonsustained ventricular tachycardia and extensive LGE, 3 *LMNA* carriers after developing conduction disorders, and 13 (*LMNA* [n = 5], *FLNC* [n = 1], *DSP* [n = 2], and *TMEM43* [n = 5]) because of family history of SCD and high-risk genetics combined in some of them with frequent ventricular ectopy on ECG Holter monitoring.

DISCUSSION

To our knowledge, the present study represents the most extensive characterization of a cohort of G+ patients without phenotypic DCM expression reported to date. Our findings reveal an approximated 11% penetrance at 5 years in relatives who do not display DCM at the first evaluation and that there are substantial differences in DCM penetrance according to underlying genotype. Furthermore, we found that several easily accessible clinical parameters are associated with disease onset, and that age of onset differs depending on affected gene (Central Illustration).

TABLE 3 Univariable and Multivariable Predictors of DCM Development by Cox Regression

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y	**1.02 (1.01-1.04)**	**<0.001**	**1.02 (1.01-1.03)**	**0.004**
Male	**1.56 (1.02-2.40)**	**0.041**		
Cardiovascular risk factors	**2.09 (1.35-3.21)**	**0.001**		
Devices				
Pacemaker	1.21 (0.26-5.54)	0.805		
ICD	1.22 (0.30-5.00)	0.778		
Environmental modifiers (intense sport, alcohol abuse or chemotherapy)	**2.67 (1.61-4.42)**	**<0.001**		
Gene group				
TTN	0.66 (0.41-1.05)	0.079		
Cytoskeleton/Z-disk	0.91 (0.45-1.82)	0.790		
Desmosomal	0.87 (0.44-1.68)	0.670		
Nuclear envelope	0.90 (0.53-1.53)	0.694		
Motor sarcomeric	**2.32 (1.28-4.20)**	**0.005**	**1.92 (1.05-3.50)**	**0.034**
Other genes	**2.05 (1.04-4.03)**	**0.037**		
Relative of a high risk proband[a]	1.33 (0.84-2.10)	0.218		
Abnormal ECG[b]	**2.13 (1.38-3.29)**	**0.001**	**1.71 (1.08-2.71)**	**0.023**
Echocardiography				
LVEDD, mm	**1.10 (1.06-1.13)**	**<0.001**	**1.08 (1.03-1.12)**	**<0.001**
LVEF, %	**0.86 (0.82-0.90)**	**<0.001**	**0.88 (0.84-0.92)**	**<0.001**
Altered LV filling pattern[c]	**1.74 (1.01-3.01)**	**0.047**		
MVR (>II grade)	0.82 (0.24-2.82)	0.755		
CMR (n = 362)[d]				
LVEDV, mL	**1.01 (1.00-1.02)**	**0.001**		
LVEF, %	**0.90 (0.89-0.92)**	**<0.001**		
Noncompaction	1.33 (0.67-2.63)	0.425		
Presence of LGE[e]	**4.19 (2.56-6.84)**	**<0.001**		

Bold indicates *P* values <0.05. [a]High-risk proband defined as those with history of sudden cardiac death, heart transplantation and/or LVEF of <30% at diagnosis. [b]Abnormal ECG: negative T waves in 2 consecutive leads, bundle branch block, atrial fibrillation, atrial flutter, second-degree atrioventricular block, or history of previous atrial fibrillation or atrial flutter. [c]Abnormal LV filling pattern: impaired relaxation, pseudonormal, or restrictive filling patterns. [d]CMR parameters were not included in the multivariable analysis. [e]LGE assessed in 360 individuals.

MVR = mitral valve regurgitation; other abbreviations as in Table 1.

PENETRANCE OF DCM. Several previous studies have evaluated disease penetrance in relatives of DCM families reporting estimates between 7% at 10 years and 2% per year.[11-14] However, these results were limited by the fact that the evaluated cohorts were relatively small and that comprised relatives who had not been genotyped.[11-14] Accordingly, reported disease penetrance values of previous studies are strongly influenced by individuals who were not carriers of the familial genetic variant and were not at risk of developing the condition.

Our study is the largest study reported to date and the first that includes only G+ relatives after a careful, centralized review of the pathogenicity of genetic variants to ensure that our results precisely reflect the DCM penetrance in this population. Interestingly, we

TABLE 4 Characteristics of G+ Relatives With CMR According to LGE Presence

	Negative LGE (n = 291)[a]	Positive LGE (n = 69)[a]	*P* Value
Median follow-up time, mo	45.5 (24.8-81.3)	37.9 (14.1-51.2)	**<0.001**
Mean follow-up time, mo	55.5 (51.2-59.9)	39.4 (31.9-47.0)	**0.001**
Female	163 (56.0)	30 (43.5)	0.060
Mean age at initial evaluation, y	35.6 (33.93-37.35)	40.5 (36.46-44.54)	**0.018**
Clinical features			
Hypertension	26 (8.9)	11 (15.9)	0.085
Diabetes	5 (1.7)	2 (2.9)	0.514
Dyslipidemia	24 (8.2)	11 (15.9)	0.054
Smoker	38 (13.1)	12 (17.4)	0.355
History of arrhythmias			
SVT	6 (2.1)	3 (4.3)	0.276
Atrial fibrillation or flutter	8 (2.7)	6 (8.7)	**0.022**
Environmental modifiers			
Intense exercise	41 (14.1)	10 (14.5)	0.956
Alcohol abuse	1 (0.34)	2 (2.9)	**0.036**
Chemotherapy	3 (1.0)	0 (0)	0.397
Gene group			**<0.001**
TTN	94 (32.3)	10 (14.5)	
Cytoskeleton/Z-disk	55 (19)	17 (24.6)	
Desmosomal	46 (15.8)	25 (36.2)	
Nuclear envelope	52 (17.9)	14 (20.3)	
Motor sarcomeric	20 (6.8)	1 (1.4)	
Others	24 (8.2)	2 (2.9)	
First degree relative of a DCM proband	173 (59.5)	46 (66.7)	0.236
ECG			
Sinus rhythm	288 (99.0)	66 (95.7)	0.070
RBBB	4 (1.3)	5 (7.2)	0.341
LBBB	2 (0.7)	7 (10.1)	0.685
Negative T-wave	61 (21.0)	16 (23.1)	0.046
Precordial leads	18 (6.2)	9 (13.0)	
Limb leads	43 (14.8)	7 (10.1)	
Abnormal ECG	66 (22.7)	26 (37.7)	**0.010**
Echocardiogram			
LVDD, mm	47.1 (46.5-47.7)	48.3 (46.9-49.8)	0.077
LVEF, %	60.0 (59.4-60.7)	60.2 (58.7-61.7)	0.802
Abnormal LV filling pattern[b]	31 (10.7)	13 (18.8)	0.056
Left atrial diameter, mm	31.4 (30.4-32.5)	33.2 (30.5-36.0)	0.171
CMR			
LVED volume, mL	142.9 (138.6-147.2)	153.7 (142.4-165.0)	**0.040**
LVEF, %	58.2 (57.5-58.9)	54.1 (51.3-56.9)	**<0.001**
Noncompaction	15 (5.2)	4 (5.8)	0.778

Values are median (Q1-Q3) or n (%), unless otherwise indicated. Bold indicates *P* values <0.05. [a]2 relatives with CMR did not have LGE assessment. [b]Abnormal LV filling pattern: impaired relaxation, pseudonormal, or restrictive filling patterns.

SVT = supraventricular tachycardia; other abbreviations as in Table 1.

found that, although the global annual DCM penetrance rate was approximately 3%, penetrance differed substantially according to the underlying genotype and also by several clinical parameters, including age, ECG, echocardiography, and CMR findings.

These findings are extremely relevant to improve the care of the relatives from patients with DCM and for health care providers when explaining the results of genetic tests and their implications on predicted disease development and trajectories.

CLINICAL SCREENING OF G+ RELATIVES IN FAMILIES WITH DCM. Current guidelines and position statements from the major cardiac societies in Europe and North America recommend periodic clinical surveillance in a 1- to 3-year basis in carriers of DCM-associated variants without phenotypic disease expression regardless of age, genotype, and other clinical findings.[7-9] However, there is an urgent need for a more tailored approach, because the increasing number of healthy G+ carriers is one of the greatest logistical problems faced by the inherited cardiac diseases units that evaluate families with DCM worldwide. According to our data, it seems reasonable to adapt screening intervals according to clinical findings on ECG and cardiac imaging tests, age, and genotype. Age at DCM onset seemed to be highly different across genes and, accordingly, there are certain genotypes like *TTN* that probably can safely extend screening intervals to 5 years in relatives <40 years old who do not exhibit alterations in ECG and cardiac imaging tests. In contrast, carriers of genetic variants affecting the nuclear envelope, motor sarcomeric or classified in the other genes groups showed a younger age of presentation in our study. Therefore, clinical screenings should be performed every 2 to 3 years in the absence of ECG and cardiac imaging abnormalities and on a yearly basis in their presence.

We found a strong signal with LGE presence as a marker for higher probabilities of developing DCM during follow-up. Based on these findings, we would recommend that all G+ relatives should have a CMR performed at baseline evaluation and periodically during follow-up. In case LGE is detected, those individuals should follow closer evaluation protocols.

IMPLICATIONS FOR PREVENTIVE TREATMENTS. Our findings are particularly relevant for future clinical trials with specific disease-modifying therapies, because data on penetrance and the factors associated with disease onset are crucial for the design of early intervention and prevention studies in the field of genetic cardiomyopathies.[22]

Similarly, these data might also be useful to select G+ relatives at high risk of developing DCM who could potentially benefit from early initiation of preventive pharmacological therapies that have been shown effective in treating DCM once the disease is established. In this regard, preventive treatment with

perindopril is nowadays accepted in male patients with Duchenne dystrophy to prevent DCM onset,[23] and a recent study has examined the usefulness of eplerenone in *PLN* G+ carriers; unfortunately, this study was underpowered to see an effect after 3 years of follow-up.[24] Additionally, EARLY-GENE (Early Treatment With Candesartan vs Placebo in Genetic Carriers of Dilated Cardiomyopathy; NCT05321875) is currently evaluating the effect of candesartan in preventing DCM development among 320 G+ carriers of DCM-associated variants without DCM.

Of note, our data apply to G+ carriers from families with DCM and cannot inform G+ patients without a history of DCM in their families from the overall population, where DCM onset might be less common. This finding has been illustrated in as a recent analysis of the UK Biobank, where around 91% of middle-aged and older adults with putative P variants in DCM-associated genes from the general population did not show a history of DCM or subclinical DCM on CMR.[25]

STUDY LIMITATIONS. This was a retrospective study and participants were first evaluated over a long period. Patients were mostly enrolled through inherited cardiac diseases units, potentially limiting the application of the results to other cohorts with other characteristics, although the distribution of variants across genes is in line with what has been reported in recent genotyped European DCM cohorts.[26] A selection bias toward individuals from families with higher DCM penetrance cannot be excluded because families with multiple affected members and a more severe phenotype are more likely to have more relatives genotyped through cascade screening. The median follow-up of participants was only 37 months, reflecting changes in familial genetic screening and progressive incorporation of genetic testing in relatives of families with DCM at many of the participating centers. The limited median follow-up of our cohort limits our ability to predict DCM onset and outcomes in the long term. Because not all participants in our work had a baseline CMR study, nor during follow-up, we cannot determine how many individuals exhibited or developed LGE in the absence of LV dysfunction or dilatation, and cannot estimate how many individuals would have met the 2023 European Society of Cardiology Guidelines' definition of nondilated LV cardiomyopathy.[7] Moreover, because we did not collect serial CMR data, our study cannot provide information about the recommended frequency of CMR during follow-up in G+ individuals. Future studies should address this important issue. Competitive events were not considered when evaluating factors associated with DCM onset. Nevertheless, only 4 individuals had competitive events (death) before developing DCM, limiting the potential impact of not considering competitive events. Information about pregnancy was not collected; therefore, we could not assess the possible influence of this variable on DCM onset. Last, our findings would need to be validated in an external cohort of G+ carriers.

TABLE 5 Univariable and Multivariable Predictors of DCM Development by Cox Regression in G+ Relatives With CMR

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, years	**1.03 (1.01-1.05)**	**<0.001**	**1.02 (1.00-1.04)**	**0.013**
Male	1.26 (0.78-2.03)	0.339		
Cardiovascular risk factors	**1.96 (1.22-3.16)**	**0.006**		
Environmental modifiers	**2.42 (1.41-4.18)**	**0.001**	**1.89 (1.01-3.55)**	**0.048**
Gene group				
TTN	1.21 (0.73-2.02)	0.455		
Cytoskeleton/Z-disk	0.75 (0.37-1.53)	0.433		
Desmosomal	0.59 (0.29-1.20)	0.145		
Nuclear envelope	0.95 (0.52-1.74)	0.864		
Motor sarcomeric	1.92 (0.94-3.90)	0.073		
Other genes	1.22 (0.56-2.70)	0.614		
Relative of a High risk proband[a]	1.34 (0.81-2.21)	0.252		
Abnormal ECG[b]	1.62 (1.00-2.63)	0.051		
Echocardiography				
LVDD, mm	**1.07 (1.03-1.10)**	**0.001**		
LVEF, %	**0.87 (0.83-0.91)**	**<0.001**		
Abnormal LV filling pattern[c]	**1.89 (1.06-3.36)**	**0.031**		
MVR (>II grade)	2.87 (0.80-10.36)	0.107		
CMR				
LVEDV, mL	**1.01 (1.00-1.02)**	**0.001**		
LVEF, %	**0.90 (0.89-0.92)**	**<0.001**	**0.93 (0.91-0.96)**	**<0.001**
Noncompaction	1.33 (0.60-2.93)	0.486		
Presence of LGE[d]	**4.19 (2.56-6.84)**	**<0.001**	**2.52 (1.43-4.45)**	**0.001**

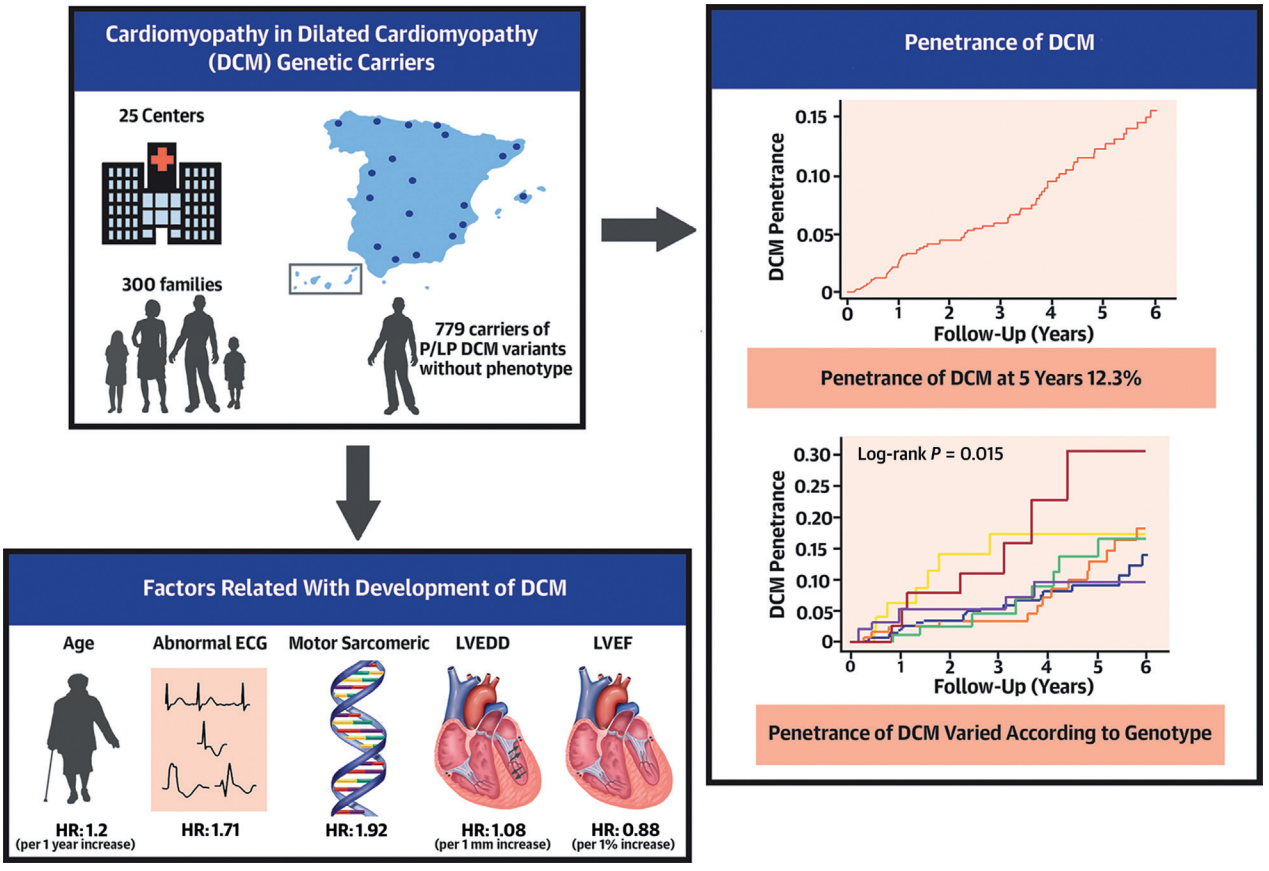
Bold indicates values that are statistically significant. [a]High-risk proband defined as those with history of sudden cardiac death, heart transplantation and/or LVEF <30% at diagnosis. [b]Abnormal ECG: negative T waves in 2 consecutive leads, bundle branch block, atrial fibrillation, atrial flutter, second-degree atrioventricular block or history of previous atrial fibrillation or atrial flutter. [c]Abnormal LV filling pattern: impaired relaxation, pseudonormal or restrictive filling patterns. [d]LGE assessed in 360 individuals.

Abbreviations as in Tables 1 and 4.

CONCLUSIONS

This study provides novel findings on the penetrance of DCM development in G+ individuals without DCM. Approximately 11% of G+ carriers developed DCM following a first negative screening, over a median follow-up of 3 years. Age, ECG abnormalities, presence of variants in motor sarcomeric genes and

CENTRAL ILLUSTRATION **Penetrance of Dilated Cardiomyopathy in G+ Relatives**



Cabrera-Romero E, et al. J Am Coll Cardiol. 2024;83(17):1640–1651.

We studied 779 patients with DCM-associated variants and without DCM at initial evaluation followed at 25 Spanish centers. DCM penetrance at 5 years was 12.3% and DCM penetrance was different according to underlying gene group. Independent predictors of DCM development were: older age, an abnormal ECG, presence of variants in motor sarcomeric genes, lower LVEF and larger LVEDD. DCM = dilated cardiomyopathy; ECG = electrocardiogram; G+ = genotype positive; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; P/LP = pathogenic/likely pathogenic.

certain cardiac imaging parameters (LVEF, LVEDD, and LGE) are associated with a higher risk of developing DCM in this population and can be used to predict the likelihood of DCM onset and to adapt screening visits schedule and procedures during follow-up.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The penetrance of DCM in relatives is related to genotype, age, and electrocardiographic and cardiac imaging features.

TRANSLATIONAL OUTLOOK: Further studies are needed to identify therapies that prevent DCM onset in apparently healthy carriers of genetic variants associated with DCM.

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KEY WORDS dilated cardiomyopathy, genetics, late gadolinium enhancement, penetrance

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.