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Genetic Architecture of Dilated Cardiomyopathy in Individuals of African and European Ancestry

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IMPORTANCE Black patients with dilated cardiomyopathy (DCM) have increased familial risk and worse outcomes than White patients, but most DCM genetic data are from White patients.

OBJECTIVE To compare the rare variant genetic architecture of DCM by genomic ancestry within a diverse population of patients with DCM.

DESIGN Cross-sectional study enrolling patients with DCM who self-identified as non-Hispanic Black, Hispanic, or non-Hispanic White from June 7, 2016, to March 15, 2020, at 25 US advanced heart failure programs. Variants in 36 DCM genes were adjudicated as pathogenic, likely pathogenic, or of uncertain significance.

EXPOSURE Presence of DCM.

MAIN OUTCOMES AND MEASURES Variants in DCM genes classified as pathogenic/likely pathogenic/uncertain significance and clinically actionable (pathogenic/likely pathogenic).

RESULTS A total of 505, 667, and 26 patients with DCM of predominantly African, European, or Native American genomic ancestry, respectively, were included. Compared with patients of European ancestry, a lower percentage of patients of African ancestry had clinically actionable variants (8.2% [95% CI, 5.2%-11.1%] vs 25.5% [95% CI, 21.3%-29.6%]), reflecting the lower odds of a clinically actionable variant for those with any pathogenic variant/likely pathogenic variant/variant of uncertain significance (odds ratio, 0.25 [95% CI, 0.17-0.37]). On average, patients of African ancestry had fewer clinically actionable variants in *TTN* (difference, −0.09 [95% CI, −0.14 to −0.05]) and other genes with predicted loss of function as a disease-causing mechanism (difference, −0.06 [95% CI, −0.11 to −0.02]). However, the number of pathogenic variants/likely pathogenic variants/variants of uncertain significance was more comparable between ancestry groups (difference, −0.07 [95% CI, −0.22 to 0.09]) due to a larger number of non-*TTN* non–predicted loss of function variants of uncertain significance, mostly missense, in patients of African ancestry (difference, 0.15 [95% CI, 0.00-0.30]). Published clinical case-based evidence supporting pathogenicity was less available for variants found only in patients of African ancestry ($P < .001$).

CONCLUSION AND RELEVANCE Patients of African ancestry with DCM were less likely to have clinically actionable variants in DCM genes than those of European ancestry due to differences in genetic architecture and a lack of representation of African ancestry in clinical data sets.

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A pervasive clinical and research issue has been the lack of genetic data from those of ancestry other than European,[1,2] even though genetic data from diverse ancestry groups have been shown to increase discovery[3] and are essential for clinical care.[4,5] This is especially the case in idiopathic dilated cardiomyopathy (DCM), which is more prevalent and has earlier onset with greater morbidity and mortality in self-identified Black patients compared with self-identified White patients.[6,7] Although considerable progress has been made to understand DCM genetics,[8] nearly all published DCM genetic case data, DCM gene-association studies,[9] and data used to develop variant interpretation guidance[10] have been from patients of European ancestry, limiting clinical genetic evaluation for patients of African ancestry with DCM.[5]

The DCM Precision Medicine Study was designed to examine rare variant DCM genetics in a diverse cohort of patients[11] using clinical variant adjudication standards specified for DCM.[12] A recent report from this study using self-identified race showed that the estimated prevalence of familial DCM was higher in Black patients than in White patients, and the DCM hazard was higher in first-degree relatives of Black patients than White patients,[13] which suggested a similar or greater degree of genetic cause in Black patients. However, a prior evaluation of genetic testing for cardiomyopathy showed that fewer non-White patients received a pathogenic or likely pathogenic result and had greater numbers of variants of uncertain significance.[5] The reasons for the observed disparity in genetic testing results were suggested to arise in part from differences in the types of variants and a lack of available case evidence to support variant adjudication. The objective of this analysis was to explore characteristics of rare variant DCM genetic architecture across a diverse population of patients with DCM by genomic ancestry.

Key Points

Question Does the rare variant genetic architecture of dilated cardiomyopathy differ between patients of African and European ancestry?

Findings In this cross-sectional study of 1198 patients with dilated cardiomyopathy, significantly fewer patients of African ancestry (8.2%) than those European ancestry (25.5%) had variants classified as pathogenic or likely pathogenic, a difference due in part to fewer predicted loss-of-function variants and less case-based evidence to support pathogenicity for variants found only in patients of African ancestry.

Meaning Assumptions regarding dilated cardiomyopathy genetic architecture derived from European ancestry may not be applicable to African ancestry; a current lack of case data limits clinical genetics care for patients of African ancestry with dilated cardiomyopathy.

Methods

The DCM Precision Medicine Study was a multisite, cross-sectional study of families at 25 sites of the DCM Consortium[13] (eFigure 1 and eTable 1 in Supplement 1). Of 1265 consenting patients,[13] 1198 with DCM (probands) were analyzed (eFigure 2 in Supplement 1). The institutional review boards at The Ohio State University and the initial 12 clinical sites approved the study[11]; oversight was ceded to a single institutional review board at the University of Pennsylvania as clinical sites beyond 12 were added.[13] All participants provided written informed consent. Exome sequence and array-based genotype data will be shared publicly through the National Library of Medicine's Database of Genotypes and Phenotypes (dbGaP) (phs002641). Additional data can be made available from the authors on reasonable request.

All probands met diagnostic criteria for DCM, defined as a left ventricular ejection fraction less than 50% and left ventricular enlargement, with other causes excluded as previously defined.[11,13] Cardiac magnetic resonance imaging data when available validated DCM diagnoses.[14]

Research exome sequencing was conducted and data processed as described previously.[12] Rare protein-altering variants in 36 DCM genes (eTable 2 in Supplement 1) were then adjudicated using American College of Medical Genetics/Association for Molecular Pathology (ACMG/AMP) and Clinical Genome Resource (ClinGen)-based criteria tailored to DCM.[12] Minor modifications to exome processing and variant interpretation are noted in eAppendix 1 in Supplement 1. After automated filtering, variants not computationally adjudicated as benign, likely benign, unlikely to impact protein function, or of low quality were manually reviewed and certified for a final classification and confirmed with Sanger sequencing (pathogenic/likely pathogenic/variants of uncertain significance only), as previously reported.[12]

Structured interviews collected participant demographic and health history; medical record review forms summarized cardiovascular clinical data.[11,13] Participant self-identified race and ethnicity were obtained using structured race (African American, Asian, Native American or Alaska Native, Native Hawaiian or Pacific Islander, White, more than 1 race, or unknown) and Hispanic ethnicity (yes, no, or unknown) categories. The DCM Consortium is aware of issues[15] for the collection, analysis, presentation, and discussion of race, ethnicity, and ancestry and has adopted recommended approaches.[16-20]

Global genomic ancestry proportions were inferred from Illumina Global Screening Array genotypes with the 1000 Genomes Phase 3 integrated call set as the reference (eAppendix 1 and eFigure 3 in Supplement 1). An individual's ancestry group was defined as the inferred continental ancestry group (African, East Asian, European, Native American, or South Asian; eFigures 4-5 in Supplement 1) accounting for the highest proportion of one's genomic ancestry, and individuals are referred to as being of that ancestry (eg, African ancestry) throughout. Individuals in an ancestry group other than African, European, or Native American were not analyzed due to small numbers (n = 4).

Statistical Analysis

Technical descriptions of statistical methods are provided in eAppendix 1 in Supplement 1. All statistical analyses were performed using SAS/STAT 15.2 software, version 9.4 (TS1M7) of the SAS System for 64-bit Linux (SAS Institute Inc) and R version 4.1.1 (R Foundation). Statistical tests and confidence intervals were 2-sided with $\alpha = .05$ unless otherwise noted.

Two trinomial outcomes were defined for each proband based on the most deleterious variant identified (none, variant of uncertain significance, or pathogenic/likely pathogenic variant) and the number of variants classified as pathogenic/likely pathogenic/uncertain significance (0, 1, or >1). These outcomes were modeled using a hierarchical logit model[21] with ancestry group, ethnicity, sex, and quartile of age at DCM diagnosis as fixed effects. Random effects to account for potential site heterogeneity were considered but found to be unnecessary. In addition to odds ratios comparing groups, this model fit was used to obtain marginally standardized estimates of outcome probabilities, as described below.

Variants were grouped by the ancestry group of the study proband(s) in whom they were identified (African, European, Native American, or multiple ancestries if observed in probands of more than 1 ancestry). Variant characteristics were compared using the exact Pearson χ^2 test for nominal variables and the Kruskal-Wallis test of no difference in group medians for continuous variables. For post hoc pairwise comparisons between ancestries, Holm-Bonferroni corrected exact Monte-Carlo *P* values for the χ^2 test involving only those 2 groups or Dwass-Steel-Critchlow-Fligner multiplicity-adjusted *P* values based on pairwise Wilcoxon rank sum tests were used.[22,23] The exact Monte Carlo *P* value estimate based on 100 000 replicates was used for the Pearson χ^2 test.

The number of pathogenic variants/likely pathogenic variants/variants of uncertain significance per proband was separated into contributions from various subsets of variants (eg, pathogenic/likely pathogenic *TTN* variants) and modeled as a multivariate outcome using a generalized estimating equations approach with the identity link and a heterogeneous variance function independent of the mean.[24] The linear predictor included fixed effects for ancestry group, ethnicity, sex, and quartile of age at DCM diagnosis; site heterogeneity was not modeled explicitly as it affects only the marginal covariance structure with the identity link. Instead, a working independence assumption was used, and potential correlation between subset counts within each proband or site was addressed by using a Morel-Bokossa-Neerchal bias-corrected empirical covariance matrix with sites as independent units.[25] This model fit was used to obtain marginally standardized estimates of mean numbers of variants in a particular subset, as described below.

Marginal standardization, which involved taking weighted averages of the estimates for each combination of covariates according to an assumed covariate distribution, was used to obtain estimates of outcome probabilities and mean variant counts in representative subpopulations of probands. Because of either the absence of site heterogeneity or the use of the identity link, these estimates apply both to patients at a typical advanced heart failure program in the US and the entire population of patients seen at all such programs. Detailed descriptions of the assumed covariate distributions are provided in the corresponding table notes. The delta method was used to provide standard errors for marginally standardized quantities that were nonlinear functions of the parameter estimates.

Results

Of 1198 probands with DCM, 43.0% were of Black race and 56.8% were of White race based on self-identification; 8.5% were of Hispanic ethnicity; and 43.7% were female. Clinical characteristics of the study cohort are summarized within ancestry groups (**Table 1**). The lower median Native American ancestry proportion in the Native American ancestry group was consistent with admixture patterns in its mostly Hispanic probands.[28]

The estimated prevalence of any variant classified as pathogenic, likely pathogenic, or of uncertain significance among African ancestry probands was 57.5% (95% CI, 51.7%-63.3%), lower than the estimated 65.1% (95% CI, 60.5%-69.6%) among European ancestry probands (odds ratio, 0.72; 95% CI, 0.57-0.92) (**Table 2** and **Table 3**). Among probands with variants classified as pathogenic, likely pathogenic, or of uncertain significance, the estimated odds of having at least 1 pathogenic/likely pathogenic variant were 75% lower for probands of African ancestry compared with probands of European ancestry (odds ratio, 0.25; 95% CI, 0.17-0.37) (Table 3). In contrast, younger age at diagnosis was positively associated with the odds of having a pathogenic variant/likely pathogenic variant/variant of uncertain significance and, given that outcome, having a pathogenic/likely pathogenic variant. No differences were observed by ethnicity or sex. The estimated prevalence of having more than 1 pathogenic variant/likely pathogenic variant/variant of uncertain significance was 23% among both probands of African ancestry and those of European ancestry (Table 2).

To explore the lower prevalence of pathogenic/likely pathogenic variants in the African ancestry group, the types and characteristics of variants by ancestry were evaluated. Counts of all variants classified as pathogenic/likely pathogenic or variants of uncertain significance in each gene are presented by the ancestry of probands in which they were observed (eTable 3 in Supplement 1). The proportion of variants classified as pathogenic/likely pathogenic varied substantially by ancestry group ($P < .001$) (**Figure**; eTable 4 in Supplement 1), with variants found only in study probands of African ancestry less likely to be classified as pathogenic/likely pathogenic than those found only in study probands of European ancestry or those observed in multiple study probands from different ancestry groups (post hoc $P < .001$ for African vs European and $P = .03$ for African vs more than 1 ancestry) (eTable 5 in Supplement 1). This in part arose from differences in the prevalence of variants in genes other than *TTN* and predicted variant effect ($P < .001$), which was primarily driven by lower frequencies of *TTN* and predicted loss of function (pLOF) variants found only in study probands of African ancestry when compared with those found only in study probands of European ancestry (post hoc $P < .001$) (Figure; eTables 4 and 5 in Supplement 1). Among *TTN* variants, there was no evidence that the distribution across *TTN* bands (A, I, M, and Z) varied by ancestry group (eTable 4 and eFigure 6 in Supplement 1). Absence in gnomAD nonfounder populations and the maximum alternate allele frequency across these also varied substantially by ancestry ($P < .001$); variants found only in study probands of African ancestry or observed in multiple

Table 1. Demographic and Clinical Characteristics of Probands by Ancestry Group

Characteristics	African (n = 505)[a]	European (n = 667)[a]	Native American (n = 26)[a]
Age at enrollment, median (IQR), y	50.8 (41.7-59.5)	55.0 (43.4-64.3)	47.0 (34.8-53.8)
Age at diagnosis of dilated cardiomyopathy, median (IQR), y	43.0 (33.2-52.4)	45.3 (35.4-55.2)	37.0 (27.2-47.9)
Sex, No. (%)			
Female	223 (44.2)	289 (43.3)	12 (46.2)
Male	282 (55.8)	378 (56.7)	14 (53.8)
Self-identified race, No. (%)[b]			
Black	504 (99.8)	10 (1.5)	1 (3.9)
White	1 (0.2)	656 (98.4)	24 (92.3)
More than 1 race[c]	0	1 (0.2)	1 (3.9)
Self-identified Hispanic ethnicity, No. (%)	9 (1.8)	68 (10.2)	25 (96.2)
Inferred continental ancestry proportion, median (IQR)[d]			
African	0.83 (0.77-0.88)	0.00 (0.00-0.01)	0.05 (0.04-0.07)
East Asian	0.01 (0.00-0.01)	0.00 (0.00-0.01)	0.04 (0.03-0.05)
European	0.15 (0.10-0.20)	0.97 (0.94-0.97)	0.39 (0.34-0.41)
Native American	0.01 (0.00-0.01)	0.01 (0.00-0.01)	0.49 (0.47-0.55)
South Asian	0.01 (0.00-0.01)	0.02 (0.01-0.03)	0.01 (0.01-0.02)
Comorbidities, No. (%)[e]			
Hypertension	342 (67.7)	278 (41.7)	15 (57.7)
High cholesterol	144 (28.5)	171 (25.6)	10 (38.5)
Diabetes	155 (30.7)	136 (20.4)	7 (26.9)
Cancer	20 (4.0)	43 (6.5)	0
Lung disease	23 (4.6)	29 (4.4)	1 (3.9)
Left ventricular function and size			
Left ventricular ejection fraction, median (IQR), %[f]	20.0 (15.0-25.0) [n = 504]	22.5 (15.4-30.0) [n = 664]	20.0 (16.0-22.5) [n = 25]
Left ventricular internal diastolic dimension, median (IQR), mm	65.0 (60.0-71.0) [n = 503]	64.0 (59.0-70.0) [n = 664]	67.2 (61.0-69.0) [n = 25]
Left ventricular internal diastolic dimension, median (IQR), *z* score[g]	4.2 (3.1-5.6) [n = 503]	4.0 (2.9-5.3) [n = 662]	4.9 (3.7-5.9) [n = 25]
Interventions, No. (%)			
Implantable cardioverter defibrillator	343 (68.5) [n = 501]	439 (66.1) [n = 664]	16 (61.5)
Left ventricular assist device	130 (25.7)	112 (16.8)	7 (26.9)
Heart transplant	57 (11.3)	109 (16.3)	10 (38.5)
Biventricular pacemaker	50 (10.3) [n = 485]	109 (16.9) [n = 646]	5 (19.2)

[a] Genomic ancestry was determined based on global ancestry proportions inferred from array-based genotypes; an individual's ancestry group was defined as the inferred continental ancestry group (African, East Asian, European, Native American, or South Asian) accounting for the highest proportion of his or her genomic ancestry. Individuals with ancestry other than African, European, or Native American (n = 4) were not analyzed due to small numbers (eFigure 2 in Supplement 1).

[b] Options for self-identified race included African American, Asian, Native American or Alaska Native, Native Hawaiian or Pacific Islander, White, more than 1 race, and unknown. Probands were not excluded from analysis based on self-identified race, but exclusions based on ancestry other than African, European, or Native American, which was highly correlated with self-identified race, limited the observed categories to those listed.

[c] Respondents selected "more than 1 race" but did not provide information on which of the listed options applied to them.

[d] Plots of individual-level ancestry proportions by self-reported race and ethnicity and genomic ancestry group are presented in eFigure 5 in Supplement 1.

[e] Data were obtained by study personnel using a standard medical record questionnaire and substantiated by medical records electronically transmitted to The Ohio State University.

[f] American College of Cardiology clinical guidelines classify left ventricular ejection fraction of 50% to 70% as normal, 40% to 49% as mild dysfunction, 30% to 39% as moderate dysfunction, and less than 30% as severe dysfunction.[26]

[g] Calculated based on sex and height[27] for all study participants with heights of at least 137 cm (female) or 152 cm (male).

study probands from different ancestry groups were less likely to be absent in gnomAD and had higher maximum allele frequencies than those found only in study probands of European ancestry (post hoc $P \leq .03$). These differences in variant characteristics were mirrored in the variant classification criteria that were met (Figure; eTables 4 and 5 in Supplement 1).

Contributions to the mean number of pathogenic variants/likely pathogenic variants/variants of uncertain significance per proband were also evaluated by variant classification, gene group, and predicted impact. In a model defining variant subsets by classification and gene group (**Table 4**), there was minimal difference between probands of African and European ancestry in the mean number of pathogenic variants/likely pathogenic variants/variants of uncertain significance. However, this overall effect included a reduction of 0.19 (95% CI, −0.25 to −0.12) in pathogenic/likely pathogenic variants that was offset by an increase of 0.12 (95% CI, −0.03 to 0.27) in variants of uncertain significance in probands of African ancestry relative to probands of European ancestry. This pattern was recapitulated within each gene grouping that contributed to the total

Table 2. Variant Classification Results in Probands With Dilated Cardiomyopathy by Ancestry Group

Outcomes	African (n = 505)		European (n = 667)		Native American (n = 26)	
	Crude No. (%)	Model-based % (joint 95% CI)[a]	Crude No. (%)	Model-based % (joint 95% CI)[a]	Crude No. (%)	Model-based % (joint 95% CI)[a]
No variants identified[b]	214 (42.4)	42.5 (36.7-48.3)	237 (35.5)	34.9 (30.4-39.5)	9 (34.6)	39.1 (13.4-64.8)
Most deleterious variant identified						
Variant of uncertain significance	247 (48.9)	49.3 (43.6-55.1)	259 (38.8)	39.6 (34.9-44.3)	9 (34.6)	28.3 (5.1-51.4)
Pathogenic/likely pathogenic variant	44 (8.7)	8.2 (5.2-11.1)	171 (25.6)	25.5 (21.3-29.6)	8 (30.8)	32.6 (8.6-56.7)
No. of pathogenic variants/likely pathogenic variants/ variants of uncertain significance identified						
1	178 (35.3)	34.5 (29.0-40.1)	281 (42.1)	42.3 (37.5-47.0)	9 (34.6)	35.9 (11.5-60.4)
>1	113 (22.4)	23.0 (18.0-27.9)	149 (22.3)	22.8 (18.7-26.8)	8 (30.8)	25.0 (3.3-46.7)

[a] Estimates from hierarchical logit models for trinomial outcomes presented in Table 3 were used to obtain marginally standardized estimates of and delta method joint 95% CIs for outcome probabilities for probands in a particular ancestry group. All 95% CIs were produced using the standard normal distribution and the Bonferroni correction over the 3 possible outcome categories. As the estimated random effects variance implied no heterogeneity across programs, these estimates can be interpreted as applicable to any US advanced heart failure program or the entire population of patients with dilated cardiomyopathy served by such programs. Each patient subpopulation defined by ancestry group was assumed to be balanced across the 8 possible sex and age quartile combinations, with a proportion of Hispanic individuals equal to the 2021 US census population estimate (18.9%).[29]

[b] As the multinomial parameter for this category is the same for both outcomes, crude frequencies and model-based estimates were identical and so are presented only once.

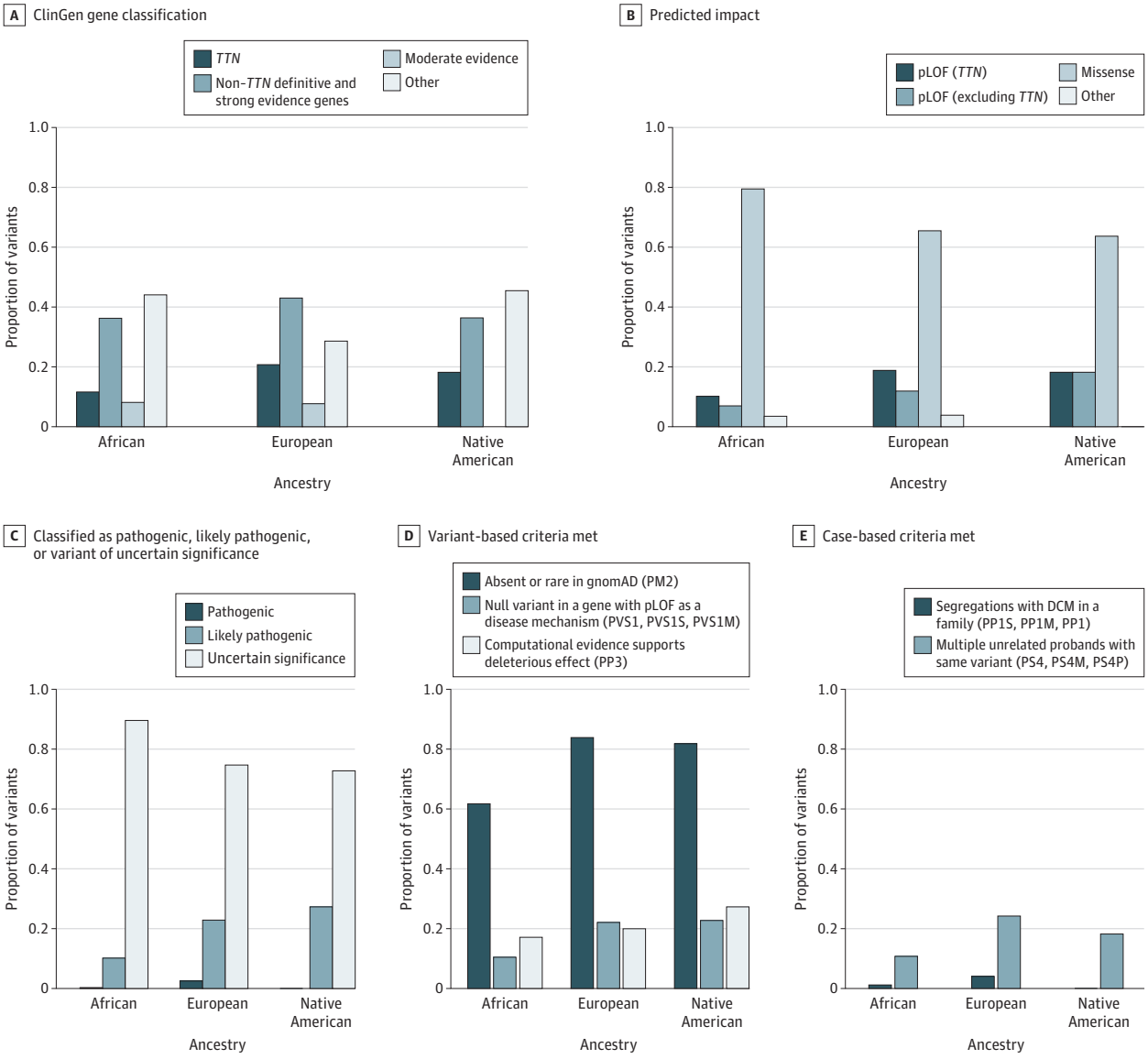
Table 3. Multivariable Hierarchical Logit Models for Variant Classification Results in Probands

Predictors	Odds of ≥1 pathogenic variant/likely pathogenic variant/variant of uncertain significance vs none		Odds of pathogenic variant/likely pathogenic variant vs variant of uncertain significance given ≥1 pathogenic variant/likely pathogenic variant/variant of uncertain significance		Odds of >1 pathogenic variant/likely pathogenic variant/variant of uncertain significance variant vs 1 given ≥1 pathogenic variant/likely pathogenic variant/variant of uncertain significance	
	Odds ratio (95% CI)[a]	*P* value[a]	Odds ratio (95% CI)[a]	*P* value[a]	Odds ratio (95% CI)[a]	*P* value[a]
Ancestry group						
African	0.72 (0.57-0.92)	.009	0.25 (0.17-0.37)	<.001	1.23 (0.90-1.69)	.19
Native American	0.83 (0.33-2.13)	.71	1.81 (0.58-5.63)	.31	1.29 (0.43-3.92)	.65
European	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Self-reported ethnicity						
Hispanic	1.13 (0.68-1.86)	.64	0.65 (0.34-1.23)	.19	1.33 (0.73-2.39)	.35
Non-Hispanic	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Sex						
Female	0.94 (0.74-1.19)	.61	1.01 (0.72-1.40)	.97	0.88 (0.65-1.19)	.41
Male	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Proband quartile of age at dilated cardiomyopathy diagnosis, y						
4.7-34.3	1.84 (1.32-2.56)	<.001	1.73 (1.05-2.83)	.03	0.91 (0.58-1.42)	.67
34.4-44.2	2.12 (1.52 - 2.96)	<.001	1.47 (0.90-2.39)	.12	1.14 (0.74-1.75)	.56
44.2-53.8	1.51 (1.09-2.09)	.01	1.35 (0.82-2.22)	.24	0.93 (0.59-1.45)	.75
53.8-82.7	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	

[a] Odds ratios and Wald 95% CIs from hierarchical logit models for trinomial outcomes based on the most deleterious variant identified (none, variant of uncertain significance, or pathogenic/likely pathogenic variant) and the number of pathogenic variants/likely pathogenic variants/variants of uncertain significance identified (0, 1, or >1) were adjusted for all other variables shown in the table. As no evidence of site heterogeneity was found, these estimates can be interpreted as comparing patients with dilated cardiomyopathy within the same US advanced heart failure program or between any 2 such programs. Two-sided Wald *P* values are for the null hypothesis that the odds ratio is 1. All *P* values and 95% CIs were produced using the standard normal distribution. A total of 1198 probands contributed to these models.

other than *TTN*. In *TTN*, the mean number of pathogenic variants/likely pathogenic variants/variants of uncertain significance in probands of African ancestry was reduced by 0.12 (95% CI, −0.18 to −0.07) relative to probands of European ancestry, driven by lower numbers of both variants of uncertain significance and pathogenic/likely pathogenic variants.

Figure. Characteristics of Pathogenic Variants, Likely Pathogenic Variants, and Variants of Uncertain Significance Observed in DCM Probands of a Given Ancestry



Variants denoted as being from African (n = 345 variants), European (n = 521), or Native American (n = 22) ancestry were observed only in study probands from that ancestry group and not in probands from other ancestry groups. For all panels, the y-axis is the proportion of variants from a particular ancestry with a given characteristic; underlying data are shown in eTables 4 and 5 in Supplement 1. For panels A-C, bars are mutually exclusive categories; proportions in each bar sum to 1 within each ancestry. For panels D-E, each bar is the proportion of variants from an ancestry meeting at least 1 of the variant interpretation criteria that provide evidence of pathogenicity in a particular domain, as denoted by American College of Medical Genetics acronyms listed in parentheses in the key (see definitions in eTable 4 in Supplement 1). As these domains are independent, space between bars indicates that the bars do not sum to 1 within each ancestry. Variant-based criteria include those in the population frequency, null variant in gene/region, and in silico prediction domains that relate to potential deleteriousness of the variant in general. Case-based criteria include those in the segregation and case counts or reported association domains, which relate to the availability of external data showing that the variant is associated specifically with dilated cardiomyopathy (DCM). A lower proportion of variants found only in probands of African ancestry were in definitive and strong evidence DCM genes (panel A) based on ClinGen classification[9] or had predicted loss-of-function (pLOF) consequences (panel B) relative to those found only in probands of European ancestry (post hoc $P < .001$ for both). As a result, a lower proportion of variants found only in probands of African ancestry were classified as pathogenic/likely pathogenic compared with those found only in probands of European ancestry (panel C; post hoc $P < .001$). A reduced ability to apply variant-based (panel D) or case-based (panel E) criteria in favor of pathogenicity to variants in probands of African ancestry contributed to this outcome. Compared with variants found only in European ancestry, smaller proportions of variants found in African ancestry were absent or rare in nonfounder gnomAD populations (post hoc $P < .001$) or had evidence for pathogenicity from case counts or reported associations (post hoc $P < .001$). Inferences for the predicted impact distribution in panel B were based on the predicted impact multinomial variable, which did not distinguish *TTN* and non-*TTN* pLOF variants to avoid confounding gene class with variant impact. For variant-based criteria in panel D, inferences were based on the population frequency domain, null variant in gene/region, and in silico prediction domain multinomial variables. Inferences for case-based criteria in panel E were based on the segregation domain and case counts or reported association domain multinomial variables.

Table 4. Number of Pathogenic Variants, Likely Pathogenic Variants, and Variants of Uncertain Significance per Proband by Variant Classification and Gene Group

Gene group	Total count	European (n = 667)		African (n = 505)				Native American (n = 26)			
					Model-based[a]				Model-based[a]		
		Crude mean (SD)	Model-based mean (95% CI)[a]	Crude mean (SD)	Mean (95% CI)	Difference from European (95% CI)	*P* value	Crude mean (SD)	Mean (95% CI)	Difference from European (95% CI)	*P* value
Pathogenic variant, likely pathogenic variant, or variant of uncertain significance											
All	1107	0.95 (0.92)	0.96 (0.86 to 1.06)	0.89 (0.98)	0.89 (0.77 to 1.01)	−0.07 (−0.22 to 0.09)	.40	1.08 (1.02)	0.98 (0.49 to 1.47)	0.03 (−0.48 to 0.54)	.92
TTN[b]	185	0.20 (0.41)	0.20 (0.16 to 0.24)	0.09 (0.29)	0.08 (0.04 to 0.12)	−0.12 (−0.18 to −0.07)	<.001	0.15 (0.37)	0.17 (0.00 to 0.36)[c]	−0.02 (−0.21 to 0.16)	.80
BAG3, *DSP*, *FLNC*, *LMNA*, *PLN*, *SCN5A*, *VCL*[b]	327	0.28 (0.53)	0.29 (0.23 to 0.34)	0.26 (0.55)	0.27 (0.20 to 0.35)	−0.01 (−0.11 to 0.09)	.82	0.35 (0.56)	0.27 (0.00 to 0.55)	−0.01 (−0.30 to 0.28)	.94
All other genes analyzed[d]	595	0.47 (0.70)	0.47 (0.40 to 0.54)	0.53 (0.74)	0.54 (0.45 to 0.63)	0.06 (−0.05 to 0.18)	.29	0.58 (0.64)	0.54 (0.22 to 0.85)	0.06 (−0.26 to 0.39)	.70
Variant of uncertain significance											
All	881	0.69 (0.86)	0.70 (0.61 to 0.79)	0.80 (0.95)	0.82 (0.70 to 0.93)	0.12 (−0.03 to 0.27)	.13	0.77 (0.82)	0.65 (0.19 to 1.12)	−0.04 (−0.52 to 0.44)	.86
TTN[b]	52	0.06 (0.23)	0.06 (0.03 to 0.08)	0.03 (0.16)	0.03 (0.01 to 0.52)	−0.03 (−0.06 to 0.00)	.09	0.04 (0.20)	0.02 (0.00 to 0.14)[c]	−0.04 (−0.17 to 0.09)	.55
BAG3, *DSP*, *FLNC*, *LMNA*, *PLN*, *SCN5A*, *VCL*[b]	257	0.19 (0.44)	0.20 (0.15 to 0.24)	0.24 (0.53)	0.25 (0.18 to 0.32)	0.05 (−0.03 to 0.13)	.19	0.23 (0.43)	0.18 (0.00 to 0.43)[c]	−0.01 (−0.26 to 0.24)	.92
All other genes analyzed[d]	572	0.44 (0.68)	0.44 (0.37 to 0.51)	0.53 (0.74)	0.54 (0.45 to 0.62)	0.09 (−0.03 to 0.21)	.13	0.50 (0.58)	0.45 (0.14 to 0.76)	0.01 (−0.32 to 0.34)	.95
Pathogenic or likely pathogenic variant											
All	226	0.26 (0.45)	0.26 (0.21 to 0.31)	0.09 (0.28)	0.07 (0.03 to 0.12)	−0.19 (−0.25 to −0.12)	<.001	0.31 (0.47)	0.33 (0.09 to 0.57)	0.07 (−0.17 to 0.31)	.56
TTN[b]	133	0.15 (0.35)	0.14 (0.11 to 0.17)	0.06 (0.24)	0.05 (0.02 to 0.08)	−0.09 (−0.14 to −0.05)	<.001	0.12 (0.33)	0.16 (0.00 to 0.34)[c]	0.02 (−0.17 to 0.20)	.87
BAG3, *DSP*, *FLNC*, *LMNA*, *PLN*, *SCN5A*, *VCL*[b]	70	0.09 (0.29)	0.09 (0.05 to 0.13)	0.02 (0.14)	0.03 (0.00 to 0.05)	−0.06 (−0.11 to −0.02)	.004	0.12 (0.33)	0.09 (0.00 to 0.20)[c]	0.00 (−0.12 to 0.12)	.98
All other genes analyzed[d]	23	0.03 (0.17)	0.03 (0.01 to 0.04)	0.00 (0.06)	0.00 (0.00 to 0.02)[c]	−0.03 (−0.05 to −0.01)	.009	0.08 (0.27)	0.08 (0.00 to 0.17)[c]	0.05 (−0.04 to 0.15)	.26

[a] Marginally standardized estimates of the mean number of variants in each subclass for the population of probands of a particular ancestry seen at US advanced heart failure programs were obtained using estimates from a generalized estimating equations model for proband variant subclass counts using the identity link and a working independence assumption. Each proband subpopulation defined by ancestry group was assumed to be balanced across the 8 possible sex and age quartile combinations, with a proportion of Hispanic individuals equal to the 2021 US census population estimate (18.9%).[29] Robust standard errors were obtained from the Morel-Bokossa-Neerchal bias-corrected estimate of the empirical covariance matrix and used to produce 95% CIs for each ancestry group mean and differences from the European ancestry group mean in other ancestry groups as well as 2-sided Wald *P* values testing the null hypothesis of zero difference using the standard normal distribution.

[b] The American College of Medical Genetics/Association for Molecular Pathology–based criteria adapted for this study of dilated cardiomyopathy stipulate that predicted loss-of-function variants in these genes have elevated evidence of pathogenicity (PVS1 rule).

[c] The actual lower bound of the 95% CI was negative and truncated at zero.

[d] Other genes analyzed are listed in eTable 2 in Supplement 1.

Clinical variant adjudication criteria systematically weight variant impact, functional, computational, clinical case, and family data to calculate a final classification. The difference in the mean number of pathogenic/likely pathogenic variants between probands of African and European ancestry was driven predominantly by differences in definitive or strong evidence DCM genes (Table 4).[9] Definitive and strong evidence genes that have pLOF as an established mechanism of DCM are more heavily weighted (ACMG criterion PVS1), facilitating a pathogenic/likely pathogenic classification, in some cases without additional clinical case or family segregation data. In contrast, genes without pLOF as an established mechanism for DCM causation often rely on larger numbers of case observations or functional studies to reach a pathogenic/likely pathogenic classification.

The overall difference between probands of African and European ancestry in *TTN* also reflected a smaller contribution from *TTN* pLOF variants in African ancestry (eTable 6 in Supplement 1) that could not be offset by a larger contribution from missense variants in *TTN*, which have been considered benign for DCM and were classified as such. For genes other than *TTN,* in which missense variants were adjudicated, a second model considering contributions by predicted impact (eTable 7 in Supplement 1) showed that the overall difference in the mean number of pathogenic variants/likely pathogenic variants/variants of uncertain significance between probands of African and European ancestry arose from a reduction of 0.05 (95% CI, −0.09 to −0.02) in non-*TTN* pLOF variants offset by an increase of 0.11 (95% CI, −0.05 to 0.27) in non-*TTN* non-pLOF variants in probands of African ancestry. The increase in non-*TTN* non-pLOF variants was composed of a larger increase of 0.15 (95% CI, 0.00-0.30) in variants of uncertain significance offset by a reduction of 0.05 (95% CI, −0.07 to −0.02) in pathogenic/likely pathogenic variants, demonstrating the effect of previously described differences in the application of population frequency, family segregation, and clinical case criteria for variants found only in probands of African ancestry.

Discussion

Patients of African ancestry with DCM had fewer variants in DCM genes classified as pathogenic or likely pathogenic relative to European ancestry, despite similar numbers of overall pathogenic variants/likely pathogenic variants/variants of uncertain significance identified, resulting in a deficit in clinically actionable molecular genetic diagnoses. This was due in part to a lower prevalence of pLOF variants in *TTN* and other high-evidence genes and in part to a lack of clinical genetics case data for variant interpretation. These findings are directly relevant for the clinical care of patients of African ancestry with DCM and their families.

This study underscores the need for greater case data from patients of African ancestry with DCM, as lack of ancestry-specific case data likely prevented the assignment of a clinically relevant classification, which could include elevation of some variants from variants of uncertain significance to pathogenic or likely pathogenic. African ancestry DCM case data have been nearly nonexistent in the research literature and only minimally represented in publicly accessible clinical genetics databases.[30] This is clinically highly relevant, as only pathogenic or likely pathogenic variants are recommended for clinical decision-making, including predictive testing of at-risk family members,[31,32] and will become a prerequisite to access gene-specific therapies.[33] Furthermore, with genotype-specific therapeutic recommendations, a variant of uncertain significance would be viewed as insufficient to justify augmented care that might be triggered by a pathogenic or likely pathogenic variant classification. The reasons for the lack of African ancestry representation in cardiomyopathy genetic research and clinical databases are complex but in large part have resulted from systemic racism and lack of access to care,[19,34,35] including insufficient access to genetic evaluation and testing.[5,36]

This study also underscores that current understanding of DCM genetic architecture has been based nearly universally on data derived from European ancestry cohorts, and this understanding has been applied to patients of African ancestry and their families without validation. DCM genes analyzed in this study were systematically curated[9] using the ClinGen approach,[37,38] but whether the gene-disease relationship ranking accurately reflects the genetic architecture of DCM for patients of African ancestry is unknown. Similarly, assumptions based on European ancestry–derived data for the types or numbers of variants expected to be observed in DCM genes may be misleading when considered for patients of African ancestry with DCM. Patients of African ancestry with DCM had fewer pLOF variants and greater numbers of non-pLOF variants, mostly missense, relative to patients of European ancestry, underscoring differences in DCM genetic architecture that are congruent with an analysis of African and European exome data.[39] This was also illustrated in this study by fewer *TTN* pLOF variants observed in patients of African ancestry with DCM. *TTN* pLOF variants have been established as the most common genetic cause of DCM in patients of European ancestry, accounting for 15% to 20% of cases.[40] As shown herein (eAppendix 2 and eTable 8 in Supplement 1), *TTN* pLOF variants were positively associated with DCM risk in patients of African ancestry but with a reduced effect compared with patients of European ancestry with DCM, even though all probands met a rigorous clinical standard of DCM,[11,13,14] and the familial risk of DCM was greater in Black patients, also supporting genetic cause.[13] A prior genomics-first study did not find statistical evidence of an association of *TTN* pLOF variants with DCM in patients of African ancestry yet did observe the association in those of European ancestry.[41]

Why the prevalence of *TTN* pLOF variants was lower in patients of African ancestry with DCM compared with patients of European ancestry with DCM is not clear, as the prevalence of such variants was similar in reference populations of both ancestries (eTable 8 in Supplement 1). One possibility, differential *TTN* splicing, has been excluded by others.[41] *TTN* posttranslational biology is complex,[42] and other ancestry-specific genetic variation could account for observed differences. Additional studies targeted to *TTN*

molecular genetics and biology will be needed to clarify these findings.

Limitations

This study has limitations, including the probabilistic nature of variant interpretation, a challenge faced across all of clinical genetics practice that is inherent to the process recommended by guiding organizations.[10] However, our DCM-targeted criteria coupled with the visibility of clinical patient and family data have been demonstrated by others to require a high degree of evidence to achieve a pathogenic or likely pathogenic classification.[43] In addition, because exome sequencing was used for this study, possible relevant variants beyond coding sequence would have been missed. Finally, because probands were identified at tertiary care centers, referral and survival biases may have affected the results.

Conclusions

Patients of African ancestry with DCM were less likely to have DCM gene variants classified as clinically actionable than those of European ancestry, due in part to DCM gene and variant architecture that differed from that of European ancestry, but also due to a lack of representation of African ancestry in clinical and reference data sets. The increased prevalence of familial DCM in patients of African ancestry with DCM[13] emphasizes that a remedy is needed.

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