Circulation

ORIGINAL RESEARCH ARTICLE

Phenotypic Refinement of Heart Failure in a National Biobank Facilitates Genetic Discovery

BACKGROUND: Heart failure (HF) is a morbid and heritable disorder for which the biological mechanisms are incompletely understood. We therefore examined genetic associations with HF in a large national biobank, and assessed whether refined phenotypic classification would facilitate genetic discovery.

METHODS: We defined all-cause HF among 488 010 participants from the UK Biobank and performed a genome-wide association analysis. We refined the HF phenotype by classifying individuals with left ventricular dysfunction and without coronary artery disease as having nonischemic cardiomyopathy (NICM), and repeated a genetic association analysis. We then pursued replication of lead HF and NICM variants in independent cohorts, and performed adjusted association analyses to assess whether identified genetic associations were mediated through clinical HF risk factors. In addition, we tested rare, loss-of-function mutations in 24 known dilated cardiomyopathy genes for association with HF and NICM. Finally, we examined associations between lead variants and left ventricular structure and function among individuals without HF using cardiac magnetic resonance imaging (n=4158) and echocardiographic data (n=30 201).

RESULTS: We identified 7382 participants with all-cause HF in the UK Biobank. Genome-wide association analysis of all-cause HF identified several suggestive loci ($P<1\times10^{-6}$), the majority linked to upstream HF risk factors, ie, coronary artery disease (*CDKN2B-AS1* and *MAP3K7CL*) and atrial fibrillation (*PITX2*). Refining the HF phenotype yielded a subset of 2038 NICM cases. In contrast to all-cause HF, genetic analysis of NICM revealed suggestive loci that have been implicated in dilated cardiomyopathy (*BAG3*, *CLCNKA-ZBTB17*). Dilated cardiomyopathy signals arising from our NICM analysis replicated in independent cohorts, persisted after HF risk factor adjustment, and were associated with indices of left ventricular dysfunction in individuals without clinical HF. In addition, analyses of loss-of-function variants implicated *BAG3* as a disease susceptibility gene for NICM (loss-of-function variant carrier frequency=0.01%; odds ratio,12.03; $P=3.62\times10^{-5}$).

CONCLUSIONS: We found several distinct genetic mechanisms of all-cause HF in a national biobank that reflect well-known HF risk factors. Phenotypic refinement to a NICM subtype appeared to facilitate the discovery of genetic signals that act independently of clinical HF risk factors and that are associated with subclinical left ventricular dysfunction.

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Clinical Perspective

What Is New?

- We performed a population-based genetic association study of all-cause heart failure that yielded multiple genetic signals for known heart failure risk factors, such as coronary artery disease and atrial fibrillation.
- Refining the heart failure phenotype to a nonischemic cardiomyopathy subset enhanced the detection of genetic loci associated with dilated cardiomyopathy, which appear to operate independent of traditional heart failure risk factors.
- Genetic variants associated with nonischemic cardiomyopathy were also associated with subclinical traits of left ventricular dysfunction.

What Are the Clinical Implications?

- Phenotypic refinement aids in the discovery of novel genetic signals that reflect distinct etiologic heart failure subtypes.
- The *BAG3* locus is a principal nonischemic cardiomyopathy susceptibility locus, and future functional characterization of this and other genetic loci may inform therapeutic development.
- Common genetic variants associated with both clinical and subclinical heart failure may be leveraged to improve heart failure risk prediction and prevention.

Heart failure (HF) is a complex clinical syndrome that affects >30 million individuals worldwide with a projected ≈40% increase in prevalence by 2030.[1–3] Despite considerable advances in HF management, nearly 50% of affected individuals die within 5 years of a first diagnosis.[4] The rising global burden of HF and its apparent heritability, estimated at ≥18% by epidemiological studies, have prompted the study of genetic determinants to inform new preventive strategies and novel therapeutics.[5–8]

Significant strides have been made in understanding rare, Mendelian forms of HF.[9] Furthermore, genetic association studies of upstream HF risk factors such as coronary artery disease (CAD), atrial fibrillation, and hypertension have yielded numerous susceptibility loci.[10–13] Yet genetic analyses of common, complex HF have achieved limited success, potentially because of insufficient power and disease heterogeneity.[14] Indeed, more recent analyses limited to recruited cohorts of specific HF subpopulations such as nonischemic dilated cardiomyopathy (DCM), the leading global cause of heart transplantation, have identified susceptibility loci that have been replicated.[15–18]

The emergence of large population-based biobanks with extensive phenotypic and genotypic data enables rigorous investigation of genetic influences on cardiovascular health and disease.[19] Yet as these biobanks grow and increasingly rely on efficient electronic phenotyping, the achievement of phenotypic precision may remain a critical challenge that limits genetic discovery and downstream interpretation of findings.[20] We therefore conducted a phenotype-driven genetic analysis of HF in the general population. Specifically, we conducted a genetic association analysis of all-cause HF and then of the more precise definition of nonischemic cardiomyopathy (NICM) to determine whether phenotypic refinement improves genetic discovery in a population-based biobank. Given the heterogeneous etiologies of HF, we then characterized putative HF loci by examining associations with relevant risk factors and intermediate traits of left ventricular (LV) structure and function.

METHODS

Summary level genetic association results cited in this article are available through the Broad Institute Cardiovascular Disease Knowledge Portal (http://broadcvdi.org) and through the UK Biobank.[21]

Study Subjects

In total, 488 010 individuals from the UK Biobank, a large, prospective population-based cohort, were considered when assessing epidemiological relationships of HF and associated risk factors. In primary genetic analyses, we included 394 156 participants of European ancestry from the UK Biobank. Analysis of the UK Biobank data was approved by the Partners Health Care institutional review board (protocol 2013P001840; application 7089; and protocol 2001P000053; application 17488). Informed consent was obtained from all participants by the UK Biobank.

For replication of genetic association results, we studied 1060 participants from the GRADE study (Genetic Risk Assessment of Defibrillator Events), a recruited cohort of predefined cardiomyopathy patients with defibrillators, and up to 9432 participants from the Vanderbilt University Biobank (BioVU), a prospective, hospital-based cohort (Methods in the online-only Data Supplement).

Phenotyping

Disease phenotypes in UK Biobank were defined by using a combination of self-reported questionnaire data (confirmed by a trained healthcare professional) and linked hospital admission and death registry data. Detailed definitions for all disease phenotypes are provided in Table I in the online-only Data Supplement.

We defined all-cause HF as the presence of self-reported HF/pulmonary edema or cardiomyopathy at any visit; or an *International Classification of Diseases, 10th Revision* (*ICD-10*) or *International Classification of Diseases, 9th Revision* (*ICD-9*) billing code indicative of heart/ventricular failure or a cardiomyopathy of any cause. Individuals with a diagnosis of hypertrophic cardiomyopathy, as ascertained by self-report or by pertinent

ICD-10 codes, were excluded from the HF and NICM phenotypes even if they met the above criteria because of the substantial Mendelian inheritance pattern of hypertrophic cardiomyopathy.

Among patients with all-cause HF, we defined NICM on the basis of LV dysfunction and the absence of CAD. A priori, individuals were considered to have LV dysfunction if they carried *ICD-10* diagnoses of DCM or LV failure, or an *ICD-9* diagnosis of left HF. Indicators for CAD included myocardial infarction or coronary revascularization, as described previously.[10] Myocardial infarction was defined as a self-report of heart attack or an *ICD-10* code of acute myocardial infarction. Coronary revascularization was defined as the presence of an operative or procedure code for coronary artery bypass surgery or coronary angioplasty (Table I in the online-only Data Supplement).

Genetic Association Testing, Replication, and Meta-Analysis

We performed primary genome-wide association testing among UK Biobank participants passing sample quality control by comparing HF or NICM cases with non-HF controls. In total, 6504 HF cases were compared with 387 652 controls, and 1816 NICM cases were compared with 388 326 controls. Only variants with minor allele frequency >1% available in the Haplotype Reference Consortium v1.1 panel and imputed with imputation quality >0.3 were included (Methods in the online-only Data Supplement).[22]

Lead variants from the HF and NICM analyses passing a suggestive threshold of $P<1\times10^{-6}$ were taken forward for replication. For lead HF variants, we pursued replication in 2 studies: (1) BioVU, comparing 2982 HF cases with 6450 controls; and (2) the GRADE study, comparing 1060 cases (classified prospectively at the time of recruitment) with an independent sample of 2327 controls from BioVU genotyped on the same platform as the GRADE samples and selected based on overlapping genetic ancestry. For lead NICM variants, we pursued replication in 3 studies: (1) BioVU, comparing 226 NICM cases (ascertained retrospectively through application of our NICM phenotyping algorithm to the medical record alongside available echocardiographic data, classifying LV dysfunction as LV ejection fraction ≤40%) with 4709 controls; (2) the GRADE study, comparing 260 NICM cases (classified prospectively at the time of recruitment) with 2327 controls; and (3) publicly available summary exome-chip association statistics from a recent study of DCM including 2796 cases and 6877 control subjects from 6 populations of European ancestry.[17] When a lead variant was not available in a replication study, the best available proxy was selected (Methods in the online-only Data Supplement).

Associations Between HF and NICM Susceptibility Variants and HF Risk Factors

Using individuals free of HF in the UK Biobank, we performed additional association testing of lead HF and NICM variants with 10 binary and 3 continuous risk factors for HF (Table I in the online-only Data Supplement). Furthermore, to determine whether lead variant associations with HF and NICM were independent of HF risk factors, we repeated genetic association analyses for all lead variants, adjusting for relevant risk factors.

Associations Between HF and NICM Susceptibility Variants and Cardiac Structure/Function

We further tested lead variants at identified HF and NICM susceptibility loci for association with intermediate traits of LV structure and function by assessing (1) individual-level data on LV ejection fraction, LV end-diastolic volume, LV end-systolic volume, LV stroke volume, cardiac output, and cardiac index in 4158 individuals without HF who underwent cardiac magnetic resonance imaging (MRI) in the UK Biobank; and (2) summary-level data of 16 echocardiographic traits in 30 201 individuals without HF in the EchoGen consortium. For cardiac MRI data in the UK Biobank, we excluded individuals with measurements falling outside 3 SDs from the mean for a given trait.

Rare Predicted Loss-of-Function Associations

To complement the above common variant analyses, we examined whether rare (minor allele frequency <1%) predicted loss-of-function (pLOF) variants at known DCM genes are associated with HF or NICM in the UK Biobank.[23] Only directly genotyped variants were included in these analyses. In total, 111 genes were considered, but only 24 had ≥2 qualifying variants and appreciable pLOF carriers for testing (carrier frequency >0.0001) (Table II in the online-only Data Supplement). We annotated genotyped variants from the UK Biobank using Ensembl Variant Effect Predictor version 88 using the "–pick_allele" option to select one consequence per variant allele.[24] Variants annotated as protein-truncating, premature stops, canonical splice sites, or frameshift mutations were classified as pLOF using the LOFTEE plugin for VEP.[25]

Statistical Analysis

Primary genome-wide association testing for HF and NICM in the UK Biobank was performed using logistic regression and adjusting for age at first visit, sex, genotyping array, and the first 10 principal components of ancestry.

To test the association of lead HF and NICM susceptibility variants with HF risk factors, we used a combination of linear and logistic regression adjusting for age at first visit, sex, genotyping array, and the first 10 principal components of ancestry. We considered significant any single nucleotide polymorphism (SNP)–risk factor association surpassing a Bonferroni-corrected threshold of $P<5.49\times10^{-4}$ [0.05/(13 traits×7 SNPs)].

To test the association of lead HF and NICM variants with intermediate traits of cardiac structure and function, we performed linear regression adjusted for age at first visit, sex, genotyping array, and the first 10 principal components of ancestry. We considered significant any SNP-trait association surpassing a Bonferroni-corrected threshold of $P<0.0012$ [0.05/(6 traits×7 SNPs)].

For rare pLOF analyses, we performed association testing using a collapsed gene-based test, classifying samples as either carriers or noncarriers of any pLOF variant in a given gene, adjusting for age at baseline, sex, genotyping array, and the first 10 principal components of ancestry. A

Bonferroni-corrected *P* value significance threshold was set at *P*=0.001 [0.05/(2 phenotypes×24 genes)].

Primary association analyses for HF and NICM were performed in PLINK2 (https://www.cog-genomics.org/plink/2.0/).[26] Association testing with HF risk factors and intermediate cardiac imaging traits was performed in R v3.3.0 (R Foundation). Rare gene-based testing was performed using EPACTS (https://genome.sph.umich.edu/wiki/EPACTS).[27]

RESULTS

Defining All-Cause HF and Assessing Overlap With HF Risk Factors

The study population comprised 488 010 individuals in the UK Biobank with available genotypic and phenotypic data. In total, 7382 individuals met criteria for the broader classification of all-cause HF. A large proportion of all-cause HF cases had comorbid HF risk factors, including CAD (47.3%) and atrial fibrillation (43.0%) (Figure 1; Table 1).

Genome-Wide Association Analyses of All-Cause HF in UK Biobank

In the UK Biobank, primary genetic association analyses for all-cause HF (n=6504 passing sample quality control) yielded 1 locus that exceeded the threshold for genome-wide statistical significance (rs1906609 upstream of *PITX2*, odds ratio [OR], 1.15; $P=9.08\times10^{-10}$) and 4 other loci with suggestive association signals ($P<1\times10^{-6}$; rs7857118 near *CDKN2B-AS1*, OR, 1.10; $P=2.15\times10^{-7}$; rs12627426 near *MAP3K7CL*, OR, 1.13; $P=2.63\times10^{-7}$; rs73839819 near *RYBP*, OR, 1.33; $P=2.65\times10^{-7}$; rs2234962 in *BAG3*, OR, 1.12; $P=3.55\times10^{-7}$). Most lead signals represented known susceptibility loci for HF risk factors, such as atrial fibrillation (*PITX2*) and CAD (*CDKN2B-AS1* and *MAP3K7CL*) (Figure 2A; Table 2).[12,28] No meaningful test statistic inflation was detected (Figure I in the online-only Data Supplement). In a sensitivity analysis in which we repeated genetic association testing after omitting cases of all-cause HF derived solely from self-reported data rather than from *ICD* codes (n=197; only 3% of all quality-controlled cases), we observed similar associations and effect estimates, suggesting that our phenotype was not unduly influenced by potential self-report misclassification (Table III in the online-only Data Supplement).

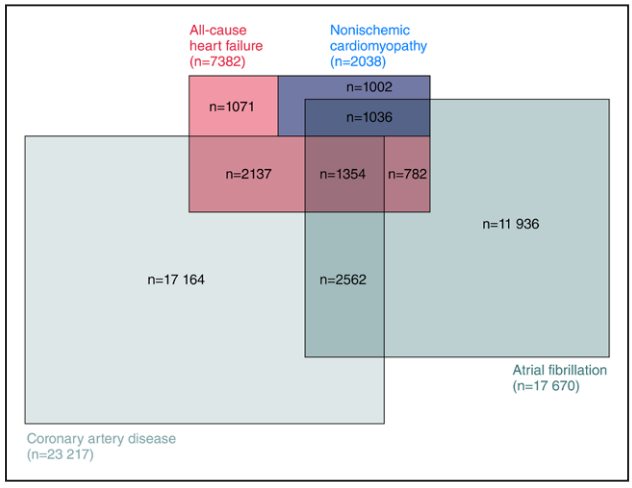

Figure 1. Epidemiological overlap between heart failure phenotypes and prominent risk factors in UK Biobank.
The overlap between all-cause heart failure, nonischemic cardiomyopathy, coronary artery disease, and atrial fibrillation cases are displayed among 488 010 study participants in the UK Biobank. Case counts represent the sum total of disease at baseline and incident cases.

Refining the All-Cause HF Phenotype to NICM

We then refined the all-cause HF phenotype to NICM on the basis of LV dysfunction without CAD and identified 2038 individuals who met phenotypic criteria (Figure 1). There was a higher proportion of women in the NICM group than in the all-cause HF group (35.0% versus 30.2%, *P*<0.001). Furthermore, in comparison with the all-cause HF group, individuals in the NICM subset were more likely to have comorbid atrial fibrillation (50.8% versus 43.0%, *P*<0.001), and less likely to have comorbid type 2 diabetes mellitus (19.4% versus 26.1%, *P*<0.001) and hypertension (69.3% versus 75.6%, *P*<0.001) (Table 1).

Validation of NICM Phenotype

To validate our NICM phenotype, we applied the above phenotyping algorithm to individuals in the Partners HealthCare Biobank (Methods in the online-only Data Supplement Methods) and performed manual chart reviews for 50 individuals who met criteria for NICM. Forty-five of the 50 study participants had evidence of a NICM diagnosis within the medical record (positive predictive value=0.90), which we considered sufficient validation to support genetic analysis.

Genome-Wide Association Analysis of NICM in UK Biobank

A genome-wide association analysis for our refined NICM phenotype resulted in 3 signals: 1 locus reaching genome-wide significance (rs2234962, a missense variant in *BAG3*, OR, 1.30; $P=2.32\times10^{-9}$) and 2 others at suggestive significance (rs12138073, an intronic variant near *CLCNKA* and *ZBTB17*, OR, 1.29; $P=5.35\times10^{-7}$; rs2634071 in high linkage disequilibrium with rs1906609 upstream of *PITX2*, OR, 1.25;

Table 1. Baseline Characteristics of UK Biobank Samples by Heart Failure Status

Characteristics	All-Cause HF (n=7382)	NICM (n=2038)	All-cause HF versus NICM *P* Value	Referents Free of All-Cause HF (n=480 628)
Age at baseline, y	62.2 (6.3)	61.6 (6.7)	<0.001	57.0 (8.1)
Male sex, n (%)	5151 (69.8)	1324 (65.0)	<0.001	218 203 (45.4)
UK BiLEVE array, n (%)	1071 (14.5)	274 (13.4)	0.12	48 830 (10.2)
Height, cm	170.3 (9.4)	170.8 (9.6)	0.003	168.5 (9.3)
Body mass index, kg/m^2	29.8 (5.8)	29.3 (5.9)	<0.001	27.4 (4.8)
Waist-hip ratio	0.94 (0.09)	0.92 (0.09)	<0.001	0.87 (0.09)
Systolic blood pressure, mm Hg	148.5 (22.4)	147.5 (22.2)	0.02	140.9 (20.7)
Diastolic blood pressure, mm Hg	86.5 (12.2)	86.8 (12.2)	0.19	84.3 (11.3)
Coronary artery disease, n (%)	3491 (47.3)	0 (0.0)	NA	19 726 (4.1)
Type 2 DM, n (%)	1929 (26.1)	395 (19.4)	<0.001	22 515 (4.7)
Atrial fibrillation, n (%)	3172 (43.0)	1036 (50.8)	<0.001	14 498 (3.0)
Hypertension, n (%)	5584 (75.6)	1413 (69.3)	<0.001	153 369 (31.9)

Values are presented as mean (SD) unless otherwise noted. Baseline characteristics of NICM samples (n=2038) were compared with all-cause heart failure samples without NICM (n=5344) using a standard *t* test for continuous measures and χ^2 test for dichotomous traits. DM indicates diabetes mellitus; HF, heart failure; NA, not available; NICM, nonischemic cardiomyopathy; and UK BiLEVE, UK Biobank Lung Exome Variant Evaluation.

P=1.06×10^{-7}), the majority at loci previously implicated in DCM (*BAG3* and *CLCNKA-ZBTB17*) (Figure 2B; Table 3).[16,17,29–31] It is notable that we observed strong association signals at *BAG3* for all-cause HF and NICM, although effect estimates were consistently stronger for NICM. No meaningful test statistic inflation was detected (Figure I in the online-only Data Supplement).

Replication of Lead All-Cause HF and NICM Signals

We sought replication for the all-cause HF and NICM variants surpassing our suggestive significance threshold of *P*<1×10^{-6}: rs1906609/rs2634071 (*PITX2*), rs7857118 (*CDKN2B-AS1*), rs12627426 (*MAP3K7CL*), rs73839819 (*RYBP*), rs2234962 (*BAG3*), and rs12138073 (*CLCNKA-ZBTB17*).

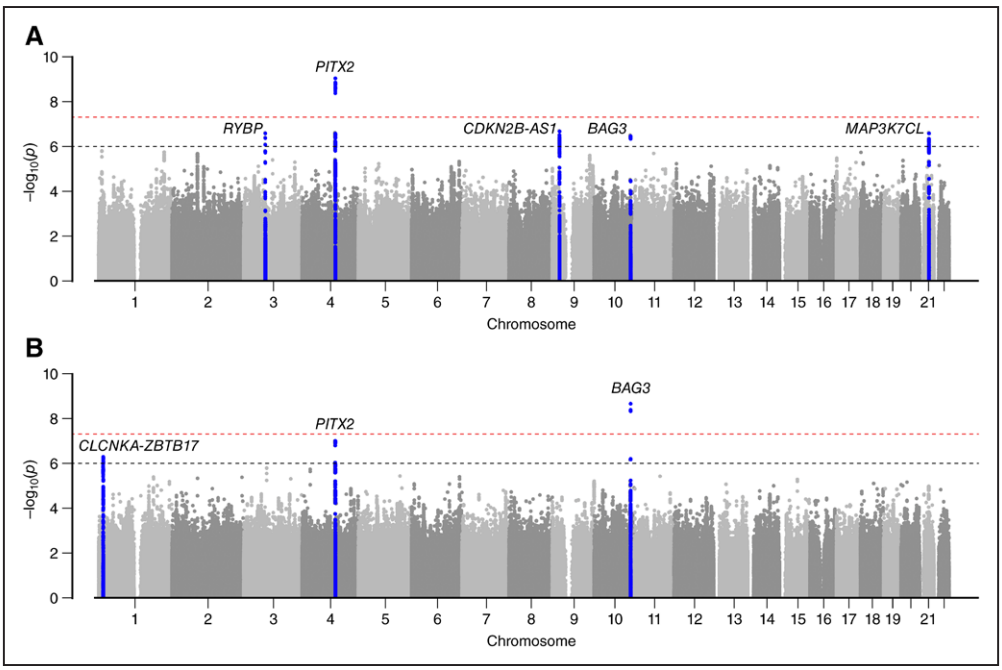

Figure 2. Manhattan plots of primary genome-wide association discovery analysis in UK Biobank for all-cause heart failure and nonischemic cardiomyopathy.

Logistic regression was used to test the association of allelic dosages for all variants with minor allele frequency >1% with (**A**) all-cause heart failure and (**B**) nonischemic cardiomyopathy. Lines are drawn at 1×10^{-6} and 5×10^{-8} to denote suggestive and genome-wide significant associations, respectively. Loci demonstrating *P* value<1×10^{-6} are highlighted in blue, and the nearest genes are labeled.

Table 2. Replication of Suggestive Signals From Genetic Association Analyses for All-Cause Heart Failure in UK Biobank

SNP	Chr	Pos	Nearest Gene	RA/ NRA	UK Biobank (n cases=6504)			BioVU Study (n cases=2982)			GRADE (n cases=1060)		
					RAF	OR (95% CI)	*P* Value	RAF	OR (95% CI)	*P* Value	RAF	OR (95% CI)	*P* Value
rs1906609	4	111666451	*PITX2*	T/G	0.16	1.15 (1.10–1.21)	9.08×10^{-10}	0.18	1.00 (0.92–1.09)	0.95	0.18	1.14 (0.99–1.33)	0.08
rs7857118	9	22124140	*CDKN2B-AS1*	T/A	0.51	1.10 (1.06–1.14)	2.15×10^{-7}	0.52	1.05 (0.99–1.12)	0.11	0.53	1.07 (0.96–1.20)	0.24
rs12627426	21	30519457	*MAP3K7CL*	A/T	0.16	1.13 (1.08–1.18)	2.63×10^{-7}	0.15	1.02 (0.93–1.11)	0.70	0.15	1.20 (1.03–1.40)	0.02
rs73839819	3	72579834	*RYBP*	G/A	0.02	1.33 (1.19–1.48)	2.65×10^{-7}	0.02	0.94 (0.75–1.17)	0.55	0.02	0.90 (0.60–1.36)	0.63
rs2234962	10	121429633	*BAG3*	T/C	0.78	1.12 (1.07–1.17)	3.55×10^{-7}	0.79	1.00 (0.92–1.07)	0.90	0.80	1.27 (1.10–1.46)	0.001

BioVU indicates Vanderbilt University Biobank; Chr, chromosome; GRADE, Genetic Risk Assessment of Defibrillator Events; HF, heart failure; NRA, all-cause HF nonrisk allele; OR, odds ratio; Pos, hg19 position; RA, all-cause HF risk allele; RAF, all-cause HF risk allele frequency; and SNP, single nucleotide polymorphism.

Of the 5 lead variants associated with all-cause HF, we observed replication in the GRADE cohort for those at *BAG3* and *MAP3K7CL*. Replication was more modest for variants at *CDKN2B-AS1* and *PITX2*, albeit with effect estimates similar to those observed in UK Biobank. In contrast, the association signal at *RYBP* did not replicate in GRADE, with an effect estimate directionally inconsistent with that observed in UK Biobank. No lead variants associated with all-cause HF were replicated in Vanderbilt BioVU (Table 2).

Of the lead NICM variants, we observed strong and consistent replication for the signal at *BAG3*, which associated with NICM in the Vanderbilt-BioVU, GRADE, and Esslinger et al[17] cohorts. The lead variant at *CLCNKA-ZBTB17* (rs12138073) demonstrated a more modest, but directionally consistent, association with NICM in GRADE, whereas a proxy-SNP (rs34471231, r^2=0.99) associated strongly with NICM in the Esslinger et al[17] cohort. Of note, an association with NICM has been reported previously for an independent variant (rs10927875, r^2=0.01) near our lead *CLCNKA-ZBTB17* signal.[17] Because this variant was associated with NICM in UK Biobank (OR, 1.15; $P=1.15\times10^{-4}$), and demonstrated modest to strong replication in the Vanderbilt-BioVU, GRADE, and Esslinger et al[17] cohorts, we included it in subsequent follow-up analyses. Finally, the lead variant for *PITX2* did not replicate in Vanderbilt-BioVU or GRADE, although a proxy SNP (rs6843082, r^2=0.82 with rs2634071) did associate strongly with NICM in the Esslinger et al[17] cohort (Table 3).

Association of Lead All-Cause HF and NICM Variants With HF Risk Factors

To assess whether lead variants for all-cause HF and NICM confer increased risk of disease through upstream risk factors, we first performed an association scan of 13 HF risk factors in UK Biobank. We observed robust associations between rs7857118 (*CDKN2B-AS1*) and CAD (OR per

Table 3. Replication of Suggestive Signals From Genetic Association Analyses for Nonischemic Cardiomyopathy in UK Biobank

Rsid	Chr	Pos	Nearest Gene	RA/ NRA	UK Biobank (n cases=1816)			BioVU Study (n cases=226)			GRADE (n cases=260)			Esslinger et al[17] (2017) (n cases=2796)		
					RAF	OR (95% CI)	*P* Value	RAF	OR (95% CI)	*P* Value	RAF	OR (95% CI)	*P* Value	RAF	OR (95% CI)	*P* Value
rs2234962	10	121429633	*BAG3*	T/C	0.78	1.30 (1.19–1.41)	2.32×10^{-9}	0.80	1.49 (1.14–1.94)	3.12×10^{-3}	0.79	1.39 (1.08–1.80)	0.01	0.81	1.61 (1.48–1.77)	1.70×10^{-25}
rs2634071	4	111669220	*PITX2*	T/C	0.16	1.25 (1.15–1.36)	1.06×10^{-7}	0.17	1.05 (0.82–1.35)	0.68	0.17	1.13 (0.87–1.46)	0.36	—	—	—
rs6843082*	4	111718067	*PITX2*	G/A	0.19	1.24 (1.14–1.34)	1.09×10^{-7}	0.21	0.93 (0.73–1.18)	0.53	0.20	1.13 (0.89–1.43)	0.33	0.23	1.11 (1.03–1.20)	7.52×10^{-3}
rs12138073	1	16354958	*CLCNKA*	T/C	0.10	1.29 (1.17–1.42)	5.35×10^{-7}	0.10	1.06 (0.78–1.44)	0.72	0.10	1.19 (0.88–1.62)	0.26	—	—	—
rs34471231†	1	16356522	*CLCNKA*	G/A	0.10	1.29 (1.17–1.42)	6.58×10^{-7}	0.10	1.05 (0.77–1.43)	0.74	0.10	1.19 (0.88–1.62)	0.26	0.10	1.20 (1.08–1.34)	9.61×10^{-4}
rs10927875	1	16299312	*ZBTB17*	C/T	0.68	1.15 (1.07–1.24)	1.15×10^{-4}	0.68	1.22 (0.98–1.50)	0.07	0.68	1.18 (0.96–1.47)	0.12	0.69	1.30 (1.21–1.40)	8.11×10^{-13}

BioVU indicates Vanderbilt University Biobank; Chr, chromosome; GRADE, Genetic Risk Assessment of Defibrillator Events; NICM, nonischemic cardiomyopathy; NRA, NICM nonrisk allele; Pos, hg19 position; RA, NICM risk allele; RAF, NICM risk allele frequency; and OR, odds ratio.

*rs6843082 is present in the exome chip analysis from Esslinger et al[17] and in linkage disequilibrium with rs2634071 in the UK Biobank (r^2=0.82).

†rs34471231 is present in the exome chip analysis from Esslinger et al[17] and in linkage disequilibrium with rs12138073 in the UK Biobank (r^2=0.99).

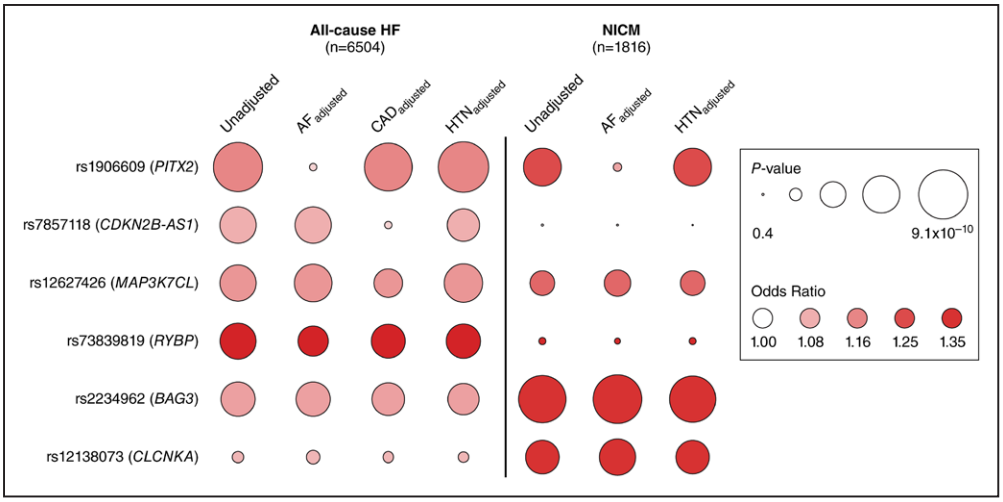

Figure 3. Association of suggestive all-cause heart failure (HF) and nonischemic cardiomyopathy (NICM) variants adjusted for known HF risk factors. Logistic regression was used to test the association of lead variants identified at suggestive loci ($P<1\times10^{-6}$) for either all-cause HF or NICM against both end points adjusted for baseline atrial fibrillation (AF), baseline coronary artery disease (CAD), and baseline hypertension. Nonischemic cardiomyopathy testing was not adjusted for CAD because CAD was an exclusion criterion. All analyses were additionally adjusted for age at baseline, sex, genotyping array, and the first 10 principal components of ancestry. Circle size denotes *P* value, and shading represents the odds ratio for a 1-allele increase of the all-cause HF/NICM risk allele.

HF/NICM risk allele=1.23; $P=1.24\times10^{-72}$), and rs1906609 (*PITX2*) and atrial fibrillation (OR per HF/NICM risk allele=1.49; $P=3.61\times10^{-143}$), both well beyond a Bonferroni-corrected level of statistical significance [$P<0.05/(7$ variants×13 traits) = 5.49×10^{-4}]. We also noted the following, more modest risk factor associations surpassing the statistical threshold for multiple testing: rs2234962 (*BAG3*) and hypertension (OR per HF/NICM risk allele=1.02; $P=4.23\times10^{-4}$), systolic blood pressure (effect per HF/NICM risk allele=0.19 mm Hg; $P=3.52\times10^{-4}$) and diastolic blood pressure (effect per HF/NICM risk allele=0.19 mm Hg; $P=1.07\times10^{-10}$); and rs10927875 (*CLCNKA-ZBTB17*) and hypertension (OR per HF/NICM risk allele=1.02; $P=1.02\times10^{-4}$), systolic blood pressure (effect per HF/NICM risk allele=0.20; $P=1.12\times10^{-5}$), and diastolic blood pressure (effect per HF/NICM risk allele=0.09; $P=5.58\times10^{-4}$) (Table IV in the online-only Data Supplement).

Coronary Artery Disease

Because *CDKN2B-AS1* on chromosome 9 represents a well-known CAD susceptibility locus, and the lead variant at this locus (rs7857118) associated strongly with CAD in the UK Biobank, we performed an association analysis for all-cause HF adjusted for baseline CAD to test whether this locus increased HF risk independent of CAD. Adjustment for baseline CAD resulted in marked attenuation of the association between rs7857118 and all-cause HF (OR, 1.04; $P=0.03$). Moreover, rs7857118 showed no association with NICM (OR, 1.04; $P=0.25$), further suggesting that the link between the *CKDN2B-AS1* locus and all-cause HF is largely mediated by CAD. Adjustment for baseline CAD did not significantly influence the strength of association between other lead variants and all-cause HF (Figure 3; Table V in the online-only Data Supplement).

Atrial Fibrillation

PITX2 on chromosome 4 is a recognized risk locus for atrial fibrillation, which may mediate the observed association between this gene region and all-cause HF/NICM. However, because the link between atrial fibrillation and HF is bidirectional, we first examined the prevailing temporal relationship between incident atrial fibrillation and incident all-cause HF/NICM in the UK Biobank.[32,33] Of the 1536 individuals who developed both incident all-cause HF and incident atrial fibrillation, 1237 (81%) carried a diagnosis of atrial fibrillation at or before a first diagnosis of HF. A similar pattern was observed for NICM, where 436 of 513 individuals with coincident disease (85%) had evidence of prior or concurrent atrial fibrillation (Figure II in the online-only Data Supplement).

We therefore performed genetic association testing for all-cause HF and NICM in UK Biobank adjusted for baseline atrial fibrillation. Adjustment for baseline atrial fibrillation resulted in marked attenuation of the association between rs1906609 and all-cause HF (OR, 1.05; $P=0.04$), and between rs2634071 and NICM (OR, 1.11; $P=0.02$), suggesting that the association between *PITX2* and all-cause HF/NICM in UK Biobank is largely mediated by coincident or antecedent atrial fibrillation. Adjustment for baseline atrial fibrillation did not significantly influence the strength of association between other lead variants and all-cause HF or NICM (Figure 3; Tables VI and VII in the online-only Data Supplement).

Hypertension

Neither *BAG3* nor *CLCNKA-ZBTB17* is an established susceptibility locus for hypertension, but variants at each were associated with hypertension and systolic/diastolic blood pressure in our analysis of the UK Biobank. We therefore pursued genetic association testing for all-

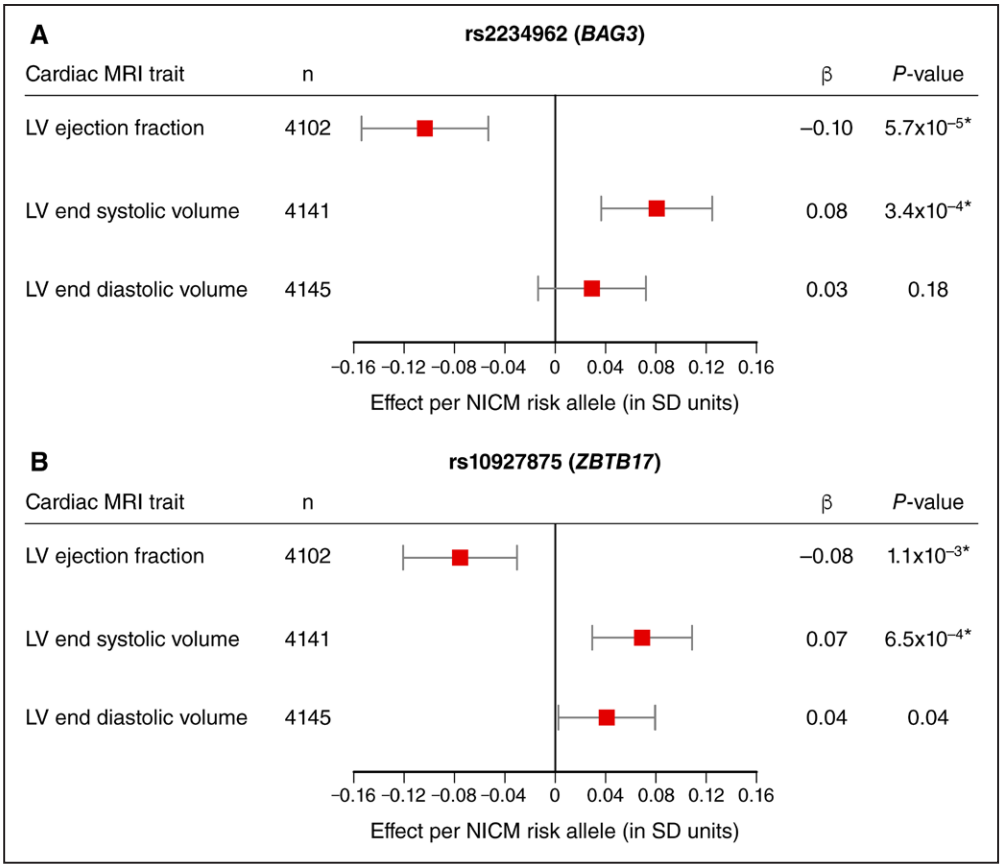

Figure 4. Association of suggestive all-cause heart failure and nonischemic cardiomyopathy (NICM) variants with selected cardiac MRI traits of left ventricular (LV) structure and function in UK Biobank.

Linear regression was used to test the association of suggestive signals for all-cause heart failure and NICM variants with measured cardiac magnetic resonance imaging (MRI) traits in up to 4158 individuals free of clinical heart failure in the UK Biobank. Testing was performed by using allelic dosages, adjusting for age at baseline, sex, genotyping chip, and the first 10 principal components of ancestry. Results are displayed for rs2234962 near *BAG3* (**A**) and rs10927875 near *ZBTB17* (**B**) against 3 selected cardiac MRI traits, because no other variants had associations reaching statistical significance. Points represent the effect in SD units of each respective cardiac MRI trait, and error bars denote 95% CIs. Significant associations passing Bonferroni significance ($P<0.05/42=1.19\times10^{-3}$) are denoted with an asterisk. β indicates effect per NICM risk allele in SD units of the cardiac MRI trait.

cause HF and NICM in UK Biobank adjusted for prevalent hypertension, systolic blood pressure, or diastolic blood pressure. Adjusted analyses demonstrated persistently strong signals at rs2234962 (*BAG3*) and rs10927875 (*CLCNKA-ZBTB17*) with minimal attenuation of the allelic effect size, suggesting that variation at *BAG3* and *CLCNKA-ZBTB17* confer risk of all-cause HF and NICM independent of elevated blood pressure (Figure 3; Tables VIII and IX in the online-only Data Supplement).

Association of Lead All-Cause HF and NICM Variants With Intermediate Traits of LV Structure and Function in Individuals Without Clinical HF

To evaluate the relationship between lead all-cause HF and NICM variants with quantitative measures of LV structure and function in the general population, we queried available imaging data in individuals without clinical HF from 2 sources: (1) cardiac MRI data from 4158 participants in the UK Biobank (Figure III in the online-only Data Supplement) and (2) summary-level data on 16 echocardiographic parameters in 30 081 individuals from a recent genome-wide association study (EchoGen Consortium).[34] Clinical characteristics of HF-free UK Biobank participants who did and did not undergo cardiac MRI are presented in Table X in the online-only Data Supplement. Individuals who underwent cardiac MRI in the UK Biobank were generally healthier than their counterparts, as evidenced by younger mean age, lower mean body mass index, and lower rates of CAD, atrial fibrillation, and type 2 diabetes mellitus.

Of the 7 lead all-cause HF and NICM variants assessed, only those at *BAG3* and *CLCNKA-ZBTB17* associated with cardiac MRI measures of LV structure and function in the UK Biobank at a Bonferroni-corrected level of statistical significance [$P<0.05/(6\ \text{traits}\times7\ \text{SNPs})=0.0012$]. Specifically, we observed associations between rs2234962 (*BAG3*) and reduced LV ejection fraction (effect per NICM risk allele=–0.58%; $P=5.68\times10^{-5}$) and increased LV end-systolic volume (effect per NICM risk allele=1.53 mL; $P=3.41\times10^{-4}$) (Figure 4A, Table XI in the online-only

Data Supplement); these associations replicated in analogous, summary-level data from the EchoGen Consortium, where rs2234962 associated with reduced fractional shortening (effect per NICM risk allele=–0.30%; P=6.05×10^{-8}) and increased LV diastolic diameter (effect per NICM risk allele=0.017 cm; P=6.59×10^{-5}).[34] In addition, rs10927875 (*CLNCKA-ZBTB17*) was significantly associated with reduced LV ejection fraction (effect per NICM risk allele=–0.42%; P=1.08×10^{-3}) and increased LV end-systolic volume (effect per NICM risk allele=1.31 mL; P=6.49×10^{-4}) in UK Biobank (Figure 4B; Table XI in the online-only Data Supplement).

Rare, Loss-of-Function Variants in DCM Genes and Risk of All-Cause HF or NICM in UK Biobank

We next investigated whether rarer mutations with predicted functional consequences might be differentially associated with all-cause HF and NICM in the UK Biobank. Rare mutations of larger effect size have been identified previously for DCM. We tested whether rare, pLOF variants in 24 known DCM genes with carrier frequency >0.0001 associated with our phenotypes for all-cause HF or NICM in the UK Biobank. Only the association between pLOF mutations at *BAG3* and NICM surpassed a Bonferroni-corrected significance threshold [P<0.05/(2 phenotypes×24 genes)=0.001]: 0.165% of NICM cases carried a rare, loss-of-function mutation in *BAG3*, whereas 0.014% of controls did (OR, 12.03; P=3.62×10^{-5}). There were no statistically significant associations between any pLOF mutations at the tested DCM genes and all-cause HF (Table XII in the online-only Data Supplement).

DISCUSSION

Genome-wide association analysis of all-cause HF in the UK Biobank identified multiple known loci for HF risk factors, ie, CAD and atrial fibrillation, highlighting major genetic determinants of this common disease. By comparison, refinement of all-cause HF to a specific, NICM phenotype yielded strong genetic signals at loci for DCM that were independent of HF risk factors and associated with intermediate traits of LV structure and function in individuals without clinical HF.

These results permit several conclusions. First, our genetic analysis of all-cause HF underscores the complexity of this condition and points to several etiologic subtypes, driven in part by a genetic predisposition to prominent HF risk factors. For instance, we found that *PITX2,* a known susceptibility locus for atrial fibrillation, and both *CDKN2B-AS1* and *MAP3K7CL*, known CAD loci, were strongly associated with all-cause HF.

Atrial fibrillation and HF are established risk factors for one another and frequently coexist.[32] A recent study noted that >50% of all patients with HF have coincident atrial fibrillation, and that atrial fibrillation is more likely to precede rather than follow a diagnosis of HF.[33] Among patients with all-cause HF and NICM in the UK Biobank, we observed comparable rates of antecedent and comorbid atrial fibrillation. Furthermore, the attenuation of the *PITX2* association signal after adjustment for prevalent atrial fibrillation indicates that the observed association between *PITX2* and HF likely reflects coincident disease. Inconsistent replication of *PITX2* in our independent cohorts may reflect the exclusion of patients with tachycardia-induced cardiomyopathy in recruited, hospital-based registries, highlighting the phenotypic precision offered by recruited cohorts capable of disentangling the complex HF–atrial fibrillation relationship a priori. In contrast, population-based approaches are complementary and enable the analysis of HF in the context of prominent risk factors.

Similarly, the association signal at *CDKN2B-AS1* was diminished after adjusting for prevalent CAD and, in the NICM sample, underscoring the importance of CAD as a driver of HF. It is noteworthy that we observed only modest attenuation of the association between the *MAP3K7CL* locus and all-cause HF, and a stronger effect estimate for the association of this locus with NICM, suggesting that variation at *MAP3K7CL* may influence HF risk via mechanisms independent of CAD. Further analyses are needed to determine how the *MAP3K7CL* locus might mediate HF beyond its contribution to CAD risk.

Second, phenotypic refinement of HF within a large, population-based biobank is feasible and may facilitate genetic discovery. Prior efforts to uncover the genetics of common, complex HF have been hindered by marked disease heterogeneity. Although recent advances have come from a small number of genetic analyses of selected HF subpopulations, there has been limited consideration to date of such disease subtypes and HF with preserved versus reduced ejection fraction.[13,16–18] Whereas large sample sizes enhance power for discovery, our data suggest that precise phenotyping is important for the discovery of subtype-specific HF susceptibility loci. In comparison with the all-cause HF phenotype, the more precise NICM definition yielded stronger genetic association signals at known loci for DCM (ie, *BAG3* and *CLCNKA-ZBTB17*) despite 3-fold fewer cases. Moreover, lead NICM variants demonstrated more consistent replication in our independent cohorts than did the lead all-cause HF variants, likely because of the heterogeneity of the all-cause HF phenotype. Also, whereas our analysis of loss-of-function variation corroborates prior data implicating *BAG3* as a bona-fide disease susceptibility gene for NICM, the association with all-cause HF was not significant, further

underscoring the importance of phenotype for specificity of associations.[16,17,29] Finally, our algorithm for ascertaining NICM in the UK Biobank used standard self-reported and billing code data and may therefore be portable to other electronic health systems and forthcoming population-based biobanks.

Third, genetic drivers of DCM, best identified by the NICM phenotype, may mediate a subclinical cardiomyopathic process that predisposes to clinical HF. Here, we demonstrate that common genetic variants associated with clinical HF are also associated with intermediate traits of LV structure and function in individuals without clinical disease. Prior epidemiological studies have noted that subtle, preclinical abnormalities in LV chamber size and function may herald progression to overt HF, prompting subsequent genetic association studies of intermediate echocardiographic traits.[34–37] Consistent associations between a genetic variant, an intermediate imaging trait, and clinical HF therefore imply a causal mechanistic pathway. In our analyses of cardiac MRI and echocardiographic traits, 2 lead NICM variants previously linked to DCM, at *BAG3* and *CLCNKA-ZBTB17*, associated significantly with reduced LV systolic function and increased LV chamber size. It is important to note that these associations were observed among those without clinical HF, suggesting a subclinical process that may portend a genetic predisposition to clinical HF. Whether such genetically mediated cardiomyopathies confer a prognosis similar to that of other cardiomyopathies, ie, with respect to the risk of sudden cardiac death, remains unclear and requires further study.

Of note, ample functional data support the mechanistic roles of both *BAG3* and *CLCNKA-ZBTB17* in the pathogenesis of HF. For example, recent studies have suggested an antiapoptotic function for *BAG3* in cardiomyocytes, with morpholino knockdown in zebrafish resulting in cardiac enlargement and systolic dysfunction.[31,38–45] Similarly, recent in vitro and in vivo analyses of *ZBTB17* have identified an antiapoptotic gene product critical for the adaptation of cardiomyocytes to biomechanical stress.[46] Alongside our human genetic observations at these 2 loci, the data advocate for the pursuit and prioritization of other DCM signals with similar prognostic and therapeutic implications to advance current understanding of HF genetics.

Several limitations should be acknowledged. First, quantitative measures of LV structure and function were unavailable for most UK Biobank participants, preventing classification of HF with reduced versus preserved ejection fraction and precluding a robust genetic association study of intermediate imaging traits. Forthcoming cardiac MRI data on 100 000 individuals in the UK Biobank will soon enable categorization of many more study participants based on LV systolic function. Second, in the absence of cohort-wide cardiac imaging data to permit morphological classifications of disease, phenotyping was predicated on data from self-reports and the medical record, which carry the potential for disease misclassification. Furthermore, our refinement of all-cause HF focuses on the NICM subset, but not on the remainder of the HF population, which remains a heterogeneous group. However, we submit that our phenotyping approach serves only as an initial strategy for addressing the heterogeneity of HF. Future studies using more sophisticated phenotyping strategies, including the integration of clinical, laboratory, and imaging data, may provide more nuanced classifications of HF and further facilitate genetic discovery. Third, temporal disease associations in the UK Biobank relied on hospitalization-based health registry data and periodic study examinations; disease status may have gone clinically unrecognized during interval periods. Fourth, analyses of rare, loss-of-function mutations were limited to those variants available on the genotyping array, and were unable to detect novel and private mutations. Fifth, our analyses were limited to participants of European ancestry; because these findings may not apply to individuals of other ancestries, validation of these results in ancestries outside of Europe is required.

In conclusion, we found evidence for distinct genetic mechanisms of HF, including those that operate through known HF risk factors. Phenotypic refinement of all-cause HF to a specific NICM subset appears to facilitate genetic discovery by better identifying genetic signals for cardiomyopathy that operate independent of HF risk factors and associate with clinical and subclinical disease. Future studies are warranted to investigate the prognostic and therapeutic implications of these findings for the prevention and management of HF.

ARTICLE INFORMATION

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APPENDIX

Genetic Risk Assessment of Defibrillator Events (GRADE) Investigators: Heather L. Bloom, MD; Samuel C. Dudley, MD, PhD; Patrick T. Ellinor, MD, PhD; Alaa A. Shalaby, MD; Raul Weiss, MD; Rebecca Gutmann, RN, BSN, CCRC; Samir Saba, MD; and Barry London, MD, PhD.

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